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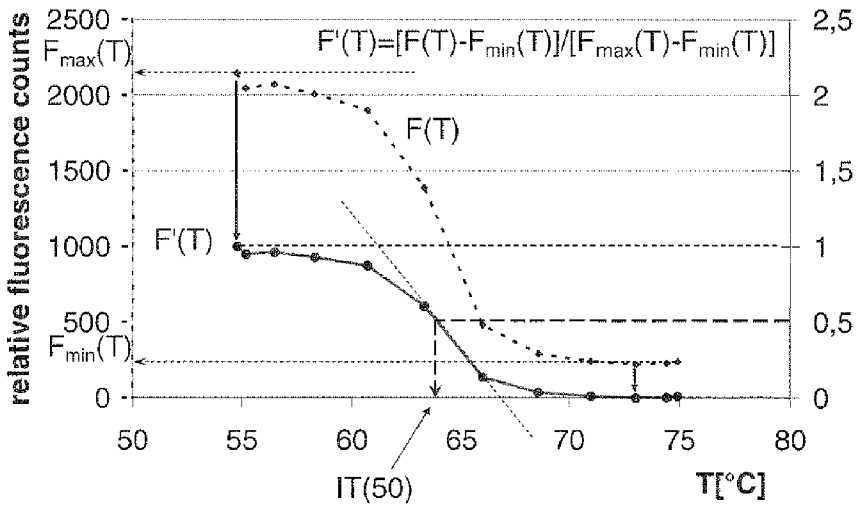
[Continued on next page]

(54) Title: OPTIMIZED CELLULASE ENZYMES

Figure 7



(57) Abstract: The invention discloses cellulase enzymes with optimized properties for processing of cellulose- and lignocellulose-containing substrates. In particular, cellobiohydrolase enzymes with preferred characteristics are disclosed. The present invention provides fusion, insertion, deletion and/or substitution variants of such enzymes. Enzyme variants have enhanced thermostability, proteolytic stability, specific activity and/or stability at extreme pH. Nucleic acid molecules encoding said enzymes, a composition comprising said enzymes, a method for preparation, and the use for cellulose processing and/or for the production of biofuels are disclosed.

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Title

Optimized Cellulase Enzymes

Field of invention

The invention discloses cellulase enzymes with optimized properties for processing of cellulose- and lignocellulose-containing substrates. In particular, cellobiohydrolase enzymes with preferred characteristics are disclosed. The present invention provides fusion, insertion, deletion and/or substitution variants of such enzymes. Enzyme variants have enhanced thermostability, proteolytic stability, specific activity and/or stability at extreme pH. Nucleic acid molecules encoding said enzymes, a composition comprising said enzymes, a method for preparation, and the use for cellulose processing and/or for the production of biofuels are disclosed.

Background of the invention

The development of production processes based on renewable resources is highly desired, for example for the generation of ethanol from cellulosic and lignocellulosic materials.

Cellulose material in pure form or in combination with hemicellulose and/or lignin is a valuable and readily available raw material for the production of chemicals and fuels. A key step in processing cellulose and lignocellulose is the hydrolysis of the beta-1,4-linked glucose polymer cellulose and the subsequent release of glucose monomers and short glucose oligomers such as cellobiose, cellotriose, etc. Enzymes that catalyze this reaction are found in various organisms, especially filamentous fungi and bacteria, that are capable of degrading and hydrolysing cellulose.

Continuous processes for converting solid lignocellulosic biomass into combustible fuel products are known. Treatment to make cellulosic substrates more susceptible to enzymatic degradation comprises milling, chemical processing and/or hydrothermal processing. Examples are wet oxidation and/or steam explosion. Such treatments increase the accessibility of cellulose fibers and separate them from hemicelluiose and lignin.

A number of enzyme mixtures for hydrolysis of treated biomass are known in the literature. Typically a mixture of endoglucanase, exoglucanase and beta-glucosidase enzymes are

required for the degradation of celiulose polymers. Among these cellobiohydrolase (CBH) enzymes, and more specifically cellobiohydrolase I (CBHI) enzymes, play a key role in the hydrolysis step as they provide the most processive enzymatic activity. CBHI enzymes catalyze the progressive hydrolytic release of cellobiose from the reducing end of the cellulose polymers. (Lynd LR, Weimer PJ, van Zyl WH, Pretorius IS. Microbial cellulose utilization: fundamentals and biotechnology. Microbiol Mol Biol Rev. 2002 Sep;66(3):506-77).

Hydrolyzed cellulosic materials contain several valuable carbohydrate molecules which can be isolated from the mixtures. Sugar containing hydrolysates of cellulosic materials can be used for microbial production of a variety of fine chemicals or biopolymers, such as organic acids, ethanol or higher alcohols (also diols or polyols) or polyhydroxyalkanoates (PHAs). One of the major uses of the sugar hydrolysates is in the production of biofuels.

Kurabi et al. (2005) describes preparations of cellulases from Trichoderma reesei and other fungi, such as Penicillium sp. The performance has been analysed on steam-exploded and ethanol organosolv-pretreated Douglas-fir. Better performance of enzyme mixtures appears to be a result of improved properties of single component enzymes as well as the effect of each compound in the mixture, especially the presence of beta-glucosidase. (Kurabi A, Berlin A, Gilkes N, Kilburn D, Bura R, Robinson J, Markov A, Skomarovsky A, Gusakov A, Okunev O, Sinitsyn A, Gregg D, Xie D, Saddler J.(2005) Enzymatic hydrolysis of steam-exploded and ethanol organosolv-pretreated Douglas-Fir by novel and commercial fungal cellulases. Appl Biochem Biotechnol.121-124: 219-30).

Cellobiohydrolase sequences of the glucohydrolase class 7 (cel7) are known to the art from several fungal sources. The Talaromyces emersonii Cel7 cellobiohydrolase is known and expression was reported in Escherichia coli (Grassick A, Murray PG, Thompson R, Collins CM, Byrnes L, Birrane G, Higgins TM, Tuohy MG. Three-dimensional structure of a thermostable native cellobiohydrolase, CBH IB, and molecular characterization of the cel7 gene from the filamentous fungus, Talaromyces emersonii. Eur J Biochem. 2004 Nov;271(22):4495-506) and Saccharomyces cerevisiae (Voutilainen SP, Murray PG, Tuohy MG, Koivula A. Expression of Talaromyces emersonii cellobiohydrolase Cel7A in Saccharomyces cerevisiae and rational mutagenesis to improve its thermostability and activity. Protein Eng Des Sel. 2010 Feb;23(2):69-79), however the protein was either produced in inactive form or at rather low yields (less or equal to 5mg/l). Hypocrea jecorina cellobiohydrolase I can be produced from wild type or engineered strains of the genus Hypocrea or Trichoderma at high yields. Improved sequences of Hypocrea jecorina Cel7A are disclosed by US7459299B2, US7452707B2, WO2005/030926, WO01/04284A1 or US2009/0162916 A1.

Positions leading to improvements were deduced from alignments with sequences from reported thermostable enzymes, suggested from structural information and shuffling of identified positions followed by limited screenings. Screening of larger libraries in transformable organisms such as *Saccharomyces cerevisiae* was reported by application of very sensitive fluorescent substrates, which resemble native substrates in a very restricted way. (Percival Zhang YH, Himmel ME, Mielenz JR. Outlook for cellulase improvement: screening and selection strategies. Biotechnol Adv. 2006 Sep-Oct;24(5):452-81).

The production of cellobiohydrolases from other fungal systems such as *Thermoascus aurantiacus*, *Chrysosporium lucknowense* or Phanerochaete chrysosporium was reported. Expression of Cel7 cellobiohydrolase from yeasts was reported, but enzymatic yields or enzyme properties remain unsatisfactory. (Penttilä ME, André L, Lehtovaara P, Bailey M, Teeri TT, Knowles JK. Efficient secretion of two fungal cellobiohydrolases by Saccharomyces cerevisiae. Gene.1988;63(1):103-12).

WO03/000941 discloses a number of CBHs and their corresponding gene sequences. Physiological properties and applications however were not disclosed. The fusion of cellulose binding domains to catalytic subunits of cellobiohydrolases is reported to improve the hydrolytic properties of proteins without a native domain.

US 2009042266 (A1) discloses fusions of Thermoascus aurantiacus Cel7A with cellulose binding domains from cellobiohydrolase I from *Chaetomium thermophilum* and *Hypocrea jecorina*.

US5686593 reports the fusion of specially designed linker regions and binding domains to cellobiohydrolases.

Hong et al. (2003) describe the production of *Thermoascus aurantiacus* CBHI in yeast and its characterization. (Hong J, Tamaki H, Yamamoto K, Kumagai H Cloning of a gene encoding thermostable cellobiohydrolase from Thermoascus aurantiacus and its expression in yeast. Appl Microbiol Biotechnol. 2003 Nov;63(1):42-50).

Tuohy et al. (2002) report the expression and characterization of *Talaromyces emersonii* CBH. (Tuohy MG, Walsh DJ, Murray PG, Claeyssens M, Cuffe MM, Savage AV, Coughlan MP.:Kinetic parameters and mode of action of the cellobiohydrolases produced by Talaromyces emersonii. Biochim Biophys Acta. 2002 Apr 29;1596(2):366-80).

Nevoigt et al. (2008) reports on the expression of cellulolytic enzymes in yeasts. (Nevoigt E. Progress in metabolic engineering of Saccharomyces cerevisiae. Microbiol Mol Biol Rev. 2008 Sep;72(3):379-412).

Fujita et al. (2004) reports on a *Saccharomyces cervisiae* strain expressing a combination of an endoglucanase, a beta glucosidase and a CBHII displayed on the cell surface. Cellobiohydrolase I (Cel7) was not used in this setup. (Fujita Y, Ito J, Ueda M, Fukuda H, Kondo A. Synergistic saccharification, and direct fermentation to ethanol, of amorphous cellulose by use of an engineered yeast strain codisplaying three types of cellulolytic enzyme. Appl Environ Microbiol. 2004 Feb;70(2):1207-12).

Boer H et al. (2000) describes the expression of GH7 classified enzymes in different yeast hosts but expressed protein levels were low. (Boer H, Teeri TT, Koivula A. Characterization of Trichoderma reesei cellobiohydrolase Cel7A secreted from Pichia pastoris using two different promoters. Biotechnol Bioeng. 2000 Sep 5;69(5):486-94).

Godbole et al (1999) and **Hong et al (2003)** found that proteins of this enzyme class expressed fom yeast were often misfolded, hyperglycosylated and hydrolytic capabilities decreased compared to the protein expressed from the homologous host. (Godbole S, Decker SR, Nieves RA, Adney WS, Vinzant TB, Baker JO, Thomas SR, Himmel ME. Cloning and expression of Trichoderma reesei cellobiohydrolase I in Pichia pastoris. Biotechnol Prog. 1999 Sep-Oct;15(5):828-33).

Kanokratana et al (2008), Li et al (2009) as well as **CN01757710** describe the efficient expression of Cel7 CBH I enzymes, however these proteins are lacking celllulose binding domains required for efficient substrate processing. (Kanokratana P, Chantasingh D, Champreda V, Tanapongpipat S, Pootanakit K, Eurwilaichitr L Identification and expression of cellobiohydrolase (CBHI) gene from an endophytic fungus, Fusicoccum sp. (BCC4124) in Pichia pastoris. LProtein Expr Purif. 2008 Mar;58(1):148-53. Epub 2007 Sep 19; Li YL, Li H, Li AN, Li DC. Cloning of a gene encoding thermostable cellobiohydrolase from the thermophilic fungus Chaetomium thermophilum and its expression in Pichia pastoris. J Appl Microbiol. 2009 Jun;106(6):1867-75).

Voutilainen (2008) and **Viikari (2007)** disclose Cel7 enzymes comprising thermostable cellobiohydrolases, however with only low to moderate expression levels from *Trichoderma reesei*. (Voutilainen SP, Puranen T, Siika-Aho M, Lappalainen A, Alapuranen M, Kallio J, Hooman S, Viikari L, Vehmaanperä J, Koivula A. Cloning, expression, and characterization

of novel thermostable family 7 cellobiohydrolases. Biotechnol Bioeng. 2008 Oct 15;101(3):515-28. PubMed PMID: 18512263; Viikari L, Alapuranen M, Puranen T, Vehmaanperä J, Siika-Aho M. Thermostable enzymes in lignocellulose hydrolysis. Adv Biochem Eng Biotechnol. 2007;108:121-45).

Grassick et al. (2004) disclose unfolded expression of Cellobiohydrolase I from *Talaromyces emersonii* in *Escherichia coli* but not in yeast. (Grassick A, Murray PG, Thompson R, Collins CM, Byrnes L, Birrane G, Higgins TM, Tuohy MG. Three-dimensional structure of a thermostable native cellobiohydrolase, CBH IB, and molecular characterization of the cel7 gene from the filamentous fungus, Talaromyces emersonii. Eur J Biochem. 2004 Nov;271(22):4495-506).

Therefore, there is a need for cellulase enzymes with improved characteristics for the use in technical processes for cellulose hydrolysis. In particular there is a need for CBH enzymes with higher catalytic activity and/or higher stability under process conditions. Moreover there is a need for CBH enzymes with higher productivity in fungal and/or yeast expression and secretion systems.

Summary of the invention

The present invention provides a polypeptide having cellobiohydrolase activity. In a preferred embodiment, the invention provides a thermostable polypeptide having cellobiohydrolase activity. That is, in this embodiment, the polypeptide maintains 50 % of its maximum substrate conversion capacity when the conversion is done for 60 minutes at 60 °C or higher, preferably 62 °C or higher, and in a particular embodiment 64 °C or higher, such as 66 °C or higher. This polypeptide comprises an amino acid sequence with at least 54 %, preferably at least 56 %, more preferably at least 58 %, particularly preferably at least 60 %, such as at least 62 %, particularly at least 64 %, such as at least 66 %, and most preferably preferably at least 68 % sequence identity to SEQ ID NO5. The invention also provides a polypeptide which comprises an amino acid sequence with at least 85 % sequence identity to SEQ ID NO: 2.

Furthermore, the present invention discloses a nucleic acid encoding the polypeptide of the present invention, preferably having at least 95 % identity to SEQ ID NO: 1, a vector comprising this nucleic acid and a host transformed with said vector.

The present invention further provides a method of producing a cellobiohydrolase protein encoded by a vector of the present invention, a method for identifying polypeptides having cellobiohydrolase activity, and a method of preparing such polypeptides having cellobiohydrolase activity. It also provides a method of identifying such polypeptides which maintain 50 % or more of maimum substrate conversion capacity at elevated temperatures, such as at 60 °C or more.

The present invention also provides a polypeptide having celiobiohydrolase activity, wherein the polypeptide comprises an amino acid sequence having at least 85 % sequence identity to SEQ ID NO: 2 wherein one or more specific amino acid residues of the sequence defined by SEQ ID NO: 2 are modified by substitution or deletion, as well as insertion mutants. Examples of such mutants include Q1, G4, A6, T15, Q28, W40, D64, E65, A72, S86, K92, V130, V152, Y155, K159, D181, E183, N194, D202, P224, T243, Y244, I277, K304, N310, S311, N318, D320, T335, T344, D346, Q349, A358, Y374, A375, T392, T393, D410, Y422, P442, N445, R446, T456, S460, P462, G463, H468 and/or V482 of amino acids 1 to 500 of SEQ ID NO: 2, but the invention is by no means limited to these. Further specific positions are given below.

Moreover, the present invention provides a polypeptide having cellobiohydrolase activity, which is obtainable by the method of preparing a polypeptide having cellobiohydrolase activity according to the present invention, and a polypeptide having celiobiohydrolase activity, wherein the polypeptide comprises an amino acid sequence having at least 80 % sequence identity to SEQ ID NO: 5, wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 5 are modified by substitution or deletion, as well as insertion mutants. Examples of such mutants include Q1, G4, A6, T15, Q28, W40, D64, E65, A72, S86, K92, V130, V152, Y155, K159, D181, E183, N194, D202, P224, T243, Y244, I277, K304, N310, S311, N318, D320, T335, T344, D346, Q349, A358, Y374, A375, T392, T393, D410 and/or Y422 of amino acids 1 to 440 of SEQ ID NO: 5, but the invention is by no means limited to these. Further specific positions are given below.

The present invention furthermore provides a polypeptide having cellobiohydrolase activity comprising an amino acid sequence having at least 85 % sequence identity to SEQ ID NO: 12 wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 12 are modified by substitution or deletion as well as insertion mutants. Examples of such mutants include Q1, T15, Q28, W40, C72, V133, V155, Y158, T162, Y247, N307, G308, E317, S341, D345, Y370, T389, Q406, N441, R442, T452, S456, P458, G459, H464 and/or V478, but the invention is by no means limited to these. Further specific positions are given below.

The present invention further provides the use of a polypeptide or the composition of the present invention for the enzymatic degradation of lignocellulosic biomass, and/or for textiles processing and/or as ingredient in detergents and/or as ingredient in food or feed compositions.

Brief description of the figures

Figure 1: Restriction Maps of pV1 for constitutive expression of Proteins in *Pichia pastoris*: pUC19 – ori: Origin of replication in E. coli; KanR: Kanamycine/G418 Resistance with TEF1 and EMZ Promoter sequences for selection in *Pichia pastoris* and *E. coli*, respectively; 5'GAP: glyceraldehyde-3- phosphate dehydrogenase Promoter region; 3'-GAP: terminator region; SP MFalpha: *Saccharomyces cerevisiae* mating factor alpha signal sequence; MCS: multiple cloning site.

Figure 2: Commassie stained SDS-PAGE of 10-fold concentrated supernatants of shake-flask cultures of *Pichia pastoris* CBS 7435 containing expression plasmids with coding sequences for the mature CBHI proteins of *Trichoderma viride* (CBH-f; lane 1), *Humicola grisea* (CBH-d; lane 2), *Talaromyces emersonii* (CBH-b; lane 3), *Thermoascus aurantiacus* (CBH-e; lane 4), as well as the *Talaromyces emersonii* CBHI-CBD fusion (CBH-a; lane 6) and the *Humicola grisea*-CBD fusion (CBH-g; lane 7) in N-terminal fusion to the signal peptide of the *Saccharomyces cerevisiae* mating factor alpha under control of the *Pichia pastoris* glyceraldehyde-3-phosphate dehydrogenase promoter

Figure 3: Map of the pV3 expression plasmid for protein expression in *Pichia pastoris*. Replicons: pUC19 – ori: Origin of replication in E. coli; ZeoR: Zeocine resistance gene with TEF1 and EM7 Promoter promoter sequences for expression in *Pichia pastoris* and *E. coli*, respectively; AOX I promoter: Promoter region of the Pichia pastoris alcohol oxidase I gene; AOX 1 transcriptional terminator: terminator region; SP MFalpha: *Saccharomyces cerevisiae* mating factor alpha signal sequence; MCS: multiple cloning site.

Figure 4: SDS-PAGE analysis of culture supernatant samples taken from the fermentation of a *Pichia pastoris* strain with a genomic integration of an AOXI-expression cassette, expressing the *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion peptide (CBH-a) in a 7l bioreactor during methanol induction. Samples P1 – P7 were are taken at the

beginning of the methanol induction and after 20, 45, 119.5, 142.5, 145.5 and 167 hours, respectively.

Figure 5: Figure 5: Map of pV4 expression plasmid for the expression of the *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion peptide (CBH-ah) in *Trichoderma reesei*. Replicon: pUC19 for replication in *E. coli*. cbh1 5': 5' promoter region of the *Trichoderma* CBHI gene; cbh1 signal peptide: Coding sequence for the *Trichoderma reesei* CBHI leader peptide; CBH-a: *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion peptide: coding region for SeqID NO. 18; cbh1 Terminator: 3' termination region of the *Trichoderma reesei* CBHI locus; hygromycine resistance: coding region of the hygromycine phosphotransferase under control of a *Trichoderma reesei* phosphoglycerate kinase promoter; cbh1 3': homology sequence to the termination region of the *Trichoderma reesei* CBHI locus for double crossover events.

Figure 6: SDS-Page of *Trichoderma reesei* culture supernatants. Lane 1 shows the expression pattern of a replacement strain carrying a *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion (CBH-ah) inplace of the *native* CBHI gene. In comparison lane 2 shows the pattern for the unmodified strain under same conditions. M: molecular size marker

Figure 7: Determination of IT50 values from Substrate Conversion Capacity vs. temperature graphs after normalization. For the normalization step the maximum and the minimum fluorescence values for the selected temperature are correlated to 1 or 0, respectively. Linear interpolation to F'(T)=0.5 between the nearest two temperature points with normalized values next to 0.5 results in the defined IT50 temperature.

Figure 8: Normalized Conversion Capacity vs. temperature graphs of "wt" *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusions (CBH-ah: SeqID NO. 18 = SeqID NO. 2 + 6x His-Tag) and mutants based on 4-Methylumbelliferyl -β-D-lactoside hydrolysis results evaluated at various temperatures. The fluorescence values were normalized according to figure 8 over the temperature range from 55°C to 75°C

A... wt;
B... G4C,A72C;
C... G4C,A72C,Q349K;
D... G4C,A72C,D181N,Q349K;
E... Q1L,G4C,A72C,D181N,E183K,Q349R;
F... Q1L,G4C,A72C,S86T,D181N,E183K,D320V,Q349R;
G.. .G4C, A72C,E183K,D202Y,N310D,Q349R;
H.. .Q1L,G4C,A72C, A145T,H203R,Q349K,T403K;

I... , Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S192S, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I

J... , Q1L, G4C, Q28K, E65K, A72C, L119L, D181N, E183M, S192S, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T

K... , Q1L, G4C, Q28K, E65V, A72C, L119L, D181N, E183M, S192S, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I

L... Q1L, G4C, Q28R, E65V, A72C, G151GCGRSG, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I

M... Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I

Figure 9: Glucose yields of hydrolysis of pretreated straw with wt and mutated *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD (CBH-ah) fusion protein after hydrolysis for 48 hours in the presence of a β-glycosidase. The variants are characterized by the following mutations with respect to SeqID NO. 18 and were expressed from *Pichia pastoris* in shake flask cultures and isolated from the supernatant by affinity chomatography using Ni-NTA.

A: wt
B: G4C, A72C
C: G4C, A72C, Q349R
D: Q1L, G4C, A72C, D181N, E183K, Q349R
E: Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
F: Q1L, G4C, Q28R, E65V, A72C, G151GCGRSG, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I

Figure 10: Alignment of SeqID. NO 2 with the *Trichoderma reesei* CBHI. The alignment matrix blosum62mt2 with gap opening penalty of 10 and gap extension penalty of 0.1 was used to create the alignment.

Detailed description of the invention

The present invention provides polypeptides having cellobiohydrolase activity. In a preferred embodiment, the invention provides a thermostable polypeptide having cellobiohydrolase activity. In a preferred aspect, the invention discloses protein variants that show a high activity at high temperature over an extended period of time. Preferably, the polypeptide of the present invention maintains 50 % of its maximum substrate conversion capacity when the conversion is done for 60 minutes at a temperature of 60 °C or higher. The respective temperature is also referred to as the IT50 value. In other words, the IT50 value is preferably 60 °C or higher, but more preferably 62 °C or higher. That is, in this embodiment, the polypeptide maintains 50 % of its maximum substrate conversion capacity when the conversion is done for 60 minutes at 60 °C or higher, preferably preferably 62 °C or higher, and in a particular embodiment 64 °C or higher, such as 66 °C or higher. Furthermore, the

polypeptides of the present invention have preferably an IT50 value in the range of 62 to 80 °C, more preferably 65 to 75 °C.

"Substrate Conversion Capacity" of an enzyme is herein defined as the degree of substrate conversion catalyzed by an amount of enzyme within a certain time period under defined conditions (Substrate concentration, pH value and buffer concentration, temperature), as can be determined by end-point assaying of the enzymatic reaction under said conditions. "Maximum Substrate Conversion Capacity" of an enzyme is herein defined as the maximum in Substrate Conversion Capacity found for the enzyme within a number of measurements performed as described before, where only one parameter, e.g. the temperature, was varied within a defined range. According to the present invention, the assay described in Example 8 is used to determine these parameters.

This polypeptide comprises an amino acid sequence with at least 54 %, preferably at least 56 %, more preferably at least 58 %, particularly preferably at least 60 %, such as at least 62 %, particularly at least 64 %, such as at least 66 %, and most preferably preferably at least 68 % sequence identity to SEQ ID NO: 5. The term "Identity over a sequence length of y residues" (wherein y is any integer, such as, as illustrative example, 200, 255, 256, 300, 400, 437, 500) means that y is a - preferably continuous - portion of the parenteral sequence (in this particular case SEQ ID NO: 5, but the same is true throughout this application, also with respect to other, specifically indicated parenteral sequences which which the sequences of this invention may be compared) which is used as a basis for the comparison of sequence identitiy. Thus, for the comparison of sequence identity (sequence alignment), preferably 200 or more, more preferably 300 or more, even more preferably 400 or more, and most preferably 437 positions of the parental sequence given in SEQ ID NO: 5 are taken into consideration. The details of how the percentages of sequence identities are calculated are given below. It should also be noted, that, unless explicitly otherwise specified in this specification, the entire sequence of the parental sequence (such as, in this particular case, SEQ ID NO:5) (i.e. from the first to the last amino acid residue) shall be used as a parent sequence.

In a preferred embodiment, the polypeptide capable of maintaining 50 % of its maximum substrate conversion capacity when the conversion is done for 60 minutes at 60 °C or higher, preferably preferably 62 °C or higher, is a polypeptide which differs from SEQ ID NO: 5 by at least one mutation, wherebey the mutation may be an insertion, deletion or substitution of one or more amino acid residues. Also preferred are at least two such mutations, such as at least 4, at least 5, at leat 6, at least 7, at least 10 such mutations with respect to the polypeptide given in SEQ ID NO: 5.

"Cellobiohydrolase" or "CBH" refers to enzymes that cleave cellulose from the end of the glucose chain and produce cellobiose as the main product. Alternative names are 1,4-beta-D-glucan cellobiohydrolases or cellulose 1,4-beta-cellobiosidases. CBHs hydrolyze the 1,4-beta-D-glucosidic linkages from the reducing or non-reducing ends of a polymer containing said linkages. "Cellobiohydrolase I" or "CBH I" act from the reducing end of the cellulose fiber. "Cellobiohydrolase II" or "CBH II" act from the non-reducing end of the cellulose fiber. Cellobiohydrolases typically have a structure consisting of a catalytic domain and one or more "cellulose-binding domains" or "CBD". Such domains can be located either at the N- or C-terminus of the catalytic domain. CBDs have carbohydrate-binding activity and they mediate the binding of the cellulase to crystalline cellulose and presence or absence of binding domains are known to have a major impact on the processivity of an enzyme especially on polymeric substrates.

In a preferred embodiment, this polypeptide is further characterized by comprising an amino acid sequence having at least 80 % sequence identity to SEQ ID NO:5, more preferably at least 85 % sequence identity to SEQ ID NO:5, such as at least 90 % % sequence identity to SEQ ID NO:5, and most preferably at least 95 % sequence identity to SEQ ID NO.5.

The polypeptide having cellobiohydrolase activity as defined above is, in an even more preferred embodiment, further characterized as follows: It is the polypeptide as defined above, wherein one or more of the amino acid residues of the sequence defined by SEQ ID NO: 5 are modified by substitution or deletion at one or more positions which are preferably selected from
Q1, Q2, G4, A6, T7, A8, N10, P12, T15, A21, G23, S24, T26, T27, Q28, N29, G30, A31, V32, N37, W40, V41, G46, Y47, T48, N49, C50, T52, N54, D57, T59, Y60, D64, E65, A68, Q69, A72, V84, S86, S89, S90, K92, S99, Q109, D110, D111, I116, F117, K118, L119, L120, D129, V130, G139, A145, M146, V152, K154, Y155, N157, N158, K159, K163, G167, Q172, F179, I180, D181, E183, E187, G188, Q190, S192, S193, N194, I200, D202, H203, D211, V212, A221, P224, D228, T229, G231, T233, M234, S236, T243, Y244, S245, N246, D247, G251, F260, G266, K275, I276, I277, T280, L290, D293, G294, T295, T297, T299, S301, K304, F306, N310, S311, V313, I314, N318, D320, I321, T325, N327, T335, A340, F341, D343, T344, D345, D346, Q349, H350, A354, K355, A358, Q361, Q362, G363, M364, V367, D373, Y374, A375, A376, P386, T387, D390, T392, T393, P394, T400, P402, T403, D404, D410, N417, S418, T421, Y422 and/or one or more insertions after positions G151, K159,

and in a more preferred embodiment are modified by substitution or deletion at one or more positions selected from Q1, Q2, G4, A6, T7, A8, N10, A21, S24, T26, T27, Q28, N29, G30, W40, Y47, D64, E65, A68, Q69, A72, S86, K92, K118, Y155, D181, E183, Q190, S192, N194, D202, H203, P224, T229, G231, M234, S236, T243, D247, S311, N318, D320, T335, A340, T344, D346, Q349, K355, Y374, A375, T387, D390, T392, T393, Y422 and/or one or more insertion of 1-8 amino acids after positions G151, K159

and in an even more preferred embodiment are modified by substitution or deletion at one or more positions selected from Q1, Q2, G4, A6, T7, A8, N10, Q28, E65, A72, S86, D181, E183, D202, P224, S311, N318, D320, T335, D346, Q349, T392, T393, Y422 and/or insertions at one or more after positions and/or one or more insertion of 5 amino acids after positions G151, K159 of
of amino acids 1 to 437 of SEQ ID NO: 5.

Also preferred are embodiments wherein the respective mutation(s) given above is (are) introduced into the polypeptide given in SEQ ID NO: 2, as outlined below.

The skilled person will understand that several of these given mutations can be combined with each other, i.e. that a polypeptide having cellobiohydrolase activity, where, for example Q69 and T232 are substituted for other amino acid residues, is comprised in this embodiment. The term "insertion after position(s) x" is to be understood that the insertion may be at any position which is on the C-terminal side (closer to the C-terminus) of the position x; however, insertions immediately following the position x are strongly preferred (wherein x is any position).

The present invention also discloses a polypeptide having cellobiohydrolase activity, which comprises an amino acid sequence with at least 85 % sequence identity to SEQ ID NO: 2. It is preferred that this polypeptide with at leat 85 % sequence identity to SEQ ID NO: 2 is a polypeptide which has also a degree of identity with SEQ ID NO: 5 as given above, such as having at least 60 % (or more, see above) sequence identity with the polypeptide given in SEQ ID NO: 5, and/or any one or more of the more particular identity embodiments of percentage identity to SEQ ID NO: 5 as given in detail above. Thus, the polypeptide having at least 85 % sequence identity to SEQ ID NO: 2 is an embodiment which is comprised in the invention relating to a polypeptide having at least 60 % sequence identity with the polypeptide given in SEQ ID NO: 5. The skilled person will readily recognize the common inventive concept underlying the thermostable variants of SEQ ID NO: 2 and SEQ ID NO: 5.

Equivalent to what has been said above for SEQ ID NO: 5, for the sequence alignment of SEQ ID NO: 2 as defined herein, preferably 200 or more, more preferably 300 or more, even more preferably 400 or more, and most prefearably 437 positions of SEQ ID NO: 5 are taken into consideration. The details of how the percentages of sequence identities are calculated are given below. In a more preferred embodiment, the respective polypeptide comprises an amino acid sequence having at least 85 % sequence identity to SEQ ID NO: 2 over a sequence length of 500 amino acid residues. Even more preferably, the present invention comprises an amino acid sequence having at least 90 %, or even more preferably of at least least 95% or 98% sequence identity to SEQ ID NO: 2 over a sequence length of 500 amino acid residues.

The parental sequence is given in SEQ ID NO: 2. The sequence derives from the C-terminal fusion of the linker domain and cellulose binding domain of *Trichoderma reesei* CBHI (SEQ ID NO: 4) to the catalytic domain of *Talaromyces* emersonii CBHI (SEQ ID NO: 5).The invention further comprises other fusion proteins comprising any cellulose binding domain and a derivative of the catalytic domain of *Talaromyces* emersonii CBHI (SEQ ID NO: 5), preferably with the temperature stability characteristics given above. The cellulose binding

domain may be from any source. The polypeptides according to the invention may additionally carry a hexahistidine tag. Thus, by means of illustration, variants of any one of the polypeptides shown in SEQ ID NO: 42, 44, 46, 48 or 50 are included in this invention. The variants are preferably such that the polypeptides exhibit temperature stability, as described and defined above.

The polypeptide of the present invention preferably comprises an amino acid sequence having at least 90 %, preferably at least 95 %, more preferably at least 99 % sequence identity to SEQ ID NO: 2. Furthermore, it is particularly preferred that the amino acid sequence of the polypeptide has the sequence as defined by SEQ ID NO: 2, or a sequence as defined by SEQ ID NO: 2 wherein 1 to 75, more preferably 1 to 35 amino acid residues are substituted, deleted, or inserted.

Particularly preferred are variants of the protein of SEQ ID NO: 2, SEQ ID NO: 5 or SEQ ID NO: 12. "Protein variants" are polypeptides whose amino acid sequence differs in one or more positions from this parental protein, whereby differences might be replacements of one amino acid by another, deletions of single or several amino acids, or insertion of additional amino acids or stretches of amino acids into the parental sequence. Per definition variants of the parental polypeptide shall be distinguished from other polypeptides by comparison of sequence identity (alignments) using the ClustalW Algorithm (Larkin M.A., Blackshields G., Brown N.P., Chenna R., McGettigan P.A., McWilliam H., Valentin F., Wallace I.M., Wilm A., Lopez R., Thompson J.D., Gibson T.J. and Higgins D.G. (2007) ClustalW and ClustalX version 2. Bioinformatics 2007 23(21): 2947-2948). Methods for the generation of such protein variants include random or site directed mutagenesis, site-saturation mutagenesis, PCR-based fragment assembly, DNA shuffling, homologous recombination in-vitro or in-vivo, and methods of gene-synthesis.

The nomenclature of amino acids, peptides, nucleotides and nucleic acids is done according to the suggestions of IUPAC. Generally amino acids are named within this document according to the one letter code.

Exchanges of single amino acids are described by naming the single letter code of the original amino acid followed by its position number and the single letter code of the replacing amino acid, i.e. the change of glutamine at position one to a leucine at this position is described as "Q1L". For deletions of single positions from the sequence the symbol of the replacing amino acid is substituted by the three letter abbreviation "del" thus the deletion of alanine at position 3 would be referred to as "A3del". Inserted additional amino acids receive

the number of the preceding position extended by a small letter in alphabetical order relative to their distance to their point of insertion. Thus, the insertion of two tryptophanes after position 3 is referred to as "3aW, 3bW" or simply as A3AWW (i.e formal replacement of "A" at position 3 by the amino acid residues "AWW"). Introduction of untranslated codons TAA, TGA and TAG into the nucleic acid sequence is indicated as "*" in the amino acid sequence, thus the introduction of a terminating codon at position 4 of the amino acid sequence is referred to as "G4*".

Multiple mutations are separated by a plus sign or a slash or a comma. For example, two mutations in positions 20 and 21 substituting alanine and glutamic acid for glycine and serine, respectively, are indicated as "A20G+E21S" or "A20G/E21S" "A20G,E21S".

When an amino acid residue at a given position is substituted with two or more alternative amino acid residues these residues are separated by a comma or a slash. For example, substitution of alanine at position 30 with either glycine or glutamic acid is indicated as "A20G,E" or "A20G/E", or "A20G, A20E".

When a position suitable for modification is identified herein without any specific modification being suggested, it is to be understood that any amino acid residue may be substituted for the amino acid residue present in the position. Thus, for instance, when a modification of an alanine in position 20 is mentioned but not specified, it is to be understood that the alanine may be deleted or substituted for any other amino acid residue (i.e. any one of R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y and V).

The terms "similar mutation" or "similar substitution" refer to an amino acid mutation that a person skilled in the art would consider similar to a first mutation. Similar in this context means an amino acid that has similar chemical characteristics. If, for example, a mutation at a specific position leads to a substitution of a non-aliphatic amino acid residue (e.g. Ser) with an aliphatic amino acid residue (e.g. Leu), then a substitution at the same position with a different aliphatic amino acid (e.g. Ile or Val) is referred to as a similar mutation. Further amino acid characteristics include size of the residue, hydrophobicity, polarity, charge, pK-value, and other amino acid characteristics known in the art. Accordingly, a similar mutation may include substitution such as basic for basic, acidic for acidic, polar for polar etc. The sets of amino acids thus derived are likely to be conserved for structural reasons. These sets can be described in the form of a Venn diagram (Livingstone CD. and Barton GJ. (1993) "Protein sequence alignments: a strategy for the hierarchical analysis of residue conservation" Comput.Appl Biosci. 9: 745-756; Taylor W. R. (1986) "The classification of amino acid

conservation" J.Theor.Biol. 119; 205-218). Similar substitutions may be made, for example, according to the following grouping of amino acids: Hydrophobic: F W Y H K M I L V A G; Aromatic: F W Y H; Aliphatic: I L V; Polar: W Y H K R E D C S T N; Charged H K R E D; Positively charged: H K R; Negatively charged: E D.

As convention for numbering of amino acids and designation of protein variants for the description of protein variants the first glutamine (Q) of the amino acid sequence QQAGTA within the parental protein sequence given in SEQ ID NO: 2 is referred to as position number 1 or Q1 or glutamine 1. The numbering of all amino acids will be according to their position in the parental sequence given in SEQ ID NO: 2 relative to this position number 1.

The present invention furthermore discloses specific variants of the polypeptides of the present invention as given above, such as variants of SEQ ID NO: 2, with changes of their sequence at one or more of the positionsgiven hereafter.I.e., the invention provides, in a particular embodiment, the polypeptide as above, wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 2 are preferably modified by substitution or deletion at positions Q1, Q2, G4, A6, T7, A8, N10, P12, T15, A21, G23, S24, T26, T27, Q28, N29, G30, A31, V32, N37, W40, V41, G46, Y47, T48, N49, C50, T52, N54, D57, T59, Y60, D64, E65, A68, Q69, A72, V84, S86, S89, S90, K92, S99, Q109, D110, D111, I116, F117, K118, L119, L120, D129, V130, G139, A145, M146, V152, K154, Y155, N157, N158, K159, K163, G167, Q172, F179, I180, D181, E183, E187, G188, Q190, S192, S193, N194, I200, D202, H203, D211, V212, A221, P224, D228, T229, G231, T233, M234, S236, T243, Y244, S245, N246, D247, G251, F260, G266, K275, I276, I277, T280, L290, D293, G294, T295, T297, T299, S301, K304, F306, N310, S311, V313, I314, N318, D320, I321, T325, N327, T335, A340, F341, D343, T344, D345, D346, Q349, H350, A354, K355, A358, Q361, Q362, G363, M364, V367, D373, Y374, A375, A376, P386, T387, D390, T392, T393, P394, T400, P402, T403, D404, D410, N417, S418, T421, Y422, F427, P429, I430, G431, T433, G434, N435, P436, S437, G439, N440, P441, P442, G443, N445, R446, T448, T449, T450, T451, R453, P454, A455, T456, T457, G459, S460, S461, P462, G463, P464, T465, S467, H468, G470, C472, G474, G476, Y477, S478, P480, V482, C483, S485, G486, T488, C489, Q490, V491, L492, N493, Y495, Y496, Q498, C499, L500 and/or by one or more insertions after positions G151, K159, G434, A455 or P464, of amino acids 1 to 500 of SEQ ID NO: 2.

In a more preferred embodiment one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 2 are preferably modified by substitution or deletion at positions selected from Q1, Q2, G4, A6, T7, A8, N10, A21, S24, T26, T27, Q28, N29, G30, W40, Y47, D64, E65, A68, Q69, A72, S86, K92, K118, Y155, D181, E183, Q190, S192,

N194, D202, H203, P224, T229, G231, M234, S236, T243, D247, S311, N318, D320, T335, A340, T344, D346, Q349, K355, Y374, A375, T387, D390, T392, T393, Y422, P436, P442, N445, R446, T448, T451, R453, P462, G463, H468, P480, V482, S485, and/or by one or more insertion of 1-8 amino acids after positions G151, K159, G434, A455 or P464, and in an even more preferred embodiment are modified by substitution or deletion at one or more positions selected from Q1, Q2, G4, A6, T7, A8, N10, Q28, E65, A72, S86, D181, E183, D202, P224, S311, N318, D320, T335, D346, Q349, T392, T393, Y422, P442, N445, R446, H468, V482, and/or by insertions at one or more after positions and/or one or more insertion of 5 amino acids after positions G151, K159, G434, A455 or P464 of amino acids 1 to 500 of SEQ ID NO: 2.

Also comprised in the invention are the respective mutations at any one or more of the specified mutations 1 to 430 of SEQ ID NO: 5. The skilled person will recognize that residues 1 to 430 of SEQ ID NO: 5 are equivalent to positions 1 to 430 of SEQ ID NO2, and can therefore readily transfer the detailed teaching given above and below for preferred modifications of SEQ ID NO: 2 for any one or more of positions 1 to 430 to the respective one or more position (1 to 430) of SEQ ID NO5. As an illustrative and non-limiting example, it is apparent for the skilled person that, since D390 is one particular position at which a modification in SEQ ID NO: 2 is preferred, D390 is likewise a position at which a modification in SEQ ID NO: 5 is preferred.

In a preferred embodiment, the variant of the polypeptide of the present invention is a polypeptide as described above, wherein specifically one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 2 are modified as shown in Table 1. Shown are preferred, more preferred and most preferred modification. Any of these mutations may be combined, with each other. However, in a particular embodiment it is preferred that the mutations are selected only among the more preferred and most preferred embodiments shown in Table 1. Even more preferably, only modifications indicated as most preferred are chosen. The skilled person will be aware that any several such mutations are combineable with each other.

Table 1: Preferred exchanges and similar mutations

Position	Preferred	More Preferred	Most Preferred
Q1	L	L	L
Q2	P,S	P,S	S
G4	C	C	C
A6	G,L,V	G,L,V	L
T7	Q	Q	Q

A8	S	S	S
N10	T,D	T,D	T,D
P12	Q		
T15	S		
A21	S,T,C	S,T,C	
G23	A,D,N		
S24	T,C,N	T,C,N	
T26	I,N	I,N	
T27	S,Q	S,Q	
Q28	L,K,R,N	L,K,R,N	K,R
N29	T,Y	T,Y	
G30	A	A	
A31	S		
V32	G		
N37	S		
W40	R	R	
V41	T		
G46	S		
Y47	S,F	S,F	
T48	A		
N49	S		
C50	S		
T52	D		
N54	S		
D57	S		
T59	M		
Y60	H		
D64	N	N	
E65	V,M,K	V,M,K	V,M,K
A68	T	T	
Q69	K,R	K,R	
A72	V,C	V,C	C
V84	A		
S86	T	T	T
S89	N		
S90	T,F		
K92	R	R	
S99	T		
Q109	R		
D110	G,S,N		
D111	H,E		
I116	V,K,E		
F117	Y		
K118	A,T,Q	A,T,Q	
L119	L,I		
L120	P,M		
D129	N		
V130	I		
G139	S		
A145	T		
M146	C		
G151	GCGRSG	GCGRSG	GCGRSG
V152	A,E		
K154	R		
Y155	S,C,H	S,C,H	
N157	S		

N158	D		
K159	E, KCGRNK	KCGRNK	KCGRNK
K163	C		
G167	C		
Q172	Q		
F179	I		
I180	N		
D181	N	N	N
E183	V,M,K	V,M,K	V,M,K
E187	K		
G188	C		
Q190	L,K	L,K	
S192	L,I,P,T,M	L,I,P,T,M	
S193	L,P,T		
N194	G,L,I,V,S,C,K,R,D,Q,Y	G,L,I,V,S,C,K,R,D,Q,Y	
I200	N,F		
D202	G,I,V,N,F,Y	G,I,V,N,F,Y	G,I,V,N,F,Y
H203	R	R	
D211	G		
V212	L		
A221	V		
P224	L	L	L
D228	N		
T229	A,S,M	A,S,M	
G231	D	D	
T233	S		
M234	L,I,V,T,K	L,I,V,T,K	
S236	F,Y	F,Y	
T243	G,A,L,I,V,P,S,C,M,R,D,Q,F,Y,W	G,A,L,I,V,P,S,C,M,R,D,Q,F,Y,W	
Y244	H,F		
S245	T		
N246	S,K,D		
D247	N	N	
G251	R		
F260	C		
G266	S		
K275	E		
I276	V		
I277	V		
T280	A		
L290	H		
D293	R,H		
G294	A		
T295	S		
T297	N		
T299	I,S		
S301	C		
K304	R		
F306	L,Y		
N310	D,E		
S311	G,D,N	G,D,N	G,D,N
V313	I		
I314	F		
N318	I,H,D,Y	I,H,D,Y	I,D,Y
D320	I,V,E,N	I,V,E,N	I,V,N
I321	N		

T325	A,I		
N327	Y		
T335	I	I	I
A340	G,S,T	G,S,T	
F341	C		
D343	A		
T344	M	M	
D345	E		
D346	G,A,V,E	G,A,V,E	G,A,V,E
Q349	K,R	K,R	K,R
H350	Y		
A354	T		
K355	Q	Q	
A358	E		
Q361	R		
Q362	G,R,H		
G363	P		
M364	L,S		
V367	A		
D373	E		
Y374	A,P,S,C,R,H,D	A,P,S,C,R,H,D	
A375	G,L,V,T,C,M,R,D,E,N,Q,Y	G,L,V,T,C,M,R,D,E,N,Q,Y	
A376	T		
P386	L,S		
T387	A,S	A,S	
D390	G,E	G,E	
T392	S,M,K	S,M,K	M
T393	A,I,V,S	A,I,V,S	A,I,V
P394	C		
T400	S		
P402	S		
T403	K		
D404	N		
D410	G		
N417	Y		
S418	P		
T421	I		
Y422	F	F	F
F427	Y		
P429	C		
I430	L		
G431	D		
T433	S,E		
G434	S,GAAATG	GAAATG	GAAATG
N435	Q		
P436	S	S	
S437	P		
G439	V,D		
N440	E		
P441	A,L,S		
P442	S,Q,del	S,Q	S
G443	D		
N445	S,D	S,D	D
R446	G,S	G,S	G,S
T448	A	A	
T449	A		

T450	I		
T451	A,S	A,S	
R453	G,S,K	G,S,K	
P454	S		
A455	V,T, AAAAPA	AAAAPA	AAAAPA
T456	A,I		
T457	P		
G459	D		
S460	P		
S461	R		
P462	L,del	L	
G463	V,D	V,D	
P464	L,Q, PTHAAA	PTHAAA	PTHAAA
T465	I,S		
S467	T		
H468	L,R,Q	L,R,Q	L,R,Q
G470	D		
C472	R		
G474	S		
G476	D		
Y477	Y		
S478	Y		
P480	S	S	
V482	A,I,T	A,I,T	A,I,T
C483	R		
S485	T	T	
G486	S,D		
T488	I		
C489	R		
Q490	L		
V491	I		
L492	Q		
N493	D		
Y495	C		
Y496	F		
Q498	K		
C499	G		
L500	I		

The inventors of the present inventions surprisingly found that introduction of these modifications can yield polyppetides having cellobiohydrolase activity with elevated IT50 values, which the skilled person can learn from the examples below, particularly example 8.

Even more preferably, the variant of the polypeptides of the present invention as generally defined above comprises in a particular embodiment an amino acid sequence selected from the sequences with mutations with respect to SEQ ID NO: 2, optionally fused with a C-terminal 6x-His Tag, listed in the following Table 2.

Table 2: Mutations with respect to SEQ ID NO: 2:

Consecutive Number	Mutation Pattern with respect to Seq. ID NO:2

1	G4C, A72C, Q349K
2	G4C, A72C, T344M, Q349K
3	G4C, A72C, T344M, D346G, Q349R
4	G4C, A72C, D320V, Q349K
5	G4C, A72C, P224L, F306Y, Q349R
6	G4C, A72C
7	A72V, D346A, T393A
8	G4C, A72C, Q349R, R446S, T456A
9	G4C, W40R, A72C, T344M, Q349K
10	A72V, D320V, D346A
11	G4C, A72C, N194Y, T243L, Q349R, Y374S, A375R
12	G4C, A72C, Q349K, T448A, T449A
13	G4C, E65V, A72C, Y244H, Q349R
14	G4C, A72C, D202G, D320N, Q349R, A358E
15	G4C, A72C, D320V, Q349R
16	G4C, A72C, Q349K, S86T
17	A72V, T335I, D346A, T393A, P436S
18	G4C, A72C, E183V, K304R, Q349K
19	G4C, A72C, T243G, Q349R, Y374P, A375M
20	G4C, A72C, Q349R, T465I
21	G4C, A72C, Q349R
22	G4C, A72C, N194V, T243M, Q349R, Y374A, A375T
23	G4C, D64N, A72C, Q349R, A358E, P464Q
24	G4C, A72C, Q349K, Q28R, S193T, Q490L
25	G4C, A72C, E183K, Q349K
26	G4C, A72C, S311N, Q349K, A455T
27	G4C, A72C, N194K, Q349R, Y374P, A375Q
28	G4C, A72C, D181N, Q349K
29	W40R, D320V, Q349K, T393A, N445D
30	W40R, T335I, D346A, T393A
31	Q1L, G4C, A72C, D181N, E183K, N327Y, Q349R
32	A72C, L119L, T335I, Q349R, G486D
33	G4C, A72C, N194K, T243P, Q349R, Y374H, A375E
34	G4C, A72V, Q349R, P462del
35	G4C, A72C, S236Y, Q349R
36	G4C, A72C, S311G, Q349K
37	A72V, D320V, T335I, D346A, T393A, N445D
38	G4C, A72C, S86T, M234V, Q349K
39	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
40	G4C, A72C, G251R, Q349R
41	G4C, A72C, Q349K, D320V
42	A72V, T335I, D346A, T393A
43	G4C, A72C, E183K, Q349R
44	Q1L, G4C, A72C, H203R, Q349K, P442S

45	G4C, A72C, Q349K, G434S, G470D
46	G4C, W40R, A72C, Q349K
47	G4C, A72C, Q349R, V367A
48	Q1L, G4C, A6V, C50S, A72C, I180N, D181N, E183K, Q349R, T457P, C472R, C499G
49	G4C, A72C, S311G, D320V, Q349K
50	W40R, T335I, D346A, T393A, P436S
51	Q1L, G4C, A72C, D181N, E183K, T243S, Q349R, P386S
52	A72V, D346A, T393A, N445D
53	Q1L, G4C, A72C, K154R, Q349K, T393I
54	G4C, A72C, N194G, T243F, Q349R, Y374P, A375R
55	A72V, D320V, D346A, T393A, N445D
56	A72C, L119L, Q172Q, Q349K, T488I
57	G4C, A72C, E183V, Q349K
58	G4C, A72C, E183K, N318Y, Q349K
59	W40R, A221V, T449A, C483R
60	G4C, A72C, K92R, Q349K, N493D
61	Q1L, G4C, A72C, S90T, D181N, E183K, Q349R
62	G4C, A72C, Q349R, G459D
63	G4C, A72C, Q349R, Y422F
64	G4C, T48A, A72C, Q349R, P480S
65	E187K, D320V, P442del
66	G4C, S24N, E65K, A72C, Q349R, I430L, G439D
67	A72V, D320V, T335I, D346A, T393A, P436S
68	Q1L, G4C, A72C, S193P, Q349K, V482I
69	G4C, A72C, D320V, Q349K, G443D, L492Q
70	Q1L, G4C, A72C, DV152-K159, D181N, E183K, Q349R
71	Q1L, G4C, A72C, Q349K
72	Q1L, G4C, A72C, D181N, E183K, M234L, V313I, Q349R, H468R
73	Q1L, G4C, A72C, D181N, E183K, I200N, Q349R
74	G4C, A72C, N194K, T243Y, Q349R, A375N
75	Q1L, G4C, Q28R, A72C, Q349K, H468L
76	G4C, E65V, A72C, Q349R
77	D320V, Q349K
78	Q1L, G4C, A72C, S311G, Q349K, H468R
79	G4C, A72C, T243Q, Q349R, Y374P, A375M
80	Q1L, G4C, A72C, D320V, Q349R
81	Q1L, G4C, T15S, A72C, Y244F, Q349K
82	G4C, A72C, E183K, D346E, Q349R
83	Q1L, G4C, A72C, Q349K, T392M
84	G4C, A72C, D202N, S311N, Q349R, N493D
85	G4C, A72C, N194D, T243A, Q349R, Y374P, A375Y
86	G4C, A72C, N194Y, T243V, Q349R, Y374P
87	Q1L, G4C, A72C, Q349R

88	G4C, Q28R, E65K, A72C, S86T, D202N, H203R, S311N, D320I, A340G, D346A, Q349K, T393A, Y422F, P442S, R446S, H468L, V482A
89	G4C, A72C, D202N, Q349R
90	G4C, A72C, P224L, Q349R
91	Q1L, G4C, A72C, D181N, E183K, T229M, A340T, Q349R, V491I
92	Q1L, G4C, A72C, D181N, Q349R
93	G4C, A72C, D320V, D346V, Q349K
94	Q1L, G4C, A72C, V152A, Q349K
95	Q1L, G4C, Q28R, A72C, Q349K
96	Q1L, G4C, A72C, Q349K, Y422F
97	G4C, A72C, D202V, D320V, Q349K
98	Q1L, G4C, A72C, Y155S, D181N, E183K, Q349R
99	Q1L, G4C, A72C, D181N, D247N, Q349K
100	Q1L, G4C, A68T, A72C, Q349K, G439D, R453S
101	Q1L, G4C, A72C, Q349K, H468R
102	Q1L, G4C, D64N, A72C, Q349K
103	G4C, A72C, E183K, Q349R, P464L
104	G4C, A72C, D181N, P224L, Q349K
105	G4C, A72C, N194I, T243Y, Q349R, Y374P, A375R
106	Q1L, G4C, A72C, Q349K, P462L
107	Q1L, G4C, A72C, E183K, Q349R
108	G4C, A72C, S311G, Q349R
109	Q1L, G4C, A72C, S311N, Q349K, G463D
110	Q1L, G4C, A72C, S86T, Q349R
111	Q1L, G4C, A72C, D181N, E183K, G231D, Q349R
112	Q1L, G4C, A72C, S89N, D181N, E183K, Q349R
113	Q1L, G4C, E65K, A72C, Q349K
114	Q1L, Q2P, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F, R446G
115	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
116	G4C, A72C, E183K, D202Y, N310D, Q349R
117	G4C, A72C, N194I, T243D, Q349R, Y374P, A375Y
118	Q1L, G4C, A72C, D181N, E183K, Q349R, T456I
119	G4C, Q28R, A72C, S86T, E183K, P224L, S311N, N318Y, T335I, D346G, Q349R, T393I, P441A, P442S, R446G, H468L, V482I
120	Q1L, G4C, A72C, D181N, Q349K, T451S
121	Q1L, G4C, A72C, D181N, E183K, T243I, N246D, Q349R, T488I
122	Q1L, G4C, G23N, A72C, D110G, I116V, L119I, D181N, E183K, D211G, D293R, N310D, Q349R, Q362R, G363P, M364S
123	G439V, N440E, P441S, P442Q
124	G431D, S431V, T433E, G434S, N435Q
125	Q1L, G4C, Q28R, E65V, A68T, A72C, Y155C,

	D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
126	Q1L, G4C, A72C, S86T, D181N, E183K, Q349R, T393S
127	Q1L, G4C, A72C, D181N, E183K, Q349R, S485T
128	Q1L, G4C, G23N, A72C, V84A, D110G, D111H, I116E, F117Y, K118A, D181N, E183K, D293R, T295S, Q349R, M364L
129	Q1L, G4C, A72C, D181N, E183K, Q349R, R453K
130	Q1L, G4C, A72C, A145T, H203R, Q349K, T403K
131	Q1L, G4C, A72C, D181N, E183K, Q349R, N445S
132	Q1L, G4C, A72C, D181N, E183K, M234I, Q349R
133	Q1L, G4C, A72C, D181N, E183K, Q349R, T465S
134	Q1L, G4C, A72C, D181N, E183K, T297N, Q349R
135	Q1L, G4C, A72C, S311G, Q349K
136	G4C, Q28R, E65M, A72C, S86T, E183K, S192I, H203R, S311N, D346E, Q349K, T392M, T393A, Y422F, N445D, R446S
137	Q1L, G4C, A72C, D202N, Q349K, G486D
138	Q1L, G4C, A72C, S99T, D181N, E183K, Q349R, T450I
139	Q1L, G4C, A72C, I200F, Q349K, L500I
140	Q1L, G4C, A72C, D181N, E183K, Q349R, G434S
141	Q1L, G4C, A31S, A72C, D181N, E183K, Q349R
142	Q1L, G4C, Q28L, A72C, D181N, E183K, Q349R
143	Q1L, G4C, A72C, D181N, E183K, Q349R, P436S
144	Q1L, G4C, A72C, D181N, E183K, T233S, Q349R
145	Q1L, G4C, A72C, D202N, Q349K
146	Q1L, G4C, A68T, A72C, Q349K
147	Q1L, G4C, A21T, A72C, D181N, E183K, Q349R, P454S
148	Q1L, G4C, A72C, D346V, Q349K
149	Q1L, G4C, Y47F, A72C, D181N, E183K, Q349R, P436S, S461R
150	Q1L, G4C, A72C, D181N, E183K, M234T, Q349R
151	Q1L, G4C, A72C, N157S, D181N, E183K, Q349R
152	Q1L, G4C, A72C, D181N, E183K, Q349R
153	G4C, A72C, N194Q, T243V, Q349R, Y374P, A375Y
154	Q1L, G4C, A72C, D181N, E183K, I314F, Q349R, N445D
155	Q1L, G4C, A72C, Q349K, T392K
156	Q1L, G4C, A72C, D181N, E183K, Q349R, T451A
157	Q1L, G4C, A72C, D181N, E183K, M234V, Q349R
158	Q1L, G4C, A21S, A72C, D181N, E183K, Q349R
159	Q1L, G4C, A72C, D181N, E183K, Q349R, N493D
160	Q1L, G4C, A72C, S311N, Q349K
161	Q1L, G4C, Q28R, E65V, A72C, D181N, E183V, D228N, S311N, N318Y, D346E, Q349R, Y422F, P442S, N445D, R446G, H468L, V482T
162	G4C, A72C, N194C, Q349R, Y374C

163	Q1L, G4C, A72C, D181N, E183K, Q349R, A455V
164	Q1L, G4C, A72C, D181N, E183K, Q349R, T400S
165	Q1L, G4C, T26I, A72C, D181N, E183K, Q349R
166	Q1L, G4C, A72C, D181N, E183K, N310D, Q349R, T392S, G463D
167	Q1L, G4C, A72C, D129N, D181N, E183K, Q190L, G266S, I276V, Q349R, P386L, F427Y
168	Q1L, G4C, A72C, D181N, E183K, D202N, Q349R
169	Q1L, G4C, A72C, Y155C, D181N, E183K, Q349R
170	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454PATAAA, H468L, V482I
171	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
172	Q1L, G4C, A72C, D181N, E183K, N246K, Q349R
173	G4C, W40R, E65V, A72C, S86T, D181N, E183K, D202I, H203R, S311D, D320N, D346V, Q349R, T392M, T393A, Y422F, P442S, H468Q, V482A
174	Q1L, G4C, A72C, Y155C, Q349K
175	Q1L, G4C, A68T, A72C, D181N, E183K, Q349R
176	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, T448A, R453G, H468L, P480S, V482I
177	Q1L, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F, R446G
178	Q1L, G4C, A72C, S86T, D181N, E183K, D320V, Q349R
179	G4C, Q28K, A72C, S86T, E183M, D202N, P224L, S311G, N318Y, D320N, D346A, Q349R, T392M, T393I, P442S, H468L, V482I
180	Q1L, Q2P, G4C, Q28R, W40R, E65K, A72C, D181N, S192L, D202I, H203R, P224L, S311G, D320I, D343A, D346A, Q349K, P442S, N445D, R446G, V482A
181	Q1L, G4C, Q28R, E65K, A72C, E183M, D202I, P224L, D320N, D346V, Q349K, T392M, T393V, Y422F, N445D, R446G, H468L, V482T
182	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202V, S311G, N318Y, D320I, D346G, Q349K, T393V, Y422F, N445D, R446S, H468Q, V482T
183	Q1L, G4C, W40R, E65M, A72C, D181N, E183K, S192P, D202N, P224L, S311D, N318Y, D320V, D346G, Q349K, T392M, N445D, R446G, H468L, V482T
184	Q1L, G4C, E65V, A72C, D181N, E183K, P224L, S311G, D320N, D346G, Q349R, T392M, T393I, R446G, H468L, V482I
185	Q1L, G4C, Q28R, E65V, A72C, G151GCGRSG, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I

186	Q1L, G4C, E65M, A72C, D181N, E183M, D202Y, P224L, S311D, N318Y, D320I, T335I, D346A, Q349K, T392M, T393I, N445D, R446G, T448A, H468Q, V482A
187	Q1L, G4C, G23A, A72C, D110S, D111H, I116V, F117Y, K118A, L120M, D181N, E183K, D293H, G294A, N310E, Q349R, Q362G, M364S
188	Q1L, G4C, A72C, D181N, E183K, Q349R, T421I, G439D
189	G4C, Q28K, E65M, A72C, S86T, V152A, D181N, E183V, S192L, D202N, S311N, D320N, D346E, Q349R, T387A, T392M, T393I, Y422F, P442S, R446S, H468L, G476D, V482I
190	Q1L, G4C, W40R, E65V, A72C, S86T, E183V, G188C, S192T, D202Y, H203R, P224L, S311N, D320V, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
191	Q1L, G4C, E65M, A72C, S86T, E183M, D202N, P224L, T335I, D346G, Q349K, T392M, T393A, P442S, N445D, R446G, H468Q, V482A
192	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, H468L, P480S, V482I
193	G4C, W40R, A72C
194	Q1L, G4C, W40R, E65K, A72C, S86T, E183K, S192L, D202Y, P224L, D320I, D346E, Q349R, P442S, R446G, H468R, V482T
195	Q1L, G4C, A21T, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, D202N, P224L, S311G, N318Y, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, P480S, V482I
196	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
197	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P464PTHAAA, H468L, V482I
198	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
199	Q1L, G4C, T7Q, A8S, N10T, S24T, T27Q, Q28R, N29T, V41T, G46S, Y47S, T52D, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
200	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
201	Q1L, G4C, Q28K, W40R, E65V, A72C, D181N, E183V, S192P, D202V, H203R, S311G, D320N, D346E, Q349K, T392M, T393A, Y422F, V482I
202	Q1L, G4C, Q28R, E65V, A72C, G139S, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I

203	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I
204	Q1L, G4C, Q28R, E65K, A72C, D181N, S311N, N318Y, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
205	Q1L, G4C, W40R, A72C, S192L, D202N, H203R, P224L, S311N, D320I, T335I, D346V, Q349R, T393I, N445D, R446G, H468Q, V482T
206	Q1L, G4C, Q28K, E65K, A72C, E183M, D202N, P224L, T229S, S311G, D320I, T335I, D346V, Q349R, T393V, H468Q, V482A
207	Q1L, G4C, Q28R, G30A, E65M, A72C, D181N, D202N, P224L, S311D, N318Y, D346E, Q349K, T392M, T393V, Y422F, P442S, N445D, R446S
208	Q1L, G4C, Q28R, E65V, A72C, S68T, E183M, S311N, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
209	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
210	T243C, A375C, N194C, Y374C
211	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, S311G, D346V, Q349R, T392M, T393V, Y422F, P442S, N445D, R446G, H468L, S478Y, V482I
212	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
213	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, S311N, N318Y, D320I, T335I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I
214	Q1L, G4C, Q28R, E65K, A72C, S86T, E183K, D202N, P224L, S311G, T335I, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
215	Q1L, G4C, Q28R, E65V, A72C, L120P, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
216	Q1L, G4C, Q28K, E65V, A72C, S86T, E183M, S311N, N318H, D320V, D346V, Q349K, T392M, T393A, R446S, H468L, V482I
217	Q1L, G4C, Q28K, E65V, A72C, D202N, H203R, S311G, T335I, D346V, Q349K, T393A, P442S, R446G, H468L, V482I
218	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
219	Q1L, G4C, Q28R, E65K, A72C, D181N, D202N, H203R, P224L, S311D, D346G, Q349K, P442S, R446S, H468Q, V482T
220	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T
221	Q1L, G4C, T27S, Q28R, E65V, Q69R, A72C, L120P, D181N, E183M, D202N, D247N, S311G, D346E, Q349K, K355Q, T387S, T393V, Y422F, N445D, R446G, T451S, G463V, H468Q, V482T,

	S485T
222	Q1L, G4C, Q28R, E65K, A72C, E183V, S192T, D202N, S311G, D320V, D346A, Q349K, P442S, N445D, R446G, H468R, V482A
223	Q1L, G4C, W40R, E65V, A72C, S86T, E183M, D202N, P224L, S311G, D320V, D346E, Q349R, T393I, P442S, R446G, H468R, V482I
224	Q1L, G4C, Q28N, E65K, A72C, D181N, E183M, D202N, H203R, S311G, N318Y, D320N, Q349R, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
225	Q1L, G4C, Q28R, V41T, G46S, Y47S, T52D, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
226	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
227	Q1L, G4C, Q28R, W40R, A72C, S86T, D181N, S192T, D202N, P224L, S311G, N318Y, D320V, D346E, Q349K, T392M, T393I, P442S, N445D, R446G, H468Q, V482I
228	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, T229M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
229	Q1L, G4C, Q28K, W40R, A72C, S86T, D181N, E183M, S192I, D202Y, T299S, S311N, N318Y, D320I, D346V, Q349R, T393I, P442S, H468L
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231	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, T448A, R453G, H468L, P480S, V482I
232	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, G463V, H468L, V482I
233	Q1L, G4C, Q28R, E65K, A72C, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
234	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
235	Q1L, G4C, Q28R, W40R, E65V, A72C, S86T, S192T, D202V, H203R, S311N, N318Y, D346A, Q349K, T392M, T393A, Y422F, P442S, N445D, V482A
236	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, T457TAAATT, H468L, V482I
237	Q1L, G4C, Q28K, E65K, A72C, D181N, H203R,

	P224L, S311G, D320V, D346G, Q349K, T392M, T393I, P442S, N445D, R446G, H468L, V482A
238	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
239	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, S311G, N318Y, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
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241	Q1L, G4C, Q28K, A72C, S86T, D181N, E183V, S192T, D202N, P224L, S311G, N318Y, D320V, D346G, Q349R, T392M, Y422F, P442S, N445D, R446S, H468L, V482A
242	G4C, Q28R, E65K, A72C, S86T, D181N, E183M, S192L, D202N, H203R, P224L, S311D, D346E, Q349R, T392M, T393A, Y422F, P442S, N445D, R446G, P462L, H468L, V482T
243	Q1L, G4C, W40R, E65K, A72C, Q109R, D181N, E183M, S192I, D202I, H203R, S245T, D346A, Q349R, T393A, Y422F, P442S, N445D, R446G, H468R, V482A
244	Q1L, G4C, Q28K, E65M, A72C, D181N, D202N, S311N, T335I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482I
245	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349R, T393V, N417Y, Y422F, P442S, N445D, R446G, H468L, V482I
246	Q1L, G4C, Q28R, W40R, E65V, A72C, D202Y, H203R, P224L, T299I, N318Y, D320V, D346A, Q349K, T392M, T393A, P442S, N445D, R446G, H468R, V482T
247	G4C, Q28R, E65V, A72C, E183M, D202N, P224L, S311G, N318Y, D320V, D346G, Q349K, T392M, Y422F, R446G, H468Q
248	Q1L, G4C, Q28K, A72C, S86T, E183K, S311G, D320V, D346A, Q349R, T392M, T393I, Y422F, P442S, R446S, H468Q
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251	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I
252	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
253	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
254	Q1L, G4C, W40R, E65V, A72C, S86T, D181N, S192T, D202N, H203R, P224L, S311G, N318Y, T335I, D346G, Q349K, T392M, T393V, Y422F, N445D, R446G, H468Q
255	Q1L, G4C, Q28R, E65K, A72C, E183M, S311N,

	D320I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482T
256	Q1L, G4C, T7Q, A8S, N10T, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
257	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202N, P224L, S311G, D346A, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482T
258	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, K92R, K118Q, D181N, E183M, D202N, T280A, S311G, T335I, D346E, Q349K, K355Q, T387S, T393V, D404N, Y422F, N445D, R446G, P462L, G463V, H468Q, V482I, S485T
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261	Q1L, G4C, Q28K, E65K, A72C, S86T, P224L, S311N, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
262	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T
263	G4C, E65K, A72C, S86T, E183M, D202I, P224L, S311N, N318Y, D320N, T335I, D346V, Q349R, T393V, Y422F, P442S, R446S, H468L
264	Q1L, G4C, Q28R, E65K, A72C, D202N, S311N, T335I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468L, V482T
265	Q1L, G4C, E65V, A72C, D181N, E183K, D202G, Q349R
266	Q1L, G4C, Q28R, E65K, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
267	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, F306L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
268	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T
269	Q1L, G4C, Q28K, E65K, A72C, D181N, E183K, S192P, P224L, S311G, N318Y, D320V, D346E, Q349R, T392M, T393I, Y422F, P442S, H468Q
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271	Q1L, G4C, Q28R, A72C, D181N, E183V, D202I, H203R, P224L, S311D, D320V, D346V, Q349R, T392M, T393I, N445D, H468L
272	Q1L, G4C, Q28K, W40R, E65K, A72C, S86T, D181N, E183K, S192L, D202I, H203R, S311N, D320N, D346V, Q349K, T392M, T393A, Y422F, N445D, R446S
273	G4C, E65V, A72C, S86T, Y155H, D181N, E183V,

	Q190K, P224L, S311N, D320V, D346V, Q349K, T392M, T393V, Y422F, P442S, N445D, R446G, H468L, V482A
274	Q1L, G4C, Q28R, E65M, A72C, S86T, E183M, D202N, S311D, N318Y, D320N, T335I, D346A, Q349R, T392M, T393I, Y422F, P442S, N445D, R446G, H468L, V482A
275	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311N, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
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278	Q1L, G4C, T7Q, A8S, N10T, S24T, T27Q, Q28R, N29T, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
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281	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
282	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
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284	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
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289	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
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291	Q1L, G4C, Q28K, E65M, A72C, E183M, S311G,

	D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
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294	Q1L, G4C, Q28R, E65K, A72C, E183V, S192T, D202N, S311G, D320V, D346A, Q349K, T393V, P442S, N445D, H468L, V482A
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308	Q1L, G4C, E65M, A72C, S86T, E183V, S192L, D202I, H203R, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468R, V482A
309	Q1L, G4C, T7Q, A8S, N10T, Q28R, E65V, A72C,

	D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
310	Q1L, G4C, E65K, A72C, S86T, D202V, S311N, D320V, T335I, D346V, Q349R, T392M, Y422F, N445D, R446G, H468L
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312	Q1L, G4C, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
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315	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I, S485T
316	G4C, Q28K, E65M, A72C, S86T, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
317	G434GAAATG, T457TAAATT, Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
318	G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202Y, P224L, S311N, D346A, Q349K, T393I, Y422F, N445D, R446S, H468Q, V482A
319	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482T
320	Q1L, G4C, T27S, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
321	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, P224L, S311G, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T
322	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
323	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
324	Q1L, G4C, Q28K, E65V, A72C, E183M, D202N, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
325	Q1L, G4C, Q28R, E65K, A72C, D181N, P224L, S311N, N318Y, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I
326	Q1L, G4C, Q28R, E65M, A72C, S90F, D181N,

	P224L, S311G, N318Y, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482I
327	G4C, Q28R, A72C, S86T, D181N, E183V, S192L, D202V, N246S, S311D, N318Y, D320V, D346A, Q349K, T393V, P442S, N445D, H468L, V482A
328	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311N, N318Y, D320I, T335I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T
329	Q1L, G4C, Q28R, A72C, S86T, E183M, S192L, H203R, S311D, D320V, T335I, D346V, Q349K, N445D, H468Q, V482A
330	Q1L, G4C, Q28R, T59M, E65K, A68T, A72C, S86T, D181N, S192L, D202N, H203R, S311D, D320V, T335I, Q349R, T393A, P442S, N445D, R446G, H468L, V482A
331	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
332	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, K355Q, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
333	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, N318Y, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
334	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T448A, R453G, H468L, V482I
335	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
336	Q1L, G4C, E65M, A72C, E183M, D202I, P224L, S311D, N318Y, D320V, T335I, D346A, Q349K, T393A, Y422F, P442S, N445D, R446G, R453G, H468Q, V482I
337	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
338	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, S311G, N318Y, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
339	Q1L, G4C, S24T, T27Q, Q28R, N29T, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
340	Q1L, G4C, E65V, A72C, D181N, E183M, S192T, P224L, S311G, D320V, T335I, D346G, Q349K, T393A, Y422F, P442S, N445D, R446G, H468L, V482T
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342	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202F, S311G, N318Y, T335I, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q
343	Q1L, G4C, Q28K, E65K, A72C, S86T, D181N,

	D202N, P224L, S311D, N318Y, D320N, D346A, Q349R, T392M, T393I, Y422F, N445D, R446G, H468R
344	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, S311N, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
345	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
346	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
347	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, S311N, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
348	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T
349	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, T229M, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, P480S, V482I
350	Q1L, G4C, Q28K, E65M, A72C, D181N, E183M, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
351	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, D404N, Y422F, P442S, N445D, R446G, T451S, H468L, V482I
352	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P462L, H468L, V482I
353	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I
354	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, T280A, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
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356	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, K275E, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
357	Q1L, G4C, Q28K, E65V, A72C, E183K, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
358	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T
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360	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
361	Q1L, G4C, Q28R, E65M, A72C, E183M, S311G, D320I, D346A, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
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363	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
364	Q1L, G4C, Q28K, E65K, A72C, D181N, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
365	Q1L, G4C, Q28R, E65V, A72C, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
366	Q1L, G4C, S24C, Q28R, G30A, E65V, A72C, Y155C, D181N, Q190K, D202N, P224L, S311G, T335I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, R453G, H468Q, P480S, V482I
367	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, P402S, Y422F, P442S, N445D, R446G, H468L, V482I
368	Q1L, G4C, Q28R, E65K, A72C, E183M, D202N, P224L, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
369	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A72C, Y155C, D181N, D202N, P224L, M234T, S311G, D320I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
370	Q1L, G4C, Q28R, E65K, A72C, S86T, D202N, P224L, S311D, D320N, T335I, D346V, Q349K, T392M, T393V, Y422F, P442S, R446S, H468L
371	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202N, S311G, N318Y, D320I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
372	Q1L, G4C, W40R, E65M, A72C, S86T, E183V, S192L, D202I, H203R, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468R, V482A
373	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
374	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, T457TAAATT, H468L, V482I
375	Q1L, G4C, Q28R, E65V, A72C, K118Q, D181N, E183M, P224L, D247N, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
376	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I

377	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
378	Q1L, G4C, Q28K, E65M, A72C, D181N, E183M, D202N, S311G, N318Y, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
379	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454PVRPQP, H468L, V482I
380	Q1L, G4C, Q28R, A72C, D181N, E183V, S192M, D202N, P224L, S311D, N318Y, D320N, D346E, Q349R, T393V, Y422F, P442S, R446G, H468L, P480S
381	Q1L, G4C, Q28R, A72C, S86T, D181N, S192L, D202N, P224L, S311G, N318Y, D320V, T335I, D345E, D346A, Q349K, Y422F, P442S, N445D, R446G, H468Q, H505Q
382	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183K, P224L, S311G, N318Y, D320I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
383	Q1L, G4C, Q28R, G30A, E65V, A68T, A72C, D181N, E183M, D202N, P224L, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, V482I
384	Q1L, G4C, Q28R, E65V, A72C, K92R, L120P, D181N, E183M, D202N, S236F, T280A, S311G, D346E, Q349K, K355Q, T387S, T393V, P402S, D404N, Y422F, N445D, R446G, T451S, G463V, H468Q, V482I, S485T
385	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, S236F, S311G, T335I, D346E, Q349K, T387S, T393V, Y422F, N445D, R446G, G463V, H468Q, V482I, S485T
386	Q1L, G4C, Q28R, E65M, A72C, D181N, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
387	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, D202N, S311G, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, H468Q, V482I
388	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, S311G, T335I, D346A, Q349K, T393I, Y422F, P442S, N445D, R446G, H468L, V482I
389	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, D247N, S311G, D320I, D346E, Q349K, T387S, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
390	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, P224L, S311G, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I
391	Q1L, G4C, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, S236F, S311N, N318I, D346E, Q349K, K355Q, T387S, T393V, D404N, Y422F, N445D, R446G, H468Q, V482I
392	Q1L, G4C, T27S, Q28R, E65V, Q69R, A72C, K118Q, D181N, E183M, D202N, D247N, I277V, S311G, T335I, D346E, Q349K, K355Q, T393V,

	Y422F, N445D, R446G, H468Q, V482T
393	Q1L, G4C, Q28R, G30A, E65V, A72C, Y155C, D181N, E183M, D202N, M234T, S311G, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, V482T
394	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, H468L, V482I
395	Q1L, G4C, Q28R, E65V, Q69R, A72C, K92R, D181N, D202N, D247N, I277V, S311G, N318D, T335I, D346E, Q349K, K355Q, T387S, T393V, Y422F, N445D, R446G, G463V, H468Q, V482I
396	Q1L, G4C, T27S, Q28R, E65V, Q69R, A72C, D181N, D202N, S236F, I277V, S311G, T335I, D346E, Q349K, K355Q, T387S, T393V, Y422F, N445D, R446G, G463V, H468Q, V482I
397	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, K92R, K118Q, D181N, E183M, D202N, S311G, T335I, D346E, Q349K, T387S, T393V, Y422F, N445D, R446G, P462L, H468Q, V482T, S485T
398	Q1L, G4C, A21T, Q28R, G30A, E65V, A72C, Y155C, D181N, E183M, D202N, M234T, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, V482T
399	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
400	Q1L, G4C, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, M234T, S311G, D320I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
401	Q1L, G4C, Q28K, E65V, A72C, S86T, E183K, S192L, D202N, D320N, T335I, D346A, Q349R, T393A, Y422F, P442S, R446G, H468R, V482A
402	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S236F, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
403	Q1L, G4C, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, D202N, M234T, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
404	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A72C, Y155C, D181N, E183M, D202N, P224L, M234T, S311G, D320I, T335I, A340S, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, P480S, V482I
405	Q1L, G4C, Q28R, E65K, A72C, D202I, P224L, S311G, N318Y, D320V, T335I, D346A, Q349R, T392M, T393A, N445D, R446G, H468L
406	Q1L, G4C, E65M, A72C, S86T, E183V, D202I, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468L, V482A
407	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, D181N, E183M, D202N, S311G, D346E, Q349K, T387S, T393V, Y422F, N445D, R446G, T451S, P462L, H468Q, V482T
408	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, E65M,

	A72C, S86T, E183M, D202N, P224L, S311G, D320I, T335I, (DeletionS437-P441), D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
409	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, T26I, Q28R, N29Y, G30A, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
410	Q1L, G4C, Q28R, E65V, A72C, K92R, D181N, E183M, P224L, I277V, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
411	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
412	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454PVRPQP, H468L, V482I
413	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P464THAAA, H468L, V482I
414	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P464PTHAAA, H468L, V482I
415	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, G151GCGRSG, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
416	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, K159KCGRNK, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
417	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454ATAAA, H468L, V482I
418	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, E65K, A72C, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
419	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, E65V, A72C, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
420	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65M, A72C, S86T, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
421	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65M, A72C, E183M, S311G, N318Y, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
422	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I

423	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, N318Y, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
424	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
425	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65K, A72C, S311N, N318Y, D346E, Q349K, T393V, Y422F, (DeletionbeiG439-G444), N445D, R446G, H468Q, V482I
426	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, N29Y, E65K, A72C, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
427	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
428	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, N445D, R446G, T448A, R453G, H468L, P480S, V482I, Y422F, P442S
429	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, K159KCGRNK, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
430	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
431	Q1L, G4C, A72C, S86T, D181N, E183K, D202V, P224L, S311G, D320V, D346E, Q349R, T393A, Y422F, P442S, N445D, R446G, H468L
432	Q1L, G4C, Q28R, E65V, A72C, K159CGRNKE183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
433	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, Q28R, E65K, A72C, D202N, S311G, T335I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T
434	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65M, A72C, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
435	Q1L, G4C, Q28K, E65M, A72C, S86T, E183M, D202N, P224L, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F, (S437-P441), N445D, R446G, H468Q, V482T
436	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
437	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L,

	V482I
438	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454PVRPQP, H468L, V482I
439	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P464THAAA, H468L, V482I
440	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454PATAAA, H468L, V482I
441	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, H468L, V482I
442	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I, Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
443	Q1L, G4C, Q28R, E65V, A72C, G151GCGRSG, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
444	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454ATAAA, H468L, V482I
445	Q1L, G4C, Q28R, E65K, A72C, S311N, N318Y, D346E, Q349K, T393V, Y422F, (DG439-G444)N445D, R446G, H468Q, V482I
446	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
447	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, N445D, R446G, T448A, R453G, H468L, P480S, V482I, Y422F, P442S
448	Q1L, G4C, A21T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, D181N, Q190K, D202N, T229M, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, T448A, H468Q, V482I
449	Q1L, G4C, N10D, T27S, Q28R, E65V, A72C, K92R, K118Q, D181N, D202N, S236F, I277V, S311G, D346E, Q349K, K355Q, T387S, T393V, D404N, N417Y, Y422F, N445D, R446G, P462L, H468Q, V482I, S485T
450	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, T229M, S311N, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
451	Q1L, G4C, N10D, T27S, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, D247N, S311G,

	D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
452	Q1L, G4C, T26I, Q28R, G30A, E65V, A72C, Y155C, D181N, D202N, T229M, G231D, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, V482T
453	Q1L, G4C, S24R, T26I, Q28R, G30A, E65V, A72C, D181N, E183M, D202N, P224L, S311N, T335I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, H468Q, V482T
454	Q1L, G4C, N10D, T27S, Q28R, E65V, Q69R, A72C, D181N, E183M, D202N, S236F, D247N, I277V, S311N, T335I, D346E, Q349K, T387S, T393V, N417Y, Y422F, T433S, N445D, R446G, P462L, H468Q, V482I
455	Q1L, G4C, A21T, Q28R, E65V, A72C, Y155C, D181N, D202N, P224L, S311G, N318Y, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, T448A, H468Q, V482I
456	Q1L, G4C, T26I, Q28R, N29Y, E65V, A68T, A72C, Y155C, D181N, E183M, D202N, P224L, M234T, S311N, N318Y, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, V482I
457	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A68T, A72C, Y155C, D181N, D202N, P224L, T229M, M234T, S311G, N318Y, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
458	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, P224L, S236F, D247N, F306L, S311G, D346E, Q349K, K355Q, T393V, D404N, N417Y, Y422F, N445D, R446G, H468Q, V482I, S485T
459	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, S236F, D247N, S311G, N318I, T335I, D346E, Q349K, K355Q, T393V, Y422F, T433S, N445D, R446G, T451S, G463V, H468Q, V482I
460	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
461	G4C, Q28K, E65M, A72C, S86T, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
462	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
463	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
464	G4C, Q28K, E65M, A72C, S86T, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
465	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S,

	N445D, R446G, T457TAAATT, H468L, V482I
466	G4C, Q28K, E65M, A72C, S86T, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, T457TAAATT, H468L, V482I
467	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, H468L, V482I, T457TAAATT,
468	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
469	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, S192L, D202V, S311G, D320I, D346V, Q349R, T393A, Y422F, P442S, N445D, R446G, H468Q, V482I
470	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311N, N318Y, D320I, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
471	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, D181N, E183M, D202N, T229M, S311G, A340S, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T

In a further aspect, the present invention discloses a nucleic acid encoding the polypeptide of the present invention. The nucleic acid is a polynucleotide sequence (DNA or RNA) which is, when set under control of an appropriate promoter and transferred into a suitable biological host or chemical environment, processed to the encoded polypeptide, whereby the process also includes all post-translational and post-transcriptional steps necessary. The coding sequence can be easily adapted by variation of degenerated base-triplets, alteration of signal sequences, or by introduction of introns, without affecting the molecular properties of the encoded protein. The nucleic acid of the present invention has preferably at least 95 %, more preferably at least 97 %, and most preferably 100% identity to SEQ ID NO: 1. The present invention also provides a vector comprising this nucleic acid and a host transformed with said vector.

The present invention also discloses methods for the production of polypeptides of the present invention and variants thereof in various host cells, including yeast and fungal hosts. It also discloses the use of the resulting strains for the improvement of protein properties by variation of the sequence. Furthermore, the present invention discloses methods for the application of such polypeptides in the hydrolysis of cellulose.

A further aspect of the invention discloses vectors and methods for the production of protein variants of SEQ ID NO: 2, expressing them in yeast and testing their activity on cellulosic material by measuring the released mono- and/or oligomeric sugar molecules.

The present invention further relates to a method of producing a cellobiohydrolase protein, comprising the steps:

a. obtaining a host cell, which has been transformed with a vector comprising the nucleic acid of the present invention;
b. cultivation of the host cell under conditions under which the cellobiohydrolase protein is expressed; and
c. recovery of the cellobiohydrolase protein.

In a particular embodiment, this method of producing a cellobiohydrolase protein is restricted to a method for the production of a cellobiohydrolase protein as provided by this invention, such as having the IT50 value given above, and/or being one of the specific variants of SEQ ID NO2 or SEQ ID NO: 5 as provided with this application and described in detail elsewhere in this specification.

In a more preferred embodiment, the host cell is derived from the group consisting of Saccharomyces, Schizosaccharomyces, Kluyveromyces, Pichia, Hansenula, Aspergillus, Trichoderma, Penicillium, Candida and Yarrowina. The host cell is preferably capable of producing ethanol, wherein most preferred yeasts include *Saccharomyces cerevisiae, Pichia stipitis, Pachysolen tannophilus*, or a methylotrophic yeast, preferably derived from the group of host cells comprising *Pichia methanolica, Pichia pastoris, Pichia angusta, Hansenula polymorpha.*

It has surprisingly been found that the polypeptide according to the present invention and variants thereof can be expressed from yeast at high levels. "Yeast" shall herein refer to all lower eukaryotic organisms showing a unicellular vegetative state in their life cycle. This especially includes organisms of the class *Saccharomycetes*, in particular of the genus *Saccharomyces, Pachysolen, Pichia, Candida, Yarrowina, Debaromyces, Klyveromyces, Zygosaccharomyces.*

Thus, one aspect of the invention relates to the expression of the claimed polypeptide and variants thereof in yeast. The efficient expression of this fusion protein (SEQ ID NO: 2) and derivative protein variants of SEQ ID NO: 2 from yeast can be achieved by insertion of the nucleic acid molecule of SEQ ID NO: 1 starting from nucleotide position 1 into an expression vector under control of at least one appropriate promoter sequence and fusion of the nucleotide molecule to an appropriate signal peptide, for example to the signal peptide of the mating factor alpha of *Saccharomyces cerevisiae.*

In a preferred embodiment, the polypeptide of the present invention and variants thereof are expressed and secreted at a level of more than 100 mg/l, more preferably of more than 200 mg/l, particularly preferably of more than 500 mg/l, or most preferably of more than 1 g/l into the supernatant after introduction of a nucleic acid encoding a polypeptide having an amino acid sequence with at least 85% sequence identity to the SEQ ID NO: 2 into a yeast. To determine the level of expression in yeast, the cultivation and isolation of the supernatant can be carried out as described in Example 3.

A further aspect the invention discloses methods for the production of a polypeptide according to the present invention in a filamentous fungus, preferably in a fungus of the genus Aspergillus or Trichoderma, more preferably in a fungus of the genus *Trichoderma,* most preferably in *Trichoderma reesei*. *"Filamentous fungi"* or *"fungi"* shall herein refer to all lower eukaryotic organisms showing hyphal growth during at least one state in their life cycle. This especially includes organisms of the *phylum Ascomycota* and *Basidiomycota*, in particular of the genus *Trichoderma, Talaromyces, Aspergillus, Penicillium, Chrysosporium, Phanerochaete, Thermoascus, Agaricus, Pleutrus, Irpex.* The polypeptide is expressed by fusion of the coding region of a compatible signal sequence to the nucleic acid molecule starting with nucleotide position 52 of SEQ ID NO: 3, as it was done in SEQ ID NO: 3 with the signal sequence of the *Trichoderma reesei* CBHI, and the positioning of the fusion peptide under control of a sufficiently strong promoter followed by transfer of the genetic construct to the host cell. Examples for such promoters and signal sequences as well as techniques for an efficient transfer have been described in the art.

In a further aspect the present invention further relates to a method for identifying a polypeptide or polypeptides having cellobiohydrolase activity, comprising the steps of:

a. Generating a library of mutant genes encoding mutant proteins by mutagenesis of a nucleic acid according to claim 9 or a nucleic acid having the sequence defined by SEQ ID NO: 6 (encoding SEQ ID NO: 5), preferably having the sequence defined by SEQ ID NO: 1;
b. Inserting each mutant gene into an expression vector;
c. Transforming yeast cells with each expression vector to provide a library of yeast transformants;
d. Cultivation of each yeast transformant under conditions under which the mutant protein is expressed and secreted;
e. Incubating the expressed mutant protein with a substrate;
f. Determining the catalytic activity of the mutant protein;
g. Selecting a mutant protein according to the determined catalytic activity.

Specifically, step d. may be performed by utilizing a well-plate format. This format preferably allows the high-throughput performance of the method for identifying polypeptides having cellobiohydrolase activity.

In a preferred embodiment, this method for identifying polypeptides having cellobiohydrolase activity is restricted to a method, wherein the polypeptide(s) having cellobiohydrolase activity

is one or more polypeptide(s) as provided by this invention, such as having the IT50 value given above, and/or being one of the specific variants of SEQ ID NO2 or SEQ ID NO: 5 as below.

Preferably, the steps e. to g. of the method for identifying polypeptides having cellobiohydrolase activity are performed as follows:

e. Incubating the expressed mutant protein with cellulosic material;
f. Determining the amount of released sugar;
g. Selecting a mutant protein according to the amount of released sugar.

In another embodiment, the method for identifying polypeptides having cellobiohydrolase activity comprises the additional steps of:

h. Sequencing the selected mutant gene or protein;
i. Identifying the amino acid modification(s) by comparing the sequence of the selected mutant protein with the amino acid sequence of SEQ ID NO: 2.

In a particular embodiment, the method is further characterized by measuring the IT50 value of the obtained polypeptide. The IT50 value may be measured as described in the examples below. Optionally, this may be followed by a step of selction of those polypeptides, which display the a desired IT 50 value, such as at least 60 °C, at least 62 °C and the like, Thus, in this particular embodiment, the method is suitable for identifying polypeptides exhibiting cellobiohydrolase activity and an elevated IT50 value, i.e. thermostable polypeptides with cellobiohydrolase activity.

The present invention further provides a method of preparing a polypeptide having cellobiohydrolase activity, comprising the steps:

a. Providing a polypeptide having cellobiohydrolase activity comprising an amino sequence having at least 54 % sequence identity to the catalytic domain of SEQ ID NO: 2 (SEQ ID NO: 5) (such as preferably, at least 60 %, at least 62 %, at least 64 %, at least 66, %, at least 68 % or at least 70 %, whereby at least 68 % or at least 70 % are the most preferred embodiments);
b. Identifying the amino acids of this polypeptide which correspond to the amino acids which are modified with respect to the amino acid sequence of SEQ ID

NO: 2, as identified in step i. of the method for identifying polypeptides having cellobiohydrolase activity; and

c. Preparing a mutant polypeptide of the polypeptide provided in step a. by carrying out the amino acid modification(s) identified in step b. through site-directed mutagenesis.

In one embodyment, preferably, the polypeptide provided in step a. of the method of preparing a polypeptide having cellobiohydrolase activity is a wild type cellobiohydrolase derived from *Trichoderma reesei*.

The present invention further provides polypeptides having cellobiohydrolase activity, which are obtainable by the method of preparing a polypeptide having cellobiohydrolase activity according to the present invention.

Furthermore, the present invention provides a composition comprising a polypeptide and/or variants thereof of the present invention and one or more cellulases, e.g. one or more endoglucanases and/or one or more beta-glucosidases and/or one or more further cellobiohydrolases and/or one or more xylanases. "Cellulases" or "Cellulolytic enzymes" are defined as enzymes capable of hydrolysing cellulosic substrates or derivatives or mixed feedstocks comprising cellulosic polymers. Such enzymes are referred to as having "cellulolytic activity", thus being able to hydrolyze cellulose molecules from such material into smaller oligo- or monosaccharides. Cellulolytic enzymes include cellulases and hemicellulases, in particular they include cellobiohydrolases (CBHs), endoglucanases (EGs) and beta-glucosidases (BGLs).

The present invention further provides a polypeptide having cellobiohydrolase activity, wherein the polypeptide comprises an amino acid sequence having at least 80 %, preferably at least 95%, more preferably at least 98%, even more preferably at least 99%, and most preferably 99, 6 % sequence identity to SEQ ID NO: 5,. Particularly, it is preferred that such a polypeptide is a polypeptide wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 5 are modified by substitution or deletion of: Q1, Q2, G4, A6, T7, A8, N10, P12, T15, A21, G23, S24, T26, T27, Q28, N29, G30, A31, V32, N37, W40, V41, G46, Y47, T48, N49, C50, T52, N54, D57, T59, Y60, D64, E65, A68, Q69, A72, V84, S86, S89, S90, K92, S99, Q109, D110, D111, I116, F117, K118, L119, L120, D129, V130, G139, A145, M146, V152, K154, Y155, N157, N158, K159, K163, G167, Q172, F179, I180, D181, E183, E187, G188, Q190, S192, S193, N194, I200, D202, H203, D211, V212, A221, P224, D228, T229, G231, T233, M234, S236, T243, Y244, S245, N246, D247, G251, F260, G266, K275, I276, I277, T280, L290, D293, G294, T295, T297, T299, S301, K304,

F306, N310, S311, V313, I314, N318, D320, I321, T325, N327, T335, A340, F341, D343, T344, D345, D346, Q349, H350, A354, K355, A358, Q361, Q362, G363, M364, V367, D373, Y374, A375, A376, P386, T387, D390, T392, T393, P394, T400, P402, T403, D404, D410, N417, S418, T421, Y422 and/or one or more insertions after positions G151, K159

In a preferred embodiment, the polypeptide having cellobiohydrolase activity with an amino acid sequence having at least 80 % sequence identity to SEQ ID NO: 5 comprises one or more modified amino acid residues of the sequence defined by SEQ ID NO: 5: Thus, the polypeptide given in SEQ ID NO: 5 may, by means of example, be modified as follows: Q1L, G4, A6G/V, T15S, Q28Q/R, W40R, D64N, E65K/V, A72V, S86T, K92K/R, V130I/V, V152A/E, Y155C, K159E, D181N, E183V/K, N194C/R/Y/D/K/I/L/G/Q/S/V, D202Y/N/G, P224L, T243I/R/Y/A/F/Q/P/D/V/W/L/M, Y244F/H, I277V, K304R, N310D, S311G/N, N318Y, D320V/E/N, T335I, T344M, D346G/A/E/V, Q349R/K, A358E, Y374C/P/R/H/S/A, A375D/N/Y/R/Q/L/V/E/G/T/M, T392C/D/K, T393A, D410G, Y422F.

More preferably, the polypeptide having cellobiohydrolase activity comprises one or more modified amino acid residues of the sequence defined by SEQ ID NO: 5 as indicated in the following Table 3. As said above, for the specific modifications of SEQ ID NO: 2, two or more of such specific modifications may be combined with each other, such as preferably two or more of the more preferred or most preferred modifications may be combined with each other, and, which is particularly preferred, two pr more of the *most* preferred modifications according to Table 3 may be combined with each other.

Table 3: Mutations with respect to SEQ ID NO: 5

Position	Preferred	More Preferred	Most Preferred
Q1	L	L	L
Q2	P,S	P,S	S
G4	C	C	C
A6	G,L,V	G,L,V	L
T7	Q	Q	Q
A8	S	S	S
N10	T,D	T,D	T,D
P12	Q		
T15	S		
A21	S,T,C	S,T,C	
G23	A,D,N		
S24	T,C,N	T,C,N	
T26	I,N	I,N	
T27	S,Q	S,Q	
Q28	L,K,R,N	L,K,R,N	K,R
N29	T,Y	T,Y	
G30	A	A	
A31	S		

V32	G		
N37	S		
W40	R	R	
V41	T		
G46	S		
Y47	S,F	S,F	
T48	A		
N49	S		
C50	S		
T52	D		
N54	S		
D57	S		
T59	M		
Y60	H		
D64	N	N	
E65	V,M,K	V,M,K	V,M,K
A68	T	T	
Q69	K,R	K,R	
A72	V,C	V,C	C
V84	A		
S86	T	T	T
S89	N		
S90	T,F		
K92	R	R	
S99	T		
Q109	R		
D110	G,S,N		
D111	H,E		
I116	V,K,E		
F117	Y		
K118	A,T,Q	A,T,Q	
L119	L,I		
L120	P,M		
D129	N		
V130	I		
G139	S		
A145	T		
M146	C		
G151	GCGRSG	GCGRSG	GCGRSG
V152	A,E		
K154	R		
Y155	S,C,H	S,C,H	
N157	S		
N158	D		
K159	E, KCGRNK	KCGRNK	KCGRNK
K163	C		
G167	C		
Q172	Q		
F179	I		
I180	N		
D181	N	N	N
E183	V,M,K	V,M,K	V,M,K
E187	K		
G188	C		
Q190	L,K	L,K	
S192	L,I,P,T,M	L,I,P,T,M	

S193	L,P,T		
N194	G,L,I,V,S,C,K,R,D,Q,Y	G,L,I,V,S,C,K,R,D,Q,Y	
I200	N,F		
D202	G,I,V,N,F,Y	G,I,V,N,F,Y	G,I,V,N,F, Y
H203	R	R	
D211	G		
V212	L		
A221	V		
P224	L	L	L
D228	N		
T229	A,S,M	A,S,M	
G231	D	D	
T233	S		
M234	L,I,V,T,K	L,I,V,T,K	
S236	F,Y	F,Y	
T243	G,A,L,I,V,P,S,C,M,R,D,Q,F,Y, W	G,A,L,I,V,P,S,C,M,R,D,Q,F,Y, W	
Y244	H,F		
S245	T		
N246	S,K,D		
D247	N	N	
G251	R		
F260	C		
G266	S		
K275	E		
I276	V		
I277	V		
T280	A		
L290	H		
D293	R,H		
G294	A		
T295	S		
T297	N		
T299	I,S		
S301	C		
K304	R		
F306	L,Y		
N310	D,E		
S311	G,D,N	G,D,N	G,D,N
V313	I		
I314	F		
N318	I,H,D,Y	I,H,D,Y	I,D,Y
D320	I,V,E,N	I,V,E,N	I,V,N
I321	N		
T325	A,I		
N327	Y		
T335	I	I	I
A340	G,S,T	G,S,T	
F341	C		
D343	A		
T344	M	M	
D345	E		
D346	G,A,V,E	G,A,V,E	G,A,V,E
Q349	K,R	K,R	K,R
H350	Y		

A354	T		
K355	Q	Q	
A358	E		
Q361	R		
Q362	G,R,H		
G363	P		
M364	L,S		
V367	A		
D373	E		
Y374	A,P,S,C,R,H,D	A,P,S,C,R,H,D	
A375	G,L,V,T,C,M,R,D,E,N,Q,Y	G,L,V,T,C,M,R,D,E,N,Q,Y	
A376	T		
P386	L,S		
T387	A,S	A,S	
D390	G,E	G,E	
T392	S,M,K	S,M,K	M
T393	A,I,V,S	A,I,V,S	A,I,V
P394	C		
T400	S		
P402	S		
T403	K		
D404	N		
D410	G		
N417	Y		
S418	P		
T421	I		
Y422	F	F	F

Table 3a. Each of these polypeptides defines a mutant version of the polypeptide given in SEQ ID NO: 5.

Table 3a: specific mutants with respect to SEQ ID NO: 5:

Mutant Number	Mutants with respect to Seq. ID NO:5
1	G4C, A72C, Q349K
2	G4C, A72C, T344M, Q349K
3	G4C, A72C, T344M, D346G, Q349R
4	G4C, A72C, D320V, Q349K
5	G4C, A72C, P224L, F306Y, Q349R
6	G4C, A72C
7	A72V, D346A, T393A
8	G4C, A72C, Q349R
9	G4C, W40R, A72C, T344M, Q349K
10	A72V, D320V, D346A
11	G4C, A72C, N194Y, T243L, Q349R, Y374S, A375R
12	G4C, E65V, A72C, Y244H, Q349R
13	G4C, A72C, D202G, D320N, Q349R, A358E
14	G4C, A72C, D320V, Q349R
15	G4C, A72C, Q349K, S86T
16	A72V, T335I, D346A, T393A
17	G4C, A72C, E183V, K304R, Q349K
18	G4C, A72C, T243G, Q349R, Y374P, A375M
19	G4C, A72C, N194V, T243M, Q349R, Y374A, A375T
20	G4C, D64N, A72C, Q349R, A358E
21	G4C, A72C, Q349K, Q28R, S193T
22	G4C, A72C, E183K, Q349K
23	G4C, A72C, S311N, Q349K
24	G4C, A72C, N194K, Q349R, Y374P, A375Q
25	G4C, A72C, D181N, Q349K
26	W40R, D320V, Q349K, T393A
27	W40R, T335I, D346A, T393A
28	Q1L, G4C, A72C, D181N, E183K, N327Y, Q349R
29	A72C, T335I, Q349R
30	G4C, A72C, N194K, T243P, Q349R, Y374H, A375E
31	G4C, A72V, Q349R, P462del
32	G4C, A72C, S236Y, Q349R
33	G4C, A72C, S311G, Q349K
34	A72V, D320V, T335I, D346A, T393A
35	G4C, A72C, S86T, M234V, Q349K
36	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
37	G4C, A72C, G251R, Q349R
38	G4C, A72C, Q349K, D320V
39	G4C, A72C, E183K, Q349R
40	Q1L, G4C, A72C, H203R, Q349K
41	G4C, W40R, A72C, Q349K
42	G4C, A72C, Q349R, V367A
43	Q1L, G4C, A6V, C50S, A72C, I180N, D181N, E183K, Q349R
44	G4C, A72C, S311G, D320V, Q349K
45	Q1L, G4C, A72C, D181N, E183K, T243S, Q349R, P386S

46	Q1L, G4C, A72C, K154R, Q349K, T393I
47	G4C, A72C, N194G, T243F, Q349R, Y374P, A375R
48	A72V, D320V, D346A, T393A
49	A72C, Q349K
50	G4C, A72C, E183V, Q349K
51	G4C, A72C, E183K, N318Y, Q349K
52	W40R, A221V
53	G4C, A72C, K92R, Q349K
54	Q1L, G4C, A72C, S90T, D181N, E183K, Q349R
55	G4C, A72C, Q349R, Y422F
56	G4C, T48A, A72C, Q349R
57	E187K, D320V
58	G4C, S24N, E65K, A72C, Q349R
59	Q1L, G4C, A72C, S193P, Q349K
60	Q1L, G4C, A72C, delV152-K159, D181N, E183K, Q349R
61	Q1L, G4C, A72C, Q349K
62	Q1L, G4C, A72C, D181N, E183K, M234L, V313I, Q349R
63	Q1L, G4C, A72C, D181N, E183K, I200N, Q349R
64	G4C, A72C, N194K, T243Y, Q349R, A375N
65	Q1L, G4C, Q28R, A72C, Q349K
66	G4C, E65V, A72C, Q349R
67	D320V, Q349K
68	Q1L, G4C, A72C, S311G, Q349K
69	G4C, A72C, T243Q, Q349R, Y374P, A375M
70	Q1L, G4C, A72C, D320V, Q349R
71	Q1L, G4C, T15S, A72C, Y244F, Q349K
72	G4C, A72C, E183K, D346E, Q349R
73	Q1L, G4C, A72C, Q349K, T392M
74	G4C, A72C, D202N, S311N, Q349R
75	G4C, A72C, N194D, T243A, Q349R, Y374P, A375Y
76	G4C, A72C, N194Y, T243V, Q349R, Y374P
77	Q1L, G4C, A72C, Q349R
78	G4C, Q28R, E65K, A72C, S86T, D202N, H203R, S311N, D320I, A340G, D346A, Q349K, T393A, Y422F
79	G4C, A72C, D202N, Q349R
80	G4C, A72C, P224L, Q349R
81	Q1L, G4C, A72C, D181N, E183K, T229M, A340T, Q349R
82	Q1L, G4C, A72C, D181N, Q349R
83	G4C, A72C, D320V, D346V, Q349K
84	Q1L, G4C, A72C, V152A, Q349K
85	Q1L, G4C, A72C, Q349K, Y422F
86	G4C, A72C, D202V, D320V, Q349K
87	Q1L, G4C, A72C, Y155S, D181N, E183K, Q349R
88	Q1L, G4C, A72C, D181N, D247N, Q349K
89	Q1L, G4C, A68T, A72C, Q349K
90	Q1L, G4C, D64N, A72C, Q349K
91	G4C, A72C, D181N, P224L, Q349K
92	G4C, A72C, N194I, T243Y, Q349R, Y374P, A375R
93	Q1L, G4C, A72C, E183K, Q349R
94	G4C, A72C, S311G, Q349R
95	Q1L, G4C, A72C, S311N, Q349K
96	Q1L, G4C, A72C, S86T, Q349R
97	Q1L, G4C, A72C, D181N, E183K, G231D, Q349R

98	Q1L, G4C, A72C, S89N, D181N, E183K, Q349R
99	Q1L, G4C, E65K, A72C, Q349K
100	Q1L, Q2P, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F
101	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
102	G4C, A72C, E183K, D202Y, N310D, Q349R
103	G4C, A72C, N194I, T243D, Q349R, Y374P, A375Y
104	Q1L, G4C, A72C, D181N, E183K, Q349R
105	G4C, Q28R, A72C, S86T, E183K, P224L, S311N, N318Y, T335I, D346G, Q349R, T393I
106	Q1L, G4C, A72C, D181N, Q349K
107	Q1L, G4C, A72C, D181N, E183K, T243I, N246D, Q349R
108	Q1L, G4C, G23N, A72C, D110G, I116V, L119I, D181N, E183K, D211G, D293R, N310D, Q349R, Q362R, G363P, M364S
109	Q1L, G4C, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
110	Q1L, G4C, A72C, S86T, D181N, E183K, Q349R, T393S
111	Q1L, G4C, G23N, A72C, V84A, D110G, D111H, I116E, F117Y, K118A, D181N, E183K, D293R, T295S, Q349R, M364L
112	Q1L, G4C, A72C, A145T, H203R, Q349K, T403K
113	Q1L, G4C, A72C, D181N, E183K, M234I, Q349R
114	Q1L, G4C, A72C, D181N, E183K, T297N, Q349R
115	G4C, Q28R, E65M, A72C, S86T, E183K, S192I, H203R, S311N, D346E, Q349K, T392M, T393A, Y422F
116	Q1L, G4C, A72C, D202N, Q349K
117	Q1L, G4C, A72C, S99T, D181N, E183K, Q349R
118	Q1L, G4C, A72C, I200F, Q349K
119	Q1L, G4C, A31S, A72C, D181N, E183K, Q349R
120	Q1L, G4C, Q28L, A72C, D181N, E183K, Q349R
121	Q1L, G4C, A72C, D181N, E183K, T233S, Q349R
122	Q1L, G4C, A21T, A72C, D181N, E183K, Q349R
123	Q1L, G4C, A72C, D346V, Q349K
124	Q1L, G4C, Y47F, A72C, D181N, E183K, Q349R
125	Q1L, G4C, A72C, D181N, E183K, M234T, Q349R
126	Q1L, G4C, A72C, N157S, D181N, E183K, Q349R
127	G4C, A72C, N194Q, T243V, Q349R, Y374P, A375Y
128	Q1L, G4C, A72C, D181N, E183K, I314F, Q349R
129	Q1L, G4C, A72C, Q349K, T392K
130	Q1L, G4C, A72C, D181N, E183K, M234V, Q349R
131	Q1L, G4C, A21S, A72C, D181N, E183K, Q349R
132	Q1L, G4C, Q28R, E65V, A72C, D181N, E183V, D228N, S311N, N318Y, D346E, Q349R, Y422F
133	G4C, A72C, N194C, Q349R, Y374C
134	Q1L, G4C, A72C, D181N, E183K, Q349R, T400S
135	Q1L, G4C, T26I, A72C, D181N, E183K, Q349R
136	Q1L, G4C, A72C, D181N, E183K, N310D, Q349R, T392S
137	Q1L, G4C, A72C, D129N, D181N, E183K, Q190L, G266S, I276V, Q349R, P386L
138	Q1L, G4C, A72C, D181N, E183K, D202N, Q349R
139	Q1L, G4C, A72C, Y155C, D181N, E183K, Q349R
140	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F

141	Q1L, G4C, A72C, D181N, E183K, N246K, Q349R
142	G4C, W40R, E65V, A72C, S86T, D181N, E183K, D202I, H203R, S311D, D320N, D346V, Q349R, T392M, T393A, Y422F
143	Q1L, G4C, A72C, Y155C, Q349K
144	Q1L, G4C, A68T, A72C, D181N, E183K, Q349R
145	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F
146	Q1L, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F
147	Q1L, G4C, A72C, S86T, D181N, E183K, D320V, Q349R
148	G4C, Q28K, A72C, S86T, E183M, D202N, P224L, S311G, N318Y, D320N, D346A, Q349R, T392M, T393I
149	Q1L, Q2P, G4C, Q28R, W40R, E65K, A72C, D181N, S192L, D202I, H203R, P224L, S311G, D320I, D343A, D346A, Q349K
150	Q1L, G4C, Q28R, E65K, A72C, E183M, D202I, P224L, D320N, D346V, Q349K, T392M, T393V, Y422F
151	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202V, S311G, N318Y, D320I, D346G, Q349K, T393V, Y422F
152	Q1L, G4C, W40R, E65M, A72C, D181N, E183K, S192P, D202N, P224L, S311D, N318Y, D320V, D346G, Q349K, T392M
153	Q1L, G4C, E65V, A72C, D181N, E183K, P224L, S311G, D320N, D346G, Q349R, T392M, T393I
154	Q1L, G4C, Q28R, E65V, A72C, G151GCGRSG, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
155	Q1L, G4C, E65M, A72C, D181N, E183M, D202Y, P224L, S311D, N318Y, D320I, T335I, D346A, Q349K, T392M, T393I
156	Q1L, G4C, G23A, A72C, D110S, D111H, I116V, F117Y, K118A, L120M, D181N, E183K, D293H, G294A, N310E, Q349R, Q362G, M364S
157	Q1L, G4C, A72C, D181N, E183K, Q349R, T421I
158	G4C, Q28K, E65M, A72C, S86T, V152A, D181N, E183V, S192L, D202N, S311N, D320N, D346E, Q349R, T387A, T392M, T393I, Y422F
159	Q1L, G4C, W40R, E65V, A72C, S86T, E183V, G188C, S192T, D202Y, H203R, P224L, S311N, D320V, D346E, Q349K, T393V, Y422F
160	Q1L, G4C, E65M, A72C, S86T, E183M, D202N, P224L, T335I, D346G, Q349K, T392M, T393A
161	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F
162	G4C, W40R, A72C
163	Q1L, G4C, W40R, E65K, A72C, S86T, E183K, S192L, D202Y, P224L, D320I, D346E, Q349R
164	Q1L, G4C, A21T, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, D202N, P224L, S311G, N318Y, D320I, D346E, Q349K, T393V, Y422F
165	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F
166	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F
167	Q1L, G4C, T7Q, A8S, N10T, S24T, T27Q, Q28R, N29T, V41T, G46S, Y47S, T52D, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
168	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
169	Q1L, G4C, Q28K, W40R, E65V, A72C, D181N, E183V, S192P, D202V, H203R, S311G, D320N, D346E, Q349K, T392M, T393A, Y422F

170	Q1L, G4C, Q28R, E65V, A72C, G139S, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
171	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F
172	Q1L, G4C, Q28R, E65K, A72C, D181N, S311N, N318Y, D346E, Q349K, T393V, Y422F
173	Q1L, G4C, W40R, A72C, S192L, D202N, H203R, P224L, S311N, D320I, T335I, D346V, Q349R, T393I
174	Q1L, G4C, Q28K, E65K, A72C, E183M, D202N, P224L, T229S, S311G, D320I, T335I, D346V, Q349R, T393V
175	Q1L, G4C, Q28R, G30A, E65M, A72C, D181N, D202N, P224L, S311D, N318Y, D346E, Q349K, T392M, T393V, Y422F
176	Q1L, G4C, Q28R, E65V, A72C, S68T, E183M, S311N, T335I, D346E, Q349K, T393V, Y422F
177	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F
178	T243C, A375C, N194C, Y374C
179	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, S311G, D346V, Q349R, T392M, T393V, Y422F
180	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311G, D346E, Q349K, T393V, Y422F
181	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, S311N, N318Y, D320I, T335I, D346E, Q349K, T393I, Y422F
182	Q1L, G4C, Q28R, E65K, A72C, S86T, E183K, D202N, P224L, S311G, T335I, D346A, Q349K, T393V, Y422F
183	Q1L, G4C, Q28R, E65V, A72C, L120P, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
184	Q1L, G4C, Q28K, E65V, A72C, S86T, E183M, S311N, N318H, D320V, D346V, Q349K, T392M, T393A
185	Q1L, G4C, Q28K, E65V, A72C, D202N, H203R, S311G, T335I, D346V, Q349K, T393A
186	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F
187	Q1L, G4C, Q28R, E65K, A72C, D181N, D202N, H203R, P224L, S311D, D346G, Q349K
188	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, D390E, T393V, Y422F
189	Q1L, G4C, T27S, Q28R, E65V, Q69R, A72C, L120P, D181N, E183M, D202N, D247N, S311G, D346E, Q349K, K355Q, T387S, T393V, Y422F
190	Q1L, G4C, Q28R, E65K, A72C, E183V, S192T, D202N, S311G, D320V, D346A, Q349K
191	Q1L, G4C, W40R, E65V, A72C, S86T, E183M, D202N, P224L, S311G, D320V, D346E, Q349R, T393I
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193	Q1L, G4C, Q28R, V41T, G46S, Y47S, T52D, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
194	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
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196	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, T229M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F
197	Q1L, G4C, Q28K, W40R, A72C, S86T, D181N, E183M, S192I, D202Y,

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198	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, T229M, G231D, M234T, S311G, D320I, D346E, Q349K, T393V, Y422F
199	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F
200	Q1L, G4C, Q28R, E65K, A72C, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F
201	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, D346E, Q349K, T393V, Y422F
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203	Q1L, G4C, Q28K, E65K, A72C, D181N, H203R, P224L, S311G, D320V, D346G, Q349K, T392M, T393I
204	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F
205	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, S311G, N318Y, D346E, Q349K, T393V, Y422F
206	Q1L, G4C, Q28R, E65V, A72C, E183K, D202I, P224L, S311G, D320I, Q349K, T393V
207	Q1L, G4C, Q28K, A72C, S86T, D181N, E183V, S192T, D202N, P224L, S311G, N318Y, D320V, D346G, Q349R, T392M, Y422F
208	G4C, Q28R, E65K, A72C, S86T, D181N, E183M, S192L, D202N, H203R, P224L, S311D, D346E, Q349R, T392M, T393A, Y422F
209	Q1L, G4C, W40R, E65K, A72C, Q109R, D181N, E183M, S192I, D202I, H203R, S245T, D346A, Q349R, T393A, Y422F
210	Q1L, G4C, Q28K, E65M, A72C, D181N, D202N, S311N, T335I, D346E, Q349K, T393I, Y422F
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220	Q1L, G4C, W40R, E65V, A72C, S86T, D181N, S192T, D202N, H203R, P224L, S311G, N318Y, T335I, D346G, Q349K, T392M, T393V, Y422F
221	Q1L, G4C, Q28R, E65K, A72C, E183M, S311N, D320I, D346E, Q349K, T393I, Y422F
222	Q1L, G4C, T7Q, A8S, N10T, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
223	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202N, P224L, S311G, D346A, Q349K, T393I, Y422F

224	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, K92R, K118Q, D181N, E183M, D202N, T280A, S311G, T335I, D346E, Q349K, K355Q, T387S, T393V, D404N, Y422F
225	Q1L, G4C, Q28R, E65M, A72C, E183M, D202N, S311G, D320I, T335I, D346E, Q349K, T393I, Y422F
226	Q1L, G4C, Q28K, E65K, A72C, D181N, E183M, D202N, S311D, D320V, T335I, D346G, Q349K, T393I, Y422F
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230	Q1L, G4C, Q28R, E65K, A72C, D202N, S311N, T335I, D346E, Q349K, T393I, Y422F
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234	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F
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238	Q1L, G4C, Q28K, W40R, E65K, A72C, S86T, D181N, E183K, S192L, D202I, H203R, S311N, D320N, D346V, Q349K, T392M, T393A, Y422F
239	G4C, E65V, A72C, S86T, Y155H, D181N, E183V, Q190K, P224L, S311N, D320V, D346V, Q349K, T392M, T393V, Y422F
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249	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, S311N, D320I, D346E, Q349K, T393V, Y422F
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251	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F
252	Q1L, G4C, E65M, A72C, S86T, E183K, D202Y, S311G, D320N, T335I, D346A, Q349K, T393V, Y422F
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256	Q1L, G4C, Q28K, N29Y, E65K, A72C, D181N, S311G, T335I, D346E, Q349K, T393V, Y422F
257	Q1L, G4C, Q28K, E65M, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F
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275	Q1L, G4C, T7Q, A8S, N10T, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
276	Q1L, G4C, E65K, A72C, S86T, D202V, S311N, D320V, T335I, D346V, Q349R, T392M, Y422F
277	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F
278	Q1L, G4C, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D,

	N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
279	Q1L, G4C, Q28R, A72C, S86T, E183M, S192T, D202N, H203R, P224L, S311N, T335I, D346V, Q349R, T392M, T393V
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281	G4C, Q28K, E65M, A72C, S86T, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
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283	G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202Y, P224L, S311N, D346A, Q349K, T393I, Y422F
284	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393I, Y422F
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358	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I,

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400	Q1L, G4C, S24R, T26I, Q28R, G30A, E65V, A72C, D181N, E183M, D202N, P224L, S311N, T335I, D346E, Q349K, D390E, T393V, Y422F
401	Q1L, G4C, N10D, T27S, Q28R, E65V, Q69R, A72C, D181N, E183M, D202N, S236F, D247N, I277V, S311N, T335I, D346E, Q349K, T387S, T393V, N417Y, Y422F
402	Q1L, G4C, A21T, Q28R, E65V, A72C, Y155C, D181N, D202N, P224L, S311G, N318Y, D346E, Q349K, D390E, T393V, Y422F
403	Q1L, G4C, T26I, Q28R, N29Y, E65V, A68T, A72C, Y155C, D181N, E183M, D202N, P224L, M234T, S311N, N318Y, D346E, Q349K, T393V, Y422F
404	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A68T, A72C, Y155C, D181N, D202N, P224L, T229M, M234T, S311G, N318Y, D346E, Q349K, T393V, Y422F
405	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, P224L, S236F, D247N, F306L, S311G, D346E, Q349K, K355Q, T393V, D404N, N417Y, Y422F
406	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, S236F, D247N, S311G, N318I, T335I, D346E, Q349K, K355Q,

	T393V, Y422F
407	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
408	G4C, Q28K, E65M, A72C, S86T, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
409	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
410	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
411	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, S192L, D202V, S311G, D320I, D346V, Q349R, T393A, Y422F
412	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311N, N318Y, D320I, D346A, Q349K, T393V, Y422F
413	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, D181N, E183M, D202N, T229M, S311G, A340S, D346E, Q349K, T393V, Y422F

Furthermore, the present invention provides a polypeptide having cellobiohydrolase activity comprising an amino acid sequence having at least 85%, preferably at least 95%, more preferably at least 98%, even more preferably at least 99%, and most preferably 100% sequence identity to SEQ ID NO:12 wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 12 are modified by substitution or deletion: Q1, S2, P12, T15, S21, G23, T26, Q28, T29, G30, V32, N37, W40, T48, C50, N54, L60, E65, K69, V84, S90, D114, E119, F120, T121, L122, L123, D132, V133, G142, S148, M149, V155, Y158, N161, T162, K166, G170, Q175, F182, I183, G191, I203, D214, I215, A224, T231, G234, I237, S248, G254, W263, G269, L282, T285, G298, Y303, N307, G308, T310, E317, L318, S322, N324, G340, S341, D345, S357, M360, V363, D369, A372, P382, S388, T389, P390, T399, S400, Q406, N413, F423, P425, I426, G427, T429, P432, G435, N436, P437, G439, N441, R442, T444, T445, T446, T447, R449, P450, A451, T452, T453, S456, S457, P458, G463, P464, S467, H459, C468, G470, G472, S474, P476, V478, C479, S481, G482, T484, V487, L488, N489, Y491, Y492, Q494, C495, L496. Preferably, this polypeptide comprises an amino acid sequence with at least 54 %, preferably at least 56 %, more preferably at least 58 %, particularly preferably at least 60 %, such as at least 62 %, particularly at least 64 %, such as at least 66 %, and most preferably preferably at least 68 % sequence identity to SEQ ID NO: 5. This polypeptide also preferably lies within the embodiment as defined above, wherein the polypeptide is temperature stable, i.e. has a high IT50 value, such as defined above, for example 62 °C or more, as described above (for more embodiments, see above, in relation to the definition of variants of SEQ ID NO: 5). The skilled person will recognize that SEQ ID NO 12: has about 68 % identity with SEQ ID NO: 5. Therefore, a polypeptide derived from the polypeptide defned by SEQ ID NO: 12, which is differs from the polypeptide defined by SEQ ID NO: 12 for example by exchange of one amino acid for another, such as Q1A, for example, is a polypeptide which also has a significant degree of identity with SEQ ID: NO: 5, i.e. at least 66 % or more, as defined above. Thus, the skilled person can readily recognize the common inventive concept of this

invention, particular when taking into consideration the temperature stability of the polypeptides of this invention.

In a preferred embodiment, the polypeptide having cellobiohydrolase activity comprises an amino acid sequence having at least 85 % sequence identity to SEQ ID NO: 12, wherein the polypeptide has the amino acid sequence of SEQ ID NO: 12 wherein one or more of the following amino acid residues are modified by substitution or deletion:Q1, S2, P12, T15, S21, G23, T26, Q28, T29, G30, V32, N37, W40, T48, C50, N54, L60, E65, K69, V84, S90, D114, E119, F120, T121, L122, L123, D132, V133, G142, S148, M149, V155, Y158, N161, T162, K166, G170, Q175, F182, I183, G191, I203, D214, I215, A224, T231, G234, I237, S248, G254, W263, G269, L282, T285, G298, Y303, N307, G308, T310, E317, L318, S322, N324, G340, S341, D345, S357, M360, V363, D369, A372, P382, S388, T389, P390, T399, S400, Q406, N413, F423, P425, I426, G427, T429, P432, G435, N436, P437, G439, N441, R442, T444, T445, T446, T447, R449, P450, A451, T452, T453, S456, S457, P458, G463, P464, S467, H459, C468, G470, G472, S474, P476, V478, C479, S481, G482, T484, V487, L488, N489, Y491, Y492, Q494, C495, L496

	Exchange with respect to SEQ ID NO: 12
1	Q1L
2	T15S
3	Q28R
4	W40R
5	C72V
6	V133I
7	V155A,E
8	Y158C
9	T162E
10	Y247F,H
11	N307D
12	G308N
13	E317V,N
14	S341M
15	D345R,K
16	Y370P,R,H,S,A
17	T389A
18	Q406G
19	N441D
20	R442S,G
21	T452A
22	S456L,P
23	P458L,del
24	G459D
25	H464L,Q,R
26	V478A,I

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invention, particular when taking into consideration the temperature stability of the polypeptides of this invention.

In a preferred embodiment, the polypeptide having cellobiohydrolase activity comprises an amino acid sequence having at least 85 % sequence identity to SEQ ID NO: 12, wherein the polypeptide has the amino acid sequence of SEQ ID NO: 12 wherein one or more of the following amino acid residues are modified by substitution or deletion:Q1, S2, P12, T15, S21, G23, T26, Q28, T29, G30, V32, N37, W40, T48, C50, N54, L60, E65, K69, V84, S90, D114, E119, F120, T121, L122, L123, D132, V133, G142, S148, M149, V155, Y158, N161, T162, K166, G170, Q175, F182, I183, G191, I203, D214, I215, A224, T231, G234, I237, S248, G254, W263, G269, L282, T285, G298, Y303, N307, G308, T310, E317, L318, S322, N324, G340, S341, D345, S357, M360, V363, D369, A372, P382, S388, T389, P390, T399, S400, Q406, N413, F423, P425, I426, G427, T429, P432, G435, N436, P437, G439, N441, R442, T444, T445, T446, T447, R449, P450, A451, T452, T453, S456, S457, P458, G463, P464, S467, H459, C468, G470, G472, S474, P476, V478, C479, S481, G482, T484, V487, L488, N489, Y491, Y492, Q494, C495, L496

Another aspect of the invention relates to the application of the isolated polypeptides and variants thereof of the present invention for the complete or partial hydrolysis of cellulosic material. The cellulosic material can be of natural, processed or artificial nature. "Cellulosic material" herein shall be defined as all sorts of pure, non-pure, mixed, blended or otherwise composed material containing at least a fraction of β-1-4-linked D-glucosyl polymers of at least 7 consecutive subunits. Prominent examples of cellulosic materials are all sort of cellulose containing plant materials like wood (soft and hard), straw, grains, elephant grass, hey, leaves, cotton and materials processed there from or waste streams derived from such processes. Cellulosic material used in an enzymatic reaction is herein also referred to as cellulosic substrate.

The hydrolysis of the cellulose material can be a sequential process following cellobiohydrolase production or contemporary to the production in the yeast cell (consolidated bioprocess). The expression of celluliolytic enzymes in yeast is of special interest due to the ability of many yeasts to ferment the released sugars (C6 or C5) to ethanol or other metabolites of interest.

A further embodiment of the invention thus relates to the application of whole cells expressing the polypeptide or variant thereof according to the present invention for the processing of cellulosic materials.

In a particular embodiment, the present invention discloses the use of a polypeptide and variants thereof or the composition of the present invention for the enzymatic degradation of cellulosic material, preferably lignocellulosic biomass, and/or for textiles processing and/or as ingredient in detergents and/or as ingredient in food or feed compositions.

Examples

Example 1: Preparation of *Pichia pastoris* expression plasmid

Expression plasmids for the constitutive expression of protein from transformed *Pichia pastoris* hosts are prepared by assembly of an expression cassette consisting of a *Pichia pastoris* gyceraldehyde phosphate dehydrogenase (GAP) promoter, a *Saccharomyces cerevisiae* SPα (mating factor alpha signal peptide), a multiple cloning site (MCS) and the 3'-GAP-terminator sequence. For selection purposes a kanamycine resistance gene is used under control of the EM7 or TEF promoter for bacterial or yeast selection purposes, respectively. The resulting plasmid vectors are designated as pV1 (Figure 1) and pV2 (alternative MCS) Transformation and expression cultivation are done essentially as

described by Waterham, H. R., Digan, M. E., Koutz, P. J., Lair, S. V., Cregg, J. M. (1997). Isolation of the *Pichia pastoris* glyceraldehyde-3-phosphate dehydrogenase gene and regulation and use of its promoter. *Gene*, 186, 37-44 and Cregg, J.M.: Pichia Protocols in Methods in Molecular Biology, Second Edition, Humana Press, Totowa New Jersey 2007.

Example 2: Construction of Pichia pastoris expression constructs for CBHI sequences

CBHI genes of *Trichoderma viride* (CBH-f), *Humicola grisea* (CBH-d), *Thermoascus aurantiacus* (CBH-e), , *Talaromyces emersonii* (CBH-b), ,and fusions of the cellulose binding domain of *Trichoderma reesei* CBHI with the *Talaromyces emersonii* CBHI (CBH-a) or the *Humicola grisea* CBHI (CBH-g) are amplified using the oligo nucleotide pairs and templates (obtained by gene synthesis) as given in the Table 4. The fusion gene encoding SeqID. NO. 2 is generated by overlap extension PCR using the PCR-Fragments generated from SeqID NO. 5 and 11. Phusion DNA polymerase (Finnzymes) is used for the amplification PCR.

Table 4: Primers and templates for the amplification of CBH-a, CBH-b, CBH-d, CBH-e, CBH-f and CBH-g

	Fragment	Primer forward	Primer reverse	Template
CBH-f	Trichoderma viride CBHI	GAGGCGGAAGCACCC TCTcaatctgcttgcaccttgca gtc	GGAGACGCAGAGCC Cttattacaggcactgcgagt agt	SEQID NO. 13
CBH-d	Humicola grisea CBHI	GAGGCGGAAGCACCC TCTcagcaggctggtactatta ctgc	GGAGACGCAGAGCC Cttacacgttcacggtagaac cgattgggc	SEQID NO. 7
CBH-e	Thermoascus aurantiacus CBHI	GAGGCGGAAGCACCC TCTcacgaggccggtaccgta accgc	GGAGACGCAGAGCC CTTAttagttggcggtgaag gtcgagt	SEQID NO. 9
CBH-b	Talaromyces emersonii CBHI	GAGGCGGAAGCACCC TCTcagcaggccggcacggc gacggc	GGAGACGCAGAGCC CTTAtcacgaagcggtgaa ggtcgagt	SEQID NO. 5
CBH-a part1	Talaromyces emersonii CBH fusion fragment part1	GAGGCGGAAGCACCC TCTcagcaggccggcacggc gacggc	ATTACCTGTGCTACC gatcggaccaaacttaatgttc g	SEQID NO. 5
CBH-a part2	Trichoderma reesei CBHI binding domain fusion fragment part2	AAGTTTGGTCCGATCg gtagcacaggtaatccttcagg	GGAGACGCAGAGCC CTTATTAtagacactgtga gtagtaagggt	SEQID NO. 11

CBH-a	Talaromyces emersonii CBHI fusion protein	GAGGCGGAAGCACCC TCTcagcaggccggcacggc gacggc	GGAGACGCAGAGCC CTTAtcattaatggtggtggt gatgatgag	5a+5b SEQID NO. 2
CBH-g part1	Humicola grisea CBHI fusion fragment part1	aggcggaagcatgctcgcagc aggctggtacaattactgc	ggattacctgttaagcttccaat tggtccgaatctgatgtt	SEQID NO. 19
CBH-g part2	Trichoderma reesei CBHI binding domain fusion fragment part2	accaattggaagcttaacaggta atccttcaggtggtaatcc	atcttgcaggtcgacttatcatt aatgatgatgatgatggtgtgc a	SEQID NO. 11
CBH-g	Humicula grisea fusion protein	aggcggaagcatgctcgcagc aggctggtacaattactgc	atcttgcaggtcgacttatcatt aatgatgatgatgatggtgtgc a	6a+6b SEQID NO. 15

PCR fragments of expected length are purified from agarose gels after electrophoresis using the Promega® SV PCR and Gel Purification kit. Concentration of DNA fragments are measured on a Spectrophotometer and 0,2pmol of fragments are treated with 9U of T4-DNA polymerase in the presence of 2,5mM dATP for 37,5 min at 22,5°C and treated fragments are annealed with T4-DNA-Polymerase/dTTP treated *Sma*I-linearized pV1 plasmid DNA and afterwards transformed into chemically competent Escherichia coli Top10 cells. Deviant from the described procedure the product generated by the primer pair according to the table lane 11 encoding the *Humicula grisea* fusion protein fragments are cloned via the introduced *Sph*I and *Sal*I site to pV2. Transformants are controlled by sequencing of isolated plasmid DNA.

Example 3: Expression of CBHI Genes in Pichia pastoris

Plasmids of Example 2 are transformed to electro-competent Pichia pastoris CBS 7435 cells and transformants are used to inoculate cultures in YPD medium containing 200mg/l, which are incubated for 5 days at 27°C in a rotary shaker at 250 rpm. Culture supernatants were separated by centrifugation at 5000xg for 30 minutes in a Sorvall Avant centrifuge. Supernatants were concentrated on spin columns with cut-off size of 10kDa. Protein pattern of such concentrated supernatants were analyzed by SDS-PAGE (Laemmli et al.) and gels were stained with colloidal Commassie blue stain. Enzymatic activity was determined by incubation of the supernatant with 2mM solutions of p-nitrophenyl-β-D-lactoside or 200µM solutions of 4-methyl-umbelliferyl-β-D-lactoside in 50 mM sodium acetate buffer (pH 5) for 1

hour. The reaction was stopped my addition of equal volumes of 1 M sodium carbonate solution and determination of released p-nitrophenol or 4-methyl umbelliferone by measurement of the absorbance at 405 nm or the fluorescence at 360 nm/ 450 nm excitation/emission.

Example 4: Genome integration and expression of the *Talaromyces emersonii* CBHI-*T. reesei* CBHII-CBD fusion sequence in *Pichia pastoris*

Table 5

	Fragment	Primer forward	Primer reverse	Template
	Talaromyces emersonii CBH fusion fragment part1	GAGGCGGAAGCACCCTCTc agcaggccggcacggcgacggc	ATTACCTGTGCTACCg atcggaccaaacttaatgttcg	SEQID NO. 5
	Trichoderma reesei CBHI binding domain fusion fragment with 6x His-Tag part2	AAGTTTGGTCCGATCggtagc acaggtaatccttcagg	GGAGACGCAGAGCC Cttatcattaatggtggtggtgat gatgag	SEQID NO. 11
	Talaromyces emersonii CBHI fusion protein with 6x His-Tag part2	GAGGCGGAAGCACCCTCTc agcaggccggcacggcgacggc	GGAGACGCAGAGCC Cttatcattaatggtggtggtgat gatgag	OE 1a+1b: SEQID NO. 17

The DNA-fragment of the fusion gene are generated by 2 step overlap extension PCR using the oligo nucleotide pairs and synthetic templates as indicated in the Table 4 (of Example 2). T4-DNA polymerase treated full length fragment was annealed with the linear pV3 vector fragment by slowly reducing the temperature from 75°C to 4°C. The pV3 plasmid contains a fusion of the mating factor alpha signal peptide to a multiple cloning site, situated downstream the of a *Pichia pastoris* AOXI promoter. Transformation of the annealed solution into chemical competent E. coli cells yields transformants, which are selected by their Teocine resistance checked for containing expected construct plasmid by restriction analysis and sequencing. pV3-CBH-a plasmid preparations are linearized with SacI and approximately 1 µg of linear DNA-fragments are transformed to Pichia pastoris electrocompetent cells. 94 Transformants from YPD-Zeocin plates are afterwards checked for expression by cultivation in 500µl 96-deepwell Plate cultures in BMMY-medium containing 1% methanol and 0.5 % methanol was fed every 24h for 5 days (350 rpm/27°C; humidified orbital shaker with 2,5 cm amplitude . Supernatants are tested for activity on 4-MUL and clones with highest expression levels are selected and again evaluated under same conditions.

For fermentation in an Infors Multifors bioreactor the strain producing the highest enzyme concentration is selected. A YPD-Zeocin (100g/l) pre-culture is chosen for inoculation of Mineral medium consisting of phosphate-buffer, magnesium sulphate and chloride, trace elements/biotin and glycerol, with pH calibration using ammonia and phosphoric acid. After metabolism of the batch glycerol (2%) additional glycerol feed is maintained for 1 day before the feed is changed to methanol to shift to inductive conditions for the AOXI promoter. Under these conditions the fermentation is kept for 5 days. Cells are separated from the fermentation liquid by centrifugation at 5000xg for 30 minutes. -Supernatants are analyzed for total Protein using Bradford Reagent and BSA Standards (Biorad). SDS-PAGE / Coomassie Brilliant blue staining is used to analyze the Protein Pattern on the SDS-PAGE.

Example 5: *Trichoderma reesei* expression vector construct

SbfI/SwaI digested pSCMB100 plasmid DNA was transformed into *Trichoderma reesei* SCF41 essentially as described by Penttilä et al 1997. 10µg of linear DNA was used for the transformation of 10^7 protoplasts. Selection of transformants was done by growth of the protoplasts on Mandel's Andreotti media plates with overlay agar, containing hygromycine as selective agent (100mg/l). Transformants were further purified by passage over sporolation media plates and re-selection of spores on hygromycin media. From re-grown mycelia genomic DNA was isolated and the replacement event verified by PCR. Transformants verified in being true replacement strains were further tested for secretion of recombinant protein.

Example 6: Expression of *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion (CBH-ah) fusion with 6x His-Tag from Trichoderma reesei

Expression of recombinant CBHI replacement strains of *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion with 6x His-Tag in *Trichoderma reesei* Q6A (ATCC 13631) was done in shakeflask cultures containing 40ml Mineral medium containing 2% Avicel in 300ml flasks and cultivation at 30°C/250rpm for 6 days. Supernatants recovered by centrifugation and further analyzed by SDS-PAGE and Bradford Protein assays.

Example 7: Screening thermo stability variants

Random mutagenesis libraries of the *Talaromyces emersonii* CBHI / *Trichoderma reesei* – CBD fusion (with 6x His-Tag) gene were generated using error prone PCR applying manganese containing bufferers and inbalanced dNTP concentrations in the *Taq*-DNA polymerase reaction micture, used for PCR-amplification, essentially as described by Craig

and Joyce (R.Craig Cadwell and G.F. Joyce, 1995. Mutagenic PCR, in PCR Primer: a laboratory manual, ed. C. W. Dieffenbach and G. S. Dveksler, Cold Spring Harbor Press, Cold Spring Harbor, ME, 583-589). As template the wild type fusion gene (SeqID. NO. 17) or mutants thereof were chosen. Mutated PCR-Fragments were cloned to the pPKGMe Plasmid using *Sph*I and *Hind*III endonucleases and T4-DNA-ligase.

Libraries of the *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion (with 6x His-Tag) gene variants were distributed in 1536 well plates with well occupation number close to 1. Enzyme was expressed over 7 days in a volume of 4µl YPG-G418 medium. For evaluation of the properties of the variants 2µl samples of culture supernatants were transferred to plates containing a suspension of milled straw, acetate buffer and beta-glucosidase. After incubation of the sealed reaction plates for 48 hours at defined temperatures the glucose concentration was determined using Amplex red in the presence of GOX and HRP by analyzing the fluorescence level. Best-performing Hits were re-cultivated and re-evaluated. Plasmids of confirmed CBH-ah variants were recovered (Pierce DNAzol Yeast genomic DNA Kit) and sequenced using oligonucleotides alpha-f (5' TACTATTGCCAGCATTGCTGC-3') and oli740 (5'-TCAGCTATTTCACATACAAATCG-3').

Example 8: Determination of Substrate Conversion Capacity at different temperatures for indication of the thermostability of CBH-ah-Variants using 4-methylumbellifery-ß-D-lactoside (4-MUL)

For precise comparison of the thermal stability culture supernatants containing the secreted cellobiohydrolase variants were diluted tenfold in sodium acetate buffer (50mM, pH 5) and 10µl samples were incubated with 90µl of 200µM 4-MUL (in buffer) in the temperature gradient of an Eppendorff Gradient Thermocycler. A temperature gradient of 20°C reaching from 55°C to 75°C was applied to 12 reaction mixtures for for each sample for one hour. The temperature profile could be recorded after addition of 100µl 1M sodium carbonate solution to each reaction and measurement of the fluorescence intensity at 360nm/454nm in a Tecan Infinite M200 plate reader. For comparison of the thermostability the values were normalized between 1 and 0 for the maximum and minimum fluorescence count (Figure 7).

Table 6: Listing of Mutants of SeqID NO. 18 with improved IT50 values.

	Mutations with respect to Seq. ID NO. 18	IT50-value (4-MUL)
1	wt	60,4 +/- 0,6
2	R446G	60,6
3	Q1L, G4C, Q28R, A72C, S86T, E183M, D202V, S311N, D320N, T335I, D346E, Q349R, P442S, N445D, R446G, H468Q	60,7
4	D346G, R453G	60,9

5	Y496F	60,9
6	T335I, D346A, T393A, D410G	61
7	T243I, T325A, V482A	61
8	N194R, T243R, Y374D, A375D	61,1
9	Q1L, G4C, Q28R, W40R, E65V, A72C, S86T, E183K, S192I, D202I, H203R, F260C, S311N, D320N, T335I, D346G, Q349K, T392M, P442S, R446G, H468L, V482A	61,1
10	E65K	61,1
11	T48A	61,2
12	G4C, A72C, T344M	61,2
13	T243R, A375D	61,3
14	W40R, K159E, N445D	61,3
15	T344M	61,3
16	W40R, M234K	61,3
17	Q349R, T393A, P436S, N445D	61,4
18	Q349R, A354T, D373E, N445D	61,4
19	G4C, W40R, A72C, T344M	61,4
20	G4C, A72C, N194L, T243Y, Q349R, Y374R, A375L	61,5
21	G4C, D64N, A72C, Q349K	61,5
22	Q349R, N445D	61,5 +/- 0,1
23	W40R, T344M	61,5
24	W40R, D346A, T393A	61,6
25	N158D, G486S, Y495C	61,6
26	D320E	61,6
27	A72V	61,6
28	E183V	61,6
29	W40R, C489R	61,7
30	A72V, T335I, D346A, T393A, N445D	61,7
31	G4C, W40R, A72C, V313I, Q349R	61,8
32	W40R, Q349K	61,9
33	Q1L, G4C, T26N, A72C, D181N, E183K, Q349R	61,9
34	G4C, A72C, Q349K, E65V, Q349R	61,9
35	S311N	62
36	D320V, D346A, Q349R, T393A, N445D	62,1
37	T335I	62,2
38	A72V, D346A	62,2
39	D320V, D346A, T393A, N445D	62,2
40	G4C, A72C, N194S, T243W, Q349R, Y374S, A375G	62,3
41	E65V, Q349R	62,3
42	Q1L, G4C, A72C, F179I, D181N, E183K, L290H, S301C, Q349R, Q361R, D390G, G474S, Q498K	62,3
43	A72V, T335I, D346A, N445D	62,3
44	G4C, A72C, N194L, T243Q, Q349R, Y374P, A375V	62,3
45	Q1L, G4C, G23D, A72C, D111E, I116V, K118A, D181N, E183K, V212L, Q349R, Q362G	62,3
46	G4C, A72C, D346G	62,3
47	W40R, T344M, Q349K	62,3
48	G4C, Y163C	62,4
49	G4C, V32G, N49S, A72C, S193L, Q349R	62,4
50	A72V, Q349R, N445D	62,4 +/- 0,4
51	G4C, A72C, D346G, Q349R	62,5 +/- 0,1
52	Q1L, G4C, A72C, D181N, E183K, I321N, Q349R	62,6

53	W40R, D320V, Q349K, P436S, N445D	62,7
54	G4C, A72C, D181N, Q349R	62,7
55	G4C, A72C, Q349K	62,7
56	G4C, A72C, T344M, Q349K	62,8
57	G4C, A72C, T344M, D346G, Q349R	62,8 +/- 0,2
58	G4C, A72C, D320V, Q349K	62,8
59	G4C, A72C, P224L, F306Y, Q349R	62,9
60	G4C, A72C	62,9 +/- 0,6
61	A72V, D346A, T393A	63
62	G4C, A72C, Q349R, R446S, T456A	63
63	G4C, W40R, A72C, T344M, Q349K	63
64	A72V, D320V, D346A	63,1
65	G4C, A72C, N194Y, T243L, Q349R, Y374S, A375R	63,1
66	G4C, A72C, Q349K, T448A, T449A	63,2
67	G4C, E65V, A72C, Y244H, Q349R	63,3
68	G4C, A72C, D202G, D320N, Q349R, A358E	63,4
69	G4C, A72C, D320V, Q349R	63,4
70	G4C, A72C, Q349K, S86T	63,4
71	A72V, T335I, D346A, T393A, P436S	63,4
72	G4C, A72C, E183V, K304R, Q349K	63,5
73	G4C, A72C, T243G, Q349R, Y374P, A375M	63,5
74	G4C, A72C, Q349R, T465I	63,6
75	G4C, A72C, Q349R	63,6 +/- 0,5
76	G4C, A72C, N194V, T243M, Q349R, Y374A, A375T	63,6
77	G4C, D64N, A72C, Q349R, A358E, P464Q	63,6
78	G4C, A72C, Q349K, Q28R, S193T, Q490L	63,6
79	G4C, A72C, E183K, Q349K	63,6
80	G4C, A72C, S311N, Q349K, A455T	63,6
81	G4C, A72C, N194K, Q349R, Y374P, A375Q	63,6
82	G4C, A72C, D181N, Q349K	63,6
83	W40R, D320V, Q349K, T393A, N445D	63,7
84	W40R, T335I, D346A, T393A	63,7
85	Q1L, G4C, A72C, D181N, E183K, N327Y, Q349R	63,7
86	A72C, L119L, T335I, Q349R, G486D	63,7
87	G4C, A72C, N194K, T243P, Q349R, Y374H, A375E	63,7
88	G4C, A72V, Q349R, P462del	63,8
89	G4C, A72C, S236Y, Q349R	63,8
90	G4C, A72C, S311G, Q349K	63,8
91	A72V, D320V, T335I, D346A, T393A, N445D	63,8
92	G4C, A72C, S86T, M234V, Q349K	63,8
93	Insertion at position K159(CGRNK)undT457(AAATT), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	63,9
94	G4C, A72C, G251R, Q349R	63,9
95	G4C, A72C, Q349K, D320V	63,9 +/- 0,7
96	A72V, T335I, D346A, T393A	63,9
97	G4C, A72C, E183K, Q349R	63,9
98	Q1L, G4C, A72C, H203R, Q349K, P442S	63,9
99	G4C, A72C, Q349K, G434S, G470D	64
100	G4C, W40R, A72C, Q349K	64

101	G4C, A72C, Q349R, V367A	64
102	Q1L, G4C, A6V, C50S, A72C, I180N, D181N, E183K, Q349R, T457P, C472R, C499G	64
103	G4C, A72C, S311G, D320V, Q349K	64
104	W40R, T335I, D346A, T393A, P436S	64
105	Q1L, G4C, A72C, D181N, E183K, T243S, Q349R, P386S	64,1
106	A72V, D346A, T393A, N445D	64,1
107	Q1L, G4C, A72C, K154R, Q349K, T393I	64,1
108	G4C, A72C, N194G, T243F, Q349R, Y374P, A375R	64,1
109	A72V, D320V, D346A, T393A, N445D	64,1
110	A72C, L119L, Q172Q, Q349K, T488I	64,1
111	G4C, A72C, E183V, Q349K	64,1
112	G4C, A72C, E183K, N318Y, Q349K	64,1
113	W40R, A221V, T449A, C483R	64,1
114	G4C, A72C, K92R, Q349K, N493D	64,1
115	M234I, G438del	64,2
116	Q1L, G4C, A72C, S90T, D181N, E183K, Q349R	64,2
117	G4C, A72C, Q349R, G459D	64,2
118	G4C, A72C, Q349R, Y422F	64,2
119	G4C, T48A, A72C, Q349R, P480S	64,2
120	E187K, D320V, P442del	64,2
121	G4C, S24N, E65K, A72C, Q349R, I430L, G439D	64,2
122	A72V, D320V, T335I, D346A, T393A, P436S	64,3
123	Q1L, G4C, A72C, S193P, Q349K, V482I	64,3
124	G4C, A72C, D320V, Q349K, G443D, L492Q	64,3
125	Q1L, G4C, A72C, DV152-K159, D181N, E183K, Q349R	64,4
126	Q1L, G4C, A72C, Q349K	64,4 +/- 0,5
127	Q1L, G4C, A72C, D181N, E183K, M234L, V313I, Q349R, H468R	64,4
128	Q1L, G4C, A72C, D181N, E183K, I200N, Q349R	64,4
129	G4C, A72C, N194K, T243Y, Q349R, A375N	64,4
130	Q1L, G4C, Q28R, A72C, Q349K, H468L	64,5
131	G4C, E65V, A72C, Q349R	64,5
132	D320V, Q349K	64,5
133	Q1L, G4C, A72C, S311G, Q349K, H468R	64,5
134	G4C, A72C, T243Q, Q349R, Y374P, A375M	64,5
135	Q1L, G4C, A72C, D320V, Q349R	64,5
136	Q1L, G4C, T15S, A72C, Y244F, Q349K	64,5
137	G4C, A72C, E183K, D346E, Q349R	64,6
138	T243C, A375C	64,6
139	Q1L, G4C, A72C, Q349K, T392M	64,6
140	G4C, A72C, D202N, S311N, Q349R, N493D	64,6
141	G4C, A72C, N194D, T243A, Q349R, Y374P, A375Y	64,6
142	G4C, A72C, N194Y, T243V, Q349R, Y374P	64,7
143	Q1L, G4C, A72C, Q349R	64,7
144	G4C, Q28R, E65K, A72C, S86T, D202N, H203R, S311N, D320I, A340G, D346A, Q349K, T393A, Y422F, P442S, R446S, H468L, V482A	64,7
145	G4C, A72C, D202N, Q349R	64,7
146	G4C, A72C, P224L, Q349R	64,7
147	N194C, Y374C	64,7

148	Q1L, G4C, A72C, D181N, E183K, T229M, A340T, Q349R, V491I	64,7
149	Q1L, G4C, A72C, D181N, Q349R	64,8
150	G4C, A72C, D320V, D346V, Q349K	64,8
151	Q1L, G4C, A72C, V152A, Q349K	64,8
152	Q1L, G4C, Q28R, A72C, Q349K	64,8
153	Q1L, G4C, A72C, Q349K, Y422F	64,8
154	G4C, A72C, D202V, D320V, Q349K	64,8
155	Q1L, G4C, A72C, Y155S, D181N, E183K, Q349R	64,8
156	Q1L, G4C, A72C, D181N, D247N, Q349K	64,8
157	Q1L, G4C, A68T, A72C, Q349K, G439D, R453S	64,9
158	Q1L, G4C, A72C, Q349K, H468R	64,9
159	Q1L, G4C, D64N, A72C, Q349K	64,9
160	G4C, A72C, E183K, Q349R, P464L	64,9
161	G4C, A72C, D181N, P224L, Q349K	65 +/- 0,6
162	G4C, A72C, N194I, T243Y, Q349R, Y374P, A375R	65
163	Q1L, G4C, A72C, Q349K, P462L	65
164	Q1L, G4C, A72C, E183K, Q349R	65
165	G4C, A72C, S311G, Q349R	65
166	Q1L, G4C, A72C, S311N, Q349K, G463D	65,1
167	Q1L, G4C, A72C, S86T, Q349R	65,1
168	Q1L, G4C, A72C, D181N, E183K, G231D, Q349R	65,1
169	Q1L, G4C, A72C, S89N, D181N, E183K, Q349R	65,2
170	Q1L, G4C, E65K, A72C, Q349K	65,2
171	Q1L, Q2P, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F, R446G	65,2
172	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	65,2
173	G4C, A72C, E183K, D202Y, N310D, Q349R	65,3 +/- 0,7
174	G4C, A72C, N194I, T243D, Q349R, Y374P, A375Y	65,3
175	Q1L, G4C, A72C, D181N, E183K, Q349R, T456I	65,3
176	G4C, Q28R, A72C, S86T, E183K, P224L, S311N, N318Y, T335I, D346G, Q349R, T393I, P441A, P442S, R446G, H468L, V482I	65,3
177	Q1L, G4C, A72C, D181N, Q349K, T451S	65,3 +/- 0,1
178	Q1L, G4C, A72C, D181N, E183K, T243I, N246D, Q349R, T488I	65,4
179	Q1L, G4C, G23N, A72C, D110G, I116V, L119I, D181N, E183K, D211G, D293R, N310D, Q349R, Q362R, G363P, M364S	65,4
180	G439V, N440E, P441S, P442Q	65,4
181	G431D, S431V, T433E, G434S, N435Q	65,5
182	Q1L, G4C, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	65,6
183	G4C, A72C, N194C, Y374C	65,6
184	Q1L, G4C, A72C, S86T, D181N, E183K, Q349R, T393S	65,6
185	Q1L, G4C, A72C, D181N, E183K, Q349R, S485T	65,7
186	Q1L, G4C, G23N, A72C, V84A, D110G, D111H, I116E, F117Y, K118A, D181N, E183K, D293R, T295S, Q349R, M364L	65,7
187	Q1L, G4C, A72C, D181N, E183K, Q349R, R453K	65,8
188	Q1L, G4C, A72C, A145T, H203R, Q349K, T403K	65,8
189	Q1L, G4C, A72C, D181N, E183K, Q349R, N445S	65,8
190	Q1L, G4C, A72C, D181N, E183K, M234I, Q349R	65,8
191	Q1L, G4C, A72C, D181N, E183K, Q349R, T465S	65,9

192	Q1L, G4C, A72C, D181N, E183K, T297N, Q349R	66
193	Q1L, G4C, A72C, S311G, Q349K	66
194	G4C, Q28R, E65M, A72C, S86T, E183K, S192I, H203R, S311N, D346E, Q349K, T392M, T393A, Y422F, N445D, R446S	66
195	Q1L, G4C, A72C, D202N, Q349K, G486D	66
196	Q1L, G4C, A72C, S99T, D181N, E183K, Q349R, T450I	66
197	Q1L, G4C, A72C, I200F, Q349K, L500I	66
198	Q1L, G4C, A72C, D181N, E183K, Q349R, G434S	66
199	Q1L, G4C, A31S, A72C, D181N, E183K, Q349R	66
200	Q1L, G4C, Q28L, A72C, D181N, E183K, Q349R	66
201	Q1L, G4C, A72C, D181N, E183K, Q349R, P436S	66,1
202	Q1L, G4C, A72C, D181N, E183K, T233S, Q349R	66,1
203	Q1L, G4C, A72C, D202N, Q349K	66,1 +/- 0,1
204	Q1L, G4C, A68T, A72C, Q349K	66,1
205	Q1L, G4C, A21T, A72C, D181N, E183K, Q349R, P454S	66,1 +/- 0,1
206	Q1L, G4C, A72C, D346V, Q349K	66,2
207	Q1L, G4C, Y47F, A72C, D181N, E183K, Q349R, P436S, S461R	66,2
208	Q1L, G4C, A72C, D181N, E183K, M234T, Q349R	66,3
209	Q1L, G4C, A72C, N157S, D181N, E183K, Q349R	66,3
210	Q1L, G4C, A72C, D181N, E183K, Q349R	66,3 +/- 0,4
211	As1-72ausT.reesei, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	66,3
212	G4C, A72C, N194Q, T243V, Q349R, Y374P, A375Y	66,3
213	Q1L, G4C, A72C, D181N, E183K, I314F, Q349R, N445D	66,3
214	Q1L, G4C, A72C, Q349K, T392K	66,3
215	Q1L, G4C, A72C, D181N, E183K, Q349R, T451A	66,4
216	Q1L, G4C, A72C, D181N, E183K, M234V, Q349R	66,4
217	Q1L, G4C, A21S, A72C, D181N, E183K, Q349R	66,5
218	A21C, P429C	66,5 +/- 0,4
219	Q1L, G4C, A72C, D181N, E183K, Q349R, N493D	66,5
220	Q1L, G4C, A72C, S311N, Q349K	66,5
221	Q1L, G4C, Q28R, E65V, A72C, D181N, E183V, D228N, S311N, N318Y, D346E, Q349R, Y422F, P442S, N445D, R446G, H468L, V482T	66,5
222	G4C, A72C, N194C, Q349R, Y374C	66,5
223	Q1L, G4C, A72C, D181N, E183K, Q349R, A455V	66,5 +/- 0,3
224	Q1L, G4C, A72C, D181N, E183K, Q349R, T400S	66,6
225	Q1L, G4C, T26I, A72C, D181N, E183K, Q349R	66,6 +/- 0
226	Q1L, G4C, A72C, D181N, E183K, N310D, Q349R, T392S, G463D	66,7
227	Q1L, G4C, A72C, D129N, D181N, E183K, Q190L, G266S, I276V, Q349R, P386L, F427Y	66,7 +/- 0,2
228	Q1L, G4C, A72C, D181N, E183K, D202N, Q349R	66,7
229	Q1L, G4C, A72C, Y155C, D181N, E183K, Q349R	66,8
230	Insertion at position P454(ATAAA), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	66,8
231	Insertion at position K159(CGRNK), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	66,8
232	Q1L, G4C, A72C, D181N, E183K, N246K, Q349R	67 +/- 0,6
233	G4C, W40R, E65V, A72C, S86T, D181N, E183K, D202I, H203R, S311D, D320N, D346V, Q349R, T392M, T393A, Y422F, P442S, H468Q, V482A	67 +/- 0,5

234	Q1L, G4C, A72C, Y155C, Q349K	67 +/- 0,4
235	Q1L, G4C, A68T, A72C, D181N, E183K, Q349R	67 +/- 0,3
236	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, T448A, R453G, H468L, P480S, V482I	67,3
237	Q1L, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F, R446G	67,3
238	Q1L, G4C, A72C, S86T, D181N, E183K, D320V, Q349R	67,3 +/- 0,4
239	G4C, Q28K, A72C, S86T, E183M, D202N, P224L, S311G, N318Y, D320N, D346A, Q349R, T392M, T393I, P442S, H468L, V482I	67,4
240	Q1L, Q2P, G4C, Q28R, W40R, E65K, A72C, D181N, S192L, D202I, H203R, P224L, S311G, D320I, D343A, D346A, Q349K, P442S, N445D, R446G, V482A	67,4
241	Q1L, G4C, Q28R, E65K, A72C, E183M, D202I, P224L, D320N, D346V, Q349K, T392M, T393V, Y422F, N445D, R446G, H468L, V482T	67,4
242	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202V, S311G, N318Y, D320I, D346G, Q349K, T393V, Y422F, N445D, R446S, H468Q, V482T	67,4
243	Q1L, G4C, W40R, E65M, A72C, D181N, E183K, S192P, D202N, P224L, S311D, N318Y, D320V, D346G, Q349K, T392M, N445D, R446G, H468L, V482T	67,4
244	Q1L, G4C, E65V, A72C, D181N, E183K, P224L, S311G, D320N, D346G, Q349R, T392M, T393I, R446G, H468L, V482I	67,6
245	Insertion at position G151(CGRSG), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	67,6
246	Q1L, G4C, E65M, A72C, D181N, E183M, D202Y, P224L, S311D, N318Y, D320I, T335I, D346A, Q349K, T392M, T393I, N445D, R446G, T448A, H468Q, V482A	67,6
247	Q1L, G4C, G23A, A72C, D110S, D111H, I116V, F117Y, K118A, L120M, D181N, E183K, D293H, G294A, N310E, Q349R, Q362G, M364S	67,6
248	Q1L, G4C, A72C, D181N, E183K, Q349R, T421I, G439D	67,7
249	G4C, Q28K, E65M, A72C, S86T, V152A, D181N, E183V, S192L, D202N, S311N, D320N, D346E, Q349R, T387A, T392M, T393I, Y422F, P442S, R446S, H468L, G476D, V482I	67,7 +/- 0,3
250	Q1L, G4C, W40R, E65V, A72C, S86T, E183V, G188C, S192T, D202Y, H203R, P224L, S311N, D320V, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	67,7
251	Q1L, G4C, E65M, A72C, S86T, E183M, D202N, P224L, T335I, D346G, Q349K, T392M, T393A, P442S, N445D, R446G, H468Q, V482A	67,7
252	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, H468L, P480S, V482I	67,8
253	Q1L, G4C, W40R, E65K, A72C, S86T, E183K, S192L, D202Y, P224L, D320I, D346E, Q349R, P442S, R446G, H468R, V482T	67,9 +/- 0,4
254	Q1L, G4C, A21T, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, D202N, P224L, S311G, N318Y, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, P480S, V482I	67,9
255	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	68
256	Insertion at position P464(THAAA), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68
257	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68
258	Q1L, G4C, T7Q, A8S, N10T, S24T, T27Q, Q28R, N29T, V41T, G46S, Y47S, T52D, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	68
259	Insertion at position K159(CGRNK)undT457(AAATT), Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,1 +/- 1,9

260	Q1L, G4C, Q28K, W40R, E65V, A72C, D181N, E183V, S192P, D202V, H203R, S311G, D320N, D346E, Q349K, T392M, T393A, Y422F, V482I	68,1
261	Q1L, G4C, Q28R, E65V, A72C, G139S, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,1
262	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I	68,2
263	Q1L, G4C, Q28R, E65K, A72C, D181N, S311N, N318Y, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	68,2 +/- 0,7
264	Q1L, G4C, W40R, A72C, S192L, D202N, H203R, P224L, S311N, D320I, T335I, D346V, Q349R, T393I, N445D, R446G, H468Q, V482T	68,2 +/- 0
265	Q1L, G4C, Q28K, E65K, A72C, E183M, D202N, P224L, T229S, S311G, D320I, T335I, D346V, Q349R, T393V, H468Q, V482A	68,2
266	Q1L, G4C, Q28R, G30A, E65M, A72C, D181N, D202N, P224L, S311D, N318Y, D346E, Q349K, T392M, T393V, Y422F, P442S, N445D, R446S	68,2
267	Q1L, G4C, Q28R, E65V, A72C, S68T, E183M, S311N, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	68,2
268	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,3
269	T243C, A375C, N194C, Y374C	68,3
270	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, S311G, D346V, Q349R, T392M, T393V, Y422F, P442S, N445D, R446G, H468L, S478Y, V482I	68,3
271	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,3
272	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, S311N, N318Y, D320I, T335I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I	68,4
273	Q1L, G4C, Q28R, E65K, A72C, S86T, E183K, D202N, P224L, S311G, T335I, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	68,4
274	Q1L, G4C, Q28R, E65V, A72C, L120P, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,4
275	Q1L, G4C, Q28K, E65V, A72C, S86T, E183M, S311N, N318H, D320V, D346V, Q349K, T392M, T393A, R446S, H468L, V482I	68,4
276	Q1L, G4C, Q28K, E65V, A72C, D202N, H203R, S311G, T335I, D346V, Q349K, T393A, P442S, R446G, H468L, V482I	68,4
277	M146C, G167C	68,5
278	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,5
279	Q1L, G4C, Q28R, E65K, A72C, D181N, D202N, H203R, P224L, S311D, D346G, Q349K, P442S, R446S, H468Q, V482T	68,5
280	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T	68,5
281	Q1L, G4C, T27S, Q28R, E65V, Q69R, A72C, L120P, D181N, E183M, D202N, D247N, S311G, D346E, Q349K, K355Q, T387S, T393V, Y422F, N445D, R446G, T451S, G463V, H468Q, V482T, S485T	68,5
282	Q1L, G4C, Q28R, E65K, A72C, E183V, S192T, D202N, S311G, D320V, D346A, Q349K, P442S, N445D, R446G, H468R, V482A	68,6 +/- 0,6
283	Q1L, G4C, W40R, E65V, A72C, S86T, E183M, D202N, P224L, S311G, D320V, D346E, Q349R, T393I, P442S, R446G, H468R, V482I	68,6
284	Q1L, G4C, Q28N, E65K, A72C, D181N, E183M, D202N, H203R, S311G, N318Y, D320N, Q349R, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,6
285	Q1L, G4C, Q28R, V41T, G46S, Y47S, T52D, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	68,6
286	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,6
287	Q1L, G4C, Q28R, W40R, A72C, S86T, D181N, S192T, D202N, P224L, S311G, N318Y, D320V, D346E, Q349K, T392M, T393I, P442S, N445D, R446G, H468Q, V482I	68,6 +/- 1

288	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, T229M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I	68,6
289	Q1L, G4C, Q28K, W40R, A72C, S86T, D181N, E183M, S192I, D202Y, T299S, S311N, N318Y, D320I, D346V, Q349R, T393I, P442S, H468L	68,6 +/- 0,4
290	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, T229M, G231D, M234T, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,6
291	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, T448A, R453G, H468L, P480S, V482I	68,7
292	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, G463V, H468L, V482I	68,7
293	Q1L, G4C, Q28R, E65K, A72C, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,7
294	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T	68,7
295	Q1L, G4C, Q28R, W40R, E65V, A72C, S86T, S192T, D202V, H203R, S311N, N318Y, D346A, Q349K, T392M, T393A, Y422F, P442S, N445D, V482A	68,7
296	insertion at position K159(CGRNK), G434(AAATG)undT457(AAATT), Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,7 +/- 1,1
297	Q1L, G4C, Q28K, E65K, A72C, D181N, H203R, P224L, S311G, D320V, D346G, Q349K, T392M, T393I, P442S, N445D, R446G, H468L, V482A	68,7 +/- 0
298	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,8
299	, ,	68,8 +/- 0,2
300	Q1L, G4C, Q28R, E65V, A72C, E183K, D202I, P224L, S311G, D320I, Q349K, T393V, P442S, N445D, R446S, H468L, V482I	68,8
301	Q1L, G4C, Q28K, A72C, S86T, D181N, E183V, S192T, D202N, P224L, S311G, N318Y, D320V, D346G, Q349R, T392M, Y422F, P442S, N445D, R446S, H468L, V482A	68,8
302	G4C, Q28R, E65K, A72C, S86T, D181N, E183M, S192L, D202N, H203R, P224L, S311D, D346E, Q349R, T392M, T393A, Y422F, P442S, N445D, R446G, P462L, H468L, V482T	68,8
303	Q1L, G4C, W40R, E65K, A72C, Q109R, D181N, E183M, S192I, D202I, H203R, S245T, D346A, Q349R, T393A, Y422F, P442S, N445D, R446G, H468R, V482A	68,8 +/- 0,2
304	Q1L, G4C, Q28K, E65M, A72C, D181N, D202N, S311N, T335I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482I	68,9
305	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349R, T393V, N417Y, Y422F, P442S, N445D, R446G, H468L, V482I	68,9
306	Q1L, G4C, Q28R, W40R, E65V, A72C, D202Y, H203R, P224L, T299I, N318Y, D320V, D346A, Q349K, T392M, T393A, P442S, N445D, R446G, H468R, V482T	68,9
307	G4C, Q28R, E65V, A72C, E183M, D202N, P224L, S311G, N318Y, D320V, D346G, Q349K, T392M, Y422F, R446G, H468Q	68,9
308	Q1L, G4C, Q28K, A72C, S86T, E183K, S311G, D320V, D346A, Q349R, T392M, T393I, Y422F, P442S, R446S, H468Q	68,9
309	Q1L, G4C, Q28R, E65M, A72C, D181N, P224L, S311N, D320N, T335I, D346E, Q349K, T392M, Y422F, N445D, R446S, H468L, V482T	68,9
310	Q1L, G4C, Q28K, E65V, A72C, D181N, D202N, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	68,9
311	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I	68,9
312	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	68,9
313	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69

314	Q1L, G4C, W40R, E65V, A72C, S86T, D181N, S192T, D202N, H203R, P224L, S311G, N318Y, T335I, D346G, Q349K, T392M, T393V, Y422F, N445D, R446G, H468Q	69 +/- 0,3
315	Q1L, G4C, Q28R, E65K, A72C, E183M, S311N, D320I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482T	69
316	Q1L, G4C, T7Q, A8S, N10T, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	69
317	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202N, P224L, S311G, D346A, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482T	69 +/- 0,9
318	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, K92R, K118Q, D181N, E183M, D202N, T280A, S311G, T335I, D346E, Q349K, K355Q, T387S, T393V, D404N, Y422F, N445D, R446G, P462L, G463V, H468Q, V482I, S485T	69
319	Q1L, G4C, Q28R, E65M, A72C, E183M, D202N, S311G, D320I, T335I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I	69
320	Q1L, G4C, Q28K, E65K, A72C, D181N, E183M, D202N, S311D, D320V, T335I, D346G, Q349K, T393I, Y422F, P442S, N445D, H468L, V482I	69
321	Q1L, G4C, Q28K, E65K, A72C, S86T, P224L, S311N, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T	69
322	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T	69
323	G4C, E65K, A72C, S86T, E183M, D202I, P224L, S311N, N318Y, D320N, T335I, D346V, Q349R, T393V, Y422F, P442S, R446S, H468L	69
324	Q1L, G4C, Q28R, E65K, A72C, D202N, S311N, T335I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468L, V482T	69
325	Q1L, G4C, E65V, A72C, D181N, E183K, D202G, Q349R	69 +/- 1,2
326	Q1L, G4C, Q28R, E65K, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69
327	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, F306L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69
328	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T	69
329	Q1L, G4C, Q28K, E65K, A72C, D181N, E183K, S192P, P224L, S311G, N318Y, D320V, D346E, Q349R, T392M, T393I, Y422F, P442S, H468Q	69 +/- 0,1
330	Q1L, G4C, Q28K, E65M, A72C, S86T, E183M, H203R, S311D, D320V, T335I, D346E, Q349R, T393A, N445D, R446G, H468Q, V482A	69
331	Q1L, G4C, Q28R, A72C, D181N, E183V, D202I, H203R, P224L, S311D, D320V, D346V, Q349R, T392M, T393I, N445D, H468L	69
332	Q1L, G4C, Q28K, W40R, E65K, A72C, S86T, D181N, E183K, S192L, D202I, H203R, S311N, D320N, D346V, Q349K, T392M, T393A, Y422F, N445D, R446S	69
333	G4C, E65V, A72C, S86T, Y155H, D181N, E183V, Q190K, P224L, S311N, D320V, D346V, Q349K, T392M, T393V, Y422F, P442S, N445D, R446G, H468L, V482A	69,1
334	Q1L, G4C, Q28R, E65M, A72C, S86T, E183M, D202N, S311D, N318Y, D320N, T335I, D346A, Q349R, T392M, T393I, Y422F, P442S, N445D, R446G, H468L, V482A	69,1
335	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311N, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	69,1
336	Q1L, G4C, Q28R, E65K, A72C, S86T, D181N, D202N, S311G, D346E, Q349K, T393I, Y422F, N445D, R446G, H468L, V482I	69,1
337	Q1L, G4C, Q28R, E65K, A72C, D181N, D202N, S311N, N318Y, D320I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468L, V482T	69,1 +/- 0,6
338	Q1L, G4C, T7Q, A8S, N10T, S24T, T27Q, Q28R, N29T, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	69,1
339	Q1L, G4C, Q28R, E65K, A72C, S86T, D202N, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468L, V482I	69,1

340	Q1L, G4C, Q28R, A72C, D181N, S311G, N318Y, D320V, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q	69,1
341	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,1
342	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,1
343	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, S311N, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T	69,1
344	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	69,2
345	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	69,2
346	Q1L, G4C, E65M, A72C, S86T, E183K, D202Y, S311G, D320N, T335I, D346A, Q349K, T393V, Y422F, R446G, H468Q, V482T	69,2
347	Q1L, G4C, Q28R, E65V, A72C, S86T, E183M, D202N, P224L, S311N, D320I, T335I, A340S, D346A, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T	69,2
348	Q1L, G4C, Q28K, E65K, A72C, S86T, D181N, E183M, H203R, P224L, S311D, D320I, D346E, Q349R, T392M, Y422F, R446G, H468L	69,2
349	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I	69,2 +/- 0,5
350	Q1L, G4C, Q28K, N29Y, E65K, A72C, D181N, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T	69,2 +/- 0,1
351	Q1L, G4C, Q28K, E65M, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T	69,3
352	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, D202N, S311N, N318Y, D320N, T335I, D346A, Q349K, T392M, T393V, P442S, N445D, R446G, H468Q	69,3
353	Q1L, G4C, Q28K, E65K, A72C, S86T, D181N, E183M, D202N, S311G, N318Y, T335I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I	69,3
354	Q1L, G4C, Q28R, E65K, A72C, E183V, S192T, D202N, S311G, D320V, D346A, Q349K, T393V, P442S, N445D, H468L, V482A	69,3 +/- 0,3
355	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, S311N, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	69,3
356	Q1L, G4C, S24T, Q28R, E65K, A72C, D202N, S311G, T335I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T	69,3 +/- 0,1
357	Q1L, G4C, A72C, S86T, D181N, S192L, D202N, P224L, S311G, N318Y, D320V, T335I, D346G, Q349K, T393I, R446G, H468Q	69,3
358	Q1L, G4C, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	69,4 +/- 0,5
359	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, D202N, P224L, S311G, D346A, Q349K, T393I, Y422F, P442S, N445D, R446G, H468L, V482T	69,4
360	Q1L, G4C, Q28K, E65V, A72C, S86T, E183V, S192I, D202V, D320I, T335I, D346V, Q349K, T392M, T393I, Y422F, P442S, N445D, R446G, H468R, V482A	69,4 +/- 0,1
361	Q1L, G4C, Q28K, E65M, A72C, S86T, D181N, E183M, D202N, P224L, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T	69,4 +/- 0,2
362	Q1L, G4C, Q28K, A72C, D181N, D202I, S311D, N318Y, T335I, D346E, Q349K, T392M, Y422F, R446G, H468L	69,4
363	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320N, D346E, Q349K, T393V, Y422F, T433S, P442S, N445D, R446G, H468L, V482I	69,4
364	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, S311G, N318Y, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I	69,4 +/- 0,2
365	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, S311G, N318Y, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T	69,4 +/- 0,5
366	Q1L, G4C, Q28R, E65K, A72C, S86T, E183M, D202N, D320I, T335I, D346A, Q349K, T392M, Y422F, N445D, R446G, H468L, V482T	69,4

367	Q1L, G4C, Q28K, E65M, A72C, S86T, E183M, S311N, N318Y, D320I, T335I, D346E, Q349K, T393I, Y422F, P442S, H468Q, V482I	69,4
368	Q1L, G4C, E65M, A72C, S86T, E183V, S192L, D202I, H203R, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468R, V482A	69,4 +/- 0,1
369	Q1L, G4C, T7Q, A8S, N10T, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	69,4
370	Q1L, G4C, E65K, A72C, S86T, D202V, S311N, D320V, T335I, D346V, Q349R, T392M, Y422F, N445D, R446G, H468L	69,4
371	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,4
372	Q1L, G4C, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	69,4
373	Q1L, G4C, Q28R, A72C, S86T, E183M, S192T, D202N, H203R, P224L, S311N, T335I, D346V, Q349R, T392M, T393V, P442S, N445D, R446G, H468Q, V482A	69,4
374	Q1L, G4C, Q28K, E65V, A72C, D181N, D202N, S311N, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I	69,4 +/- 0,8
375	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I, S485T	69,5
376	G4C, Q28K, E65M, A72C, S86T, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,5
377	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, G434(AAATG) P442S, N445D, R446G, T457(AAATT), H468L, V482I	69,5 +/- 0,4
378	G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202Y, P224L, S311N, D346A, Q349K, T393I, Y422F, N445D, R446S, H468Q, V482A	69,5
379	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482T	69,5 +/- 1,8
380	Q1L, G4C, T27S, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,5
381	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, P224L, S311G, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T	69,5
382	As1-10ausT.reesei, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	69,5
383	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	69,5
384	Q1L, G4C, Q28K, E65V, A72C, E183M, D202N, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,6 +/- 0,1
385	Q1L, G4C, Q28R, E65K, A72C, D181N, P224L, S311N, N318Y, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I	69,6
386	Q1L, G4C, Q28R, E65M, A72C, S90F, D181N, P224L, S311G, N318Y, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482I	69,6
387	G4C, Q28R, A72C, S86T, D181N, E183V, S192L, D202V, N246S, S311D, N318Y, D320V, D346A, Q349K, T393V, P442S, N445D, H468L, V482A	69,6
388	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311N, N318Y, D320I, T335I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T	69,6
389	Q1L, G4C, Q28R, A72C, S86T, E183M, S192L, H203R, S311D, D320V, T335I, D346V, Q349K, N445D, H468Q, V482A	69,6
390	Q1L, G4C, Q28R, T59M, E65K, A68T, A72C, S86T, D181N, S192L, D202N, H203R, S311D, D320V, T335I, Q349R, T393A, P442S, N445D, R446G, H468L, V482A	69,6
391	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I	69,6

392	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, K355Q, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,6
393	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, N318Y, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T	69,6
394	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T448A, R453G, H468L, V482I	69,6
395	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	69,6 +/- 0,5
396	Q1L, G4C, E65M, A72C, E183M, D202I, P224L, S311D, N318Y, D320V, T335I, D346A, Q349K, T393A, Y422F, P442S, N445D, R446G, R453G, H468Q, V482I	69,6
397	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,7
398	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, S311G, N318Y, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	69,7 +/- 1
399	Q1L, G4C, S24T, T27Q, Q28R, N29T, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I	69,7
400	Q1L, G4C, E65V, A72C, D181N, E183M, S192T, P224L, S311G, D320V, T335I, D346G, Q349K, T393A, Y422F, P442S, N445D, R446G, H468L, V482T	69,7
401	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,8 +/- 0,8
402	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202F, S311G, N318Y, T335I, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q	69,8
403	Q1L, G4C, Q28K, E65K, A72C, S86T, D181N, D202N, P224L, S311D, N318Y, D320N, D346A, Q349R, T392M, T393I, Y422F, N445D, R446G, H468R	69,8
404	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, S311N, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T	69,8 +/- 0
405	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	69,8
406	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,8
407	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, S311N, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T	69,8
408	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T	69,8
409	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, T229M, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, P480S, V482I	69,9
410	Q1L, G4C, Q28K, E65M, A72C, D181N, E183M, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	69,9
411	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, D404N, Y422F, P442S, N445D, R446G, T451S, H468L, V482I	69,9
412	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P462L, H468L, V482I	69,9
413	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I	69,9
414	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, T280A, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,9
415	Q1L, G4C, Q28R, E65V, Q69R, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,9

416	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, K275E, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	69,9
417	Q1L, G4C, Q28K, E65V, A72C, E183K, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T	69,9
418	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T	69,9 +/- 0,2
419	Insertion at position A455(AAAPA), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70
420	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70
422	Q1L, G4C, Q28R, E65M, A72C, E183M, S311G, D320I, D346A, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	70
423	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, S311G, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I	70,1
424	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,1
425	Q1L, G4C, Q28K, E65K, A72C, D181N, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T	70,1 +/- 0,2
426	Q1L, G4C, Q28R, E65V, A72C, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	70,1
427	Q1L, G4C, S24C, Q28R, G30A, E65V, A72C, Y155C, D181N, Q190K, D202N, P224L, S311G, T335I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, R453G, H468Q, P480S, V482I	70,1
428	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, P402S, Y422F, P442S, N445D, R446G, H468L, V482I	70,1
429	Q1L, G4C, Q28R, E65K, A72C, E183M, D202N, P224L, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I	70,1
430	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A72C, Y155C, D181N, D202N, P224L, M234T, S311G, D320I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I	70,1
431	Q1L, G4C, Q28R, E65K, A72C, S86T, D202N, P224L, S311D, D320N, T335I, D346V, Q349K, T392M, T393V, Y422F, P442S, R446S, H468L	70,2
432	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202N, S311G, N318Y, D320I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I	70,2
433	Q1L, G4C, W40R, E65M, A72C, S86T, E183V, S192L, D202I, H203R, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468R, V482A	70,2 +/- 0,3
434	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,2
435	Insertion at position G434(AAATG) andT457(AAATT), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,2 +/- 0,2
436	Q1L, G4C, Q28R, E65V, A72C, K118Q, D181N, E183M, P224L, D247N, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,3
437	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I	70,4 +/- 0
438	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	70,4 +/- 0,9
439	Q1L, G4C, Q28K, E65M, A72C, D181N, E183M, D202N, S311G, N318Y, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T	70,4 +/- 0,5
440	Insertion at position P454(VRPQP), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,5

441	Q1L, G4C, Q28R, A72C, D181N, E183V, S192M, D202N, P224L, S311D, N318Y, D320N, D346E, Q349R, T393V, Y422F, P442S, R446G, H468L, P480S	70,5
442	Q1L, G4C, Q28R, A72C, S86T, D181N, S192L, D202N, P224L, S311G, N318Y, D320V, T335I, D345E, D346A, Q349K, Y422F, P442S, N445D, R446G, H468Q, H505Q	70,5
443	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183K, P224L, S311G, N318Y, D320I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,6 +/- 0
444	Q1L, G4C, Q28R, E65M, A72C, D181N, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I	70,6 +/- 0,6
445	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, S311G, T335I, D346A, Q349K, T393I, Y422F, P442S, N445D, R446G, H468L, V482I	70,7 +/- 0,5
446	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, D247N, S311G, D320I, D346E, Q349K, T387S, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,7
447	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, P224L, S311G, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I	70,8 +/- 0,4
448	insertion at G434(AAATG), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,9
449	insertion at T457(AAATT), Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	70,9
450	Q1L, G4C, Q28K, E65V, A72C, S86T, E183K, S192L, D202N, D320N, T335I, D346A, Q349R, T393A, Y422F, P442S, R446G, H468R, V482A	71
451	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S236F, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	71
452	Q1L, G4C, Q28R, E65K, A72C, D202I, P224L, S311G, N318Y, D320V, T335I, D346A, Q349R, T392M, T393A, N445D, R446G, H468L	71,1
453	Q1L, G4C, E65M, A72C, S86T, E183V, D202I, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468L, V482A	71,1
454	Q1L, G4C, Q28R, E65V, A72C, K92R, D181N, E183M, P224L, I277V, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I	71,1
455	Q1L, G4C, A72C, S86T, D181N, E183K, D202V, P224L, S311G, D320V, D346E, Q349R, T393A, Y422F, P442S, N445D, R446G, H468L	71,1
456	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I	71,1 +/- 0
457	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, S192L, D202V, S311G, D320I, D346V, Q349R, T393A, Y422F, P442S, N445D, R446G, H468Q, V482I	71,1
458	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311N, N318Y, D320I, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T	71,2 +/- 0
459	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, D181N, E183M, D202N, T229M, S311G, A340S, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T	71,3

Example 9: Characterization of Variants of the *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion (with 6x His-Tag)

80 mL of fermentation broth were concentrated to a final volume of approx. 1mL. After determination of protein concentration (Bradford reagent, Biorad, Germany, Standard is BSA form Sigma-Aldrich, Germany) 1.2mg of protein were purified with the Ni-NTA Spin kit (Qiagen, Germany). The purified CBH1 fraction was subsequently assayed by performing a

hydrolysis reaction on pretreated (acid pretreatment) wheat straw. 12,5mg (dry mass) of pre-treated wheat straw is mixed with 0,0125mg of purified CBH1 and 40CBU Novo188 (Novozymes, Denmark) per mg of CBH1. 50mM sodium acetate (Sigma-Aldrich, Germany) is added up to 500µL. The assay is kept at temperatures ranging from 50°C to 65°C for 48 hours and analysed by HPLC to determine the temperature dependent glucose content.

Example 10: Hydrolysis of Straw with Seq. ID NO:2 Variant Proteins expressed from *Trichoderma reesei*

Selected cellobiohydrolase sequences (Table 7) are expressed from Trichoderma reesei as described in Example 5 by replacement of the native CBHI reading frame with the corresponding sequence fusions to the CBHI signal peptide. Samples of the mutant proteins are isolated from the culture supernatant and purified by Ni-NTA affinity chromatography. The characterization of the proteins is done by incubation of the proteins (E) with acid-pretreated straw substrate (S) (2,5% dry matter content and E/S = 0,1% w/w in the reaction) at temperatures between 50°C and 75°C for 48 hours in the presence of a non-limiting amount of beta-glucosidase followed by determination of the released glucose concentration by HPLC. The results are shown in the Table 7. As indication for the performance the glucose release after 48 hours at 60°C was taken and found significantly increased in comparison to the wild type protein. In the Table 7 the Temperatures where still 50% of the maximum glucose yield is reached are given.

Table 7: Performance of Trichoderma expressed Cellobiohydrolases on straw

	Mutation with respect to Seq. ID NO:2	Temperature [°C] of halve optimum sugar release from acid pretreated straw (48h 0,1% Enzyme to Substrate ratio (40 CBU/mg Cellulase BGL added)
1		59,3 ± 0,4
2	,Q1L,G4C,A72C,D181N,E183K,Q349R	61,3
3	,Q1L,G4C,A72C,Y155C,Q349K	64,3
4	,G4C,Q28K,E65M,A72C,S86T,E183M,D202N,P224L,S311G,T335I,D346E,Q349K,T393V,Y422F,P442S,N445D,R446G,H468L,V482I	73,0
5	,Q1L,G4C,Q28R,E65V,A72C,D181N,P224L,S311D,N318Y,D320N,D346A,Q349K,T392M,T393I,Y422F,N445D,R446G,H468Q,V482I	68,7
6	,Q1L,G4C,Q28R,E65V,A72C,D181N,E183M,P224L,S311G,D320I,D346E,Q349K,T393V,Y422F,P442	69,3

	S,N445D,R446G,H468L,V482I	
7	,Q1L,G4C,Q28R,E65V,A72C,E183M,D202N,P224L,S311G,N318Y,T335I,D346E,Q349K,T393V,Y422F,N445D,R446G,H468L,V482I	69,5
8	,Q1L,G4C,Q28R,E65V,A72C,S86T,E183K,D202N,S311G,N318Y,D320I,D346A,Q349K,T393V,Y422F,P442S,N445D,R446G,H468Q,V482I	67,5
9	,Q1L,G4C,Q28R,E65V,A72C,E183M,P224L,S311G,D320I,D346E,Q349K,T393V,Y422F,P442S,N445D,R446G,H468L,V482I	68,2
10	,Q1L,G4C,Q28R,E65V,A72C,P224L,S311G,D320I,D346E,Q349K,T393V,Y422F,P442S,N445D,R446G,H468L,V482I	68,4
11	,Q1L,G4C,Q28R,E65V,A72C,D202N,S311N,D320I,T335I,D346E,Q349K,T393V,Y422F,N445D,R446G,H468Q,V482T	67,8
12	,Q1L,G4C,Q28K,E65V,A72C,E183M,D202N,S311G,N318Y,D346E,Q349K,T393I,Y422F,N445D,R446G,H468Q,V482I	68,0
13	,Q2S,G4C,A6L,T7Q,A8S,N10T,Q28K,E65K,A72C,E183M,S311G,N318Y,D320I,T335I,D346E,Q349K,T393V,Y422F,N445D,R446G,H468Q,V482T	72,0
14	,Q2S,G4C,A6L,T7Q,A8S,N10T,Q28K,E65V,A72C,E183M,D202N,P224L,S311G,T335I,D346E,Q349K,T393V,Y422F,P442S,N445D,R446G,H468Q,V482I	73,8
15	,Q2S,G4C,A6L,T7Q,A8S,N10T,Q28R,E65V,A72C,P224L,S311D,N318Y,D320N,D346A,Q349K,T392M,T393I,Y422F,N445D,R446G,H468Q,V482I	73,6
16	,Q2S,G4C,A6L,T7Q,A8S,N10T,Q28K,N29Y,E65K,A72C,S311G,T335I,D346E,Q349K,T393V,Y422F,N445D,R446G,H468Q,V482T	71,9
17	,Q1L,G4C,Q28R,E65V,A72C,K159KCGRNK,E183M,P224L,S311G,D320I,D346E,Q349K,T393V,Y422F,T433TGAAAT,P442S,N445D,R446G,H468L,V482I	70,5

18	,Q2S,G4C,A6L,T7Q,A8S,N10T,S24T,Q28R,E65K,A72C,D202N,S311G,T335I,D346E,Q349K,T393I,Y422F,N445D,R446G,H468Q,V482T	72,2
19	,Q1L,G4C,Q28R,E65V,A72C,E183M,P224L,S311G,D320I,D346E,Q349K,T393V,Y422F,P442S,N445D,R446G,P454PVRPQP,H468L,V482I	69,1
20	,Q1L,G4C,Q28R,E65V,A72C,K159KCGRNK,E183M,P224L,S311G,D320I,D346E,Q349K,T393V,Y422F,P442S,N445D,R446G,H468L,V482I	68,2
21	,Q1L,G4C,S24T,T26I,Q28R,N29Y,G30A,E65V,A68T,A72C,E183M,Q190K,P224L,S311G,D320I,D346E,Q349K,T393V,Y422F,P442S,N445D,R446G,H468L,V482I	70,2
22	Seq ID No. 12	58,6 ± 0,4

Example 11: Performance of Seq. ID NO: 5 Variants with Improved thermostability

PCR-Techniques were user for the transfer of selected mutations into the Seq. ID NO:5 backbone, as deduced from screened Seq. ID NO: 2 Mutants with superior performance. Protein expressed from Pichia pastoris was taken from the culture supernatant and tested for their Substrate Conversion Capacity by the procedure given in example 8. In the table the calculated IT50 values for the 4-MUL Substrate are given. Slightly higher stability of Proteins without CBD compared to the fusion proteins are found under these conditions. Results are shown in Table 8.

Table 8: Comparison of IT50 Values of SEQ. ID NO:5 and SEQ. ID NO2 Mutants

	Mutation Pattern with respect to Seq. ID NO:5	**IT50 of the original Seq. ID NO:5 mutant**	**IT50 of the original Seq. ID NO:2 mutant**
1	wt	61,3	60,4 +/- 0,5
2	,G4C,Q28K,E65M,A72C,S86T,E183M,D202N,P224L,S311G,T335I,D346E,Q349K,T393V,Y422F	70,0	69,5
3	,Q1L,G4C,Q28R,E65V,A72C,D181N,E183M,P224L,S311G,D320I,D346E,Q349K,T393V,Y422F	72,0	69,8 +/- 0,8
4	,Q1L,G4C,Q28K,E65K,A72C,D181N,E183M,S311G,N318Y,D320I,T335I,D346E,Q349K,T393V,Y422F	70,3	70,1 +/- 0,2
5	,Q1L,G4C,Q28K,E65V,A72C,D181N,E18	71,9	71,1 +/- 0

	3M,D202N,P224L,S311G,T335I,D346E, Q349K,T393V,Y422F		
6	Q1L,G4C,Q28R,E65V,A72C,G151GCGR SG,D181N,E183M,P224L,S311G,D320I, D346E,Q349K,T393V,Y422F	72,7	68,2

Example 12: Influence of different cellulose binding domains on IT 50 values

To evaluate the interchangeability of the CBDs a stabilized Seq.ID NO: 5 mutant (Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F) is connected with a series of cellulose binding domains and linker regions from cellobiohydrolases from different sources by OE-PCR. The resulting coding sequences (SEQ. IDs NO: 21, 23, 25, 27 and 29) are cloned to a *Pichia pastoris* expression vector for the expression of the corresponding fusion proteins according to SEQ. IDs NO: 20, 22, 24, 26 and 28). IT50 values for the variants are evaluated as described before and are listed in the Table 9. Only small influences of different CBD modules on the stability are observed.

Table 9: Performance of different fusions of CBD with their linkers to stabilized and non-stabilized Seq. ID. NO:5 variants in comparison

	DNA Sequence Listing	Protein Sequence Listing	Origin of linker and CBD	IT50 [°C] (4-MUL Test)	Temperature [°C] of halve optimum sugar release from celluiose (48h 0,1% Enzyme to Substrate ratio (40 CBU/mg Cellulase BGL added)	Comment
1	1	2	*T. reesei*	60,4 +/- 0,5	57,4 +/- 0,5	non stabilized core (wild type)
2	21	20	*C. thermophilum*	69,5 +/- 0,5	65,6	
3	23	22	*P. chrysosporium*	69,3 +/- 0,2	65,6	
4	25	24	*P. janthinellum*	68,4 +/- 1,2	65,0	
5	27	26	*I. lacteus*	68,8 +/- 0,1	65,2	
6	29	28	*T. reesei*	69,8 +/- 0,8	65,0 +/- 0,7	stabilized core and CBD-linker region

Table 10: Sequence Listings (Overview)

SEQID	Nucleic acid [N]/Protein [P]	Description	ID
SEQID NO 01	[N]	Coding Sequence for *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion including the alpha factor signal peptide.	
SEQID NO 02	[P]	Mature Sequence of *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD	CBH-a
SEQID NO 03	[N]	Coding sequence of the fusion of CBH-a with *Trichoderma reesei* CBHI Signal peptide	
SEQID NO 04	[P]	*Trichoderma reesei* CBHI cellulose binding domain and linker sequence	
SEQID NO 05	[P]	*Talaromyces emersonii* CBHI	CBH-b
SEQID NO 06	[N]	*Talaromyces emersonii* CBHI	
SEQID NO 07	[N]	*Humicola grisea* CBHI	
SEQID NO 08	[P]	*Humicola grisea* CBHI	CBH-d
SEQID NO 09	[N]	*Thermoascus aurantiacus* CBHI	
SEQID NO 10	[P]	*Thermoascus aurantiacus* CBHI	CBH-e
SEQID NO 11	[N]	*Trichoderma reesei* CBHI	
SEQID NO 12	[P]	*Trichoderma reesei* CBHI	CBH-c
SEQID NO 13	[N]	*Trichoderma viridae* CBHI	
SEQID NO 14	[P]	*Trichoderma viridae* CBHI	CBH-f
SEQID NO 15	[N]	fusion *Humicola grisea* CBHI / *Trichoderma reesei* – CBD	
SEQID NO 16	[P]	fusion *Humicola grisea* CBHI / *Trichoderma reesei* – CBD	CBH-g
SEQID NO 17	[N]	Coding Sequence for *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD including the alpha factor signal peptide and a 6x His Tag.	
SEQID NO 18	[P]	Mature Sequence of *Talaromyces emersonii* CBHI / *Trichoderma reesei* –CBD fusion peptide with 6x His Tag	CBH-ah
SEQID NO 19	[N]	*Humicola grisea* CBHI, alternative coding sequence	
SEQ ID NO: 20 to 41	[N]	Oligonucleotide primers used with this invention	
SEQID NO 42	[P]	*Talaromyces emersonii* CBHI Mutant with Chaetmium thermophilum cellobiohydrolase I CBD	

		with 6x His-TAG	
SEQID NO 43	[N]	Coding Sequence for *Talaromyces emersonii* CBHI with 6x His-TAG Mutant with Chaetmium thermophilum cellobiohydrolase I CBD	
SEQID NO 44	[P]	*Talaromyces emersonii* CBHI Mutant with *Phanerochaete chrysosporium* cellobiohydrolase CBD with 6x His-TAG	
SEQID NO 45	[N]	Coding Sequence for *Talaromyces emersonii* CBHI Mutant with *Phanerochaete chrysosporium* cellobiohydrolase CBD with 6x His-TAG	
SEQID NO 46	[P]	*Talaromyces emersonii* CBHI Mutant with *Penicillium jantinellum* cellobiohydrolase CBD with 6x His-TAG	
SEQID NO 47	[N]	Coding Sequence for *Talaromyces emersonii* CBHI Mutant with *Penicillium jantinellum* cellobiohydrolase CBD with 6x His-TAG	
SEQID NO 48	[P]	*Talaromyces emersonii* CBHI Mutant with *Irpex lacteus* cellobiohydrolase CBD with 6x His-TAG	
SEQID NO 49	[N]	Coding Sequence for *Talaromyces emersonii* CBHI Mutant with *Irpex lacteus* cellobiohydrolase CBD with 6x His-TAG	
SEQID NO 50	[P]	*Talaromyces emersonii* CBHI Mutant with mutated *Trichoderma reesei* CBD with 6x His-TAG	
SEQID NO51	[N]	Coding Sequence for *Talaromyces emersonii* CBHI Mutant with mutated *Trichoderma reesei* CBD with 6x His-TAG	

SEQID.NO. 01

cagcaggccggcacggcgacggcagagaaccacccgcccctgacatggcaggaatgcaccgcccctgggagctgc
accacccagaacggggcggtcgttcttgatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgc
tacacgggcaatacctgggaccccacgtactgccctgacgacgaaacctgcgcccagaactgtgcgctggacggc
gcggattacgagggcacctacggcgtgacttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaac
gtcggatcccgtctctacctgctgcaggacgactcgacctatcagatcttcaagctcctgaaccgcgagttcagc
tttgacgtcgatgtctccaatcttccgtgcggattgaacggcgctctgtactttgtcgccatggacgccgacggc
ggcgtgtccaagtacccgaacaacaaggctggtgccaagtacggaaccgggtattgcgactcccaatgcccacgg
gacctcaagttcatcgacggcgaggccaacgtcgagggctggcagccgtcttcgaacaacgccaacaccggaatt
ggcgaccacggctcctgctgtgcggagatggatgtctgggaagcaaacagcatctccaatgcggtcactccgcac
ccgtgcgacacgccaggccagacgatgtgctctggagatgactgcggtggcacatactctaacgatcgctacgcg
ggaacctgcgatcctgacggctgtgacttcaacccttaccgcatgggcaacacttctttctacgggcctggcaag
atcatcgataccaccaagcccttcactgtcgtgacgcagttcctcactgatgatggtacggatactggaactctc
agcgagatcaagcgcttctacatccagaacagcaacgtcattccgcagcccaactcggacatcagtggcgtgacc
ggcaactcgatcacgacggagttctgcactgctcagaagcaggcctttggcgacacggacgacttctctcagcac
ggtggcctggccaagatgggagcggccatgcagcagggtatggtcctggtgatgagtttgtgggacgactacgcc
gcgcagatgctgtggttggattccgactacccgacggatgcggaccccacgacccctggtattgcccgtggaacg
tgtccgacggactcgggcgtcccatcggatgtcgagtcgcagagccccaactcctacgtgacctactcgaacatt
aagtttggtccgatcggtagcacaggtaatccttcaggtggtaatcctccaggtggaaacagaggaacaacgaca

actagaagaccagctactacaactggttcaagtccaggtccaactcaatcacactacggtcaatgtggtggtata
ggttactctggtcccactgtttgtgcttctggtactacttgccaagttctgaacccttactactcacagtgtcta
taatgataa

Coding Sequence for CBH-a (mature)

SEQID.NO. 02

QQAGTATAENHPPLTWQECTAPGSCTTQNGAVVLDANWRWVHDVNGYTNCYTGNTWDPTYCPDDETCAQNCALDG
ADYEGTYGVTSSGSSLKLNFVTGSNVGSRLYLLQDDSTYQIFKLLNREFSFDVDVSNLPCGLNGALYFVAMDADG
GVSKYPNNKAGAKYGTGYCDSQCPRDLKFIDGEANVEGWQPSSNNANTGIGDHGSCCAEMDVWEANSISNAVTPH
PCDTPGQTMCSGDDCGGTYSNDRYAGTCDPDGCDFNPYRMGNTSFYGPGKIIDTTKPFTVVTQFLTDDGTDTGTL
SEIKRFYIQNSNVIPQPNSDISGVTGNSITTEFCTAQKQAFGDTDDFSQHGGLAKMGAAMQQGMVLVMSLWDDYA
AQMLWLDSDYPTDADPTTPGIARGTCPTDSGVPSDVESQSPNSYVTYSNIKFGPIGSTGNPSGGNPPGGNRGTTT
TRRPATTTGSSPGPTQSHYGQCGGIGYSGPTVCASGTTCQVLNPYYSQCL

Mature Sequence of CBH-a

SEQID.NO. 03

atgtatcggaagttggccgtcatctcggccttcttggccacagctcgtgctcagcaggccggcacggcgacggca
gagaaccacccgcccctgacatggcaggaatgcaccgcccctgggagctgcaccacccagaacggggcggtcgtt
cttgatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgctacacgggcaatacctgggacccc
acgtactgccctgacgacgaaacctgcgcccagaactgtgcgctggacggcgcggattacgagggcacctacggc
gtgacttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaacgtcggatcccgtctctacctgctg
caggacgactcgacctatcagatcttcaagctcctgaaccgcgagttcagctttgacgtcgatgtctccaatctt
ccgtgcggattgaacggcgctctgtactttgtcgccatggacgccgacggcggcgtgtccaagtacccgaacaac
aaggctggtgccaagtacggaacccgggtattgcgactcccaatgcccacgggacctcaagttcatcgacggcgag
gccaacgtcgagggctggcagccgtcttcgaacaacgccaacaccggaattggcgaccacggctcctgctgtgcg
gagatggatgtctgggaagcaaacagcatctccaatgcggtcactccgcacccgtgcgacacgccaggccagacg
atgtgctctggagatgactgcggtggcacatactctaacgatcgctacgcgggaacctgcgatcctgacggctgt
gacttcaacccttaccgcatgggcaacacttctttctacgggcctggcaagatcatcgataccaccaagcccttc
actgtcgtgacgcagttcctcactgatgatggtacggatactggaactctcagcgagatcaagcgcttctacatc
cagaacagcaacgtcattccgcagcccaactcggacatcagtggcgtgaccggcaactcgatcacgacggagttc
tgcactgctcagaagcaggcctttggcgacacggacgacttctctcagcacggtggcctggccaagatgggagcg
gccatgcagcagggtatggtcctggtgatgagtttgtgggacgactacgccgcgcagatgctgtggttggattcc
gactacccgacggatgcggaccccacgacccctggtattgcccgtggaacgtgtccgacggactcgggcgtccca
tcggatgtcgagtcgcagagccccaactcctacgtgacctactcgaacattaagtttggtccgatcggtagcaca
ggtaatccttcaggtggtaatcctccaggtggaaacagaggaacaacgacaactagaagaccagctactacaact
ggttcaagtccaggtccaactcaatcacactacggtcaatgtggtggtataggttactctggtcccactgtttgt
gcttctggtactacttgccaagttctgaacccttactactcacagtgtctagcttctgcacatcatcaccaccac
cattaa

Coding sequence of the fusion of CBH-a with *Trichoderma reesei* CBHI Signal peptide

SEQID.NO. 04

GSTGNPSGGNPPGGNRGTTTTRRPATTTGSSPGPTQSHYGQCGGIGYSGPTVCASGTTCQVLNPYYSQCL

Trichoderma reesei CBHI cellulose binding domain and linker sequence

SEQID.NO. 05

QQAGTATAENHPPLTWQECTAPGSCTTQNGAVVLDANWRWVHDVNGYTNCYTGNTWDPTYCPDDETCAQNCALDG
ADYEGTYGVTSSGSSLKLNFVTGSNVGSRLYLLQDDSTYQIFKLLNREFSFDVDVSNLPCGLNGALYFVAMDADG
GVSKYPNNKAGAKYGTGYCDSQCPRDLKFIDGEANVEGWQPSSNNANTGIGDHGSCCAEMDVWEANSISNAVTPH
PCDTPGQTMCSGDDCGGTYSNDRYAGTCDPDGCDFNPYRMGNTSFYGPGKIIDTTKPFTVVTQFLTDDGTDTGTL

SEIKRFYIQNSNVIPQPNSDISGVTGNSITTEFCTAQKQAFGDTDDFSQHGGLAKMGAAMQQGMVLVMSLWDDYA
AQMLWLDSDYPTDADPTTPGIARGTCPTDSGVPSDVESQSPNSYVTYSNIKFGPINSTFTAS

Talaromyces emersonii CBHI sequence (CBH-b)

SEQID.NO. 06

atgagatttccttcaatttttactgcagttttattcgcagcatcctccgcattagctgctccagtcaacactaca
acagaagatgaaacggcacaaattccggctgaagctgtcatcggttacttagatttagaaggggatttcgatgtt
gctgttttgccatttttccaacagcacaaataacgggttattgtttataaatactactattgccagcattgctgct
aaagaagaaggggtatctttggataaacgtgaggcggaagcaccctctcagcaggccggcacggcgacggcagag
aaccacccgcccctgacatggcaggaatgcaccgcccctgggagctgcaccacccagaacggggcggtcgttctt
gatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgctacacgggcaatacctgggaccccacg
tactgccctgacgacgaaacctgcgcccagaactgtgcgctggacggcgcggattacgagggcacctacggcgtg
acttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaacgtcggatcccgtctctacctgctgcag
gacgactcgacctatcagatcttcaagcttctgaaccgcgagttcagctttgacgtcgatgtctccaatcttccg
tgcggattgaacggcgctctgtactttgtcgccatggacgccgacggcggcgtgtccaagtacccgaacaacaag
gctggtgccaagtacggaaccgggtattgcgactcccaatgcccacgggacctcaagttcatcgacggcgaggcc
aacgtcgagggctggcagccgtcttcgaacaacgccaacaccggaattggcgaccacggctcctgctgtgcggag
atggatgtctgggaagcaaacagcatctccaatgcggtcactccgcacccgtgcgacacgccaggccagacgatg
tgctctggagatgactgcggtggcacatactctaacgatcgctacgcgggaacctgcgatcctgacggctgtgac
ttcaacccttaccgcatgggcaacacttctttctacgggcctggcaagatcatcgataccaccaagcccttcact
gtcgtgacgcagttcctcactgatgatggtacggatactggaactctcagcgagatcaagcgcttctacatccag
aacagcaacgtcattccgcagcccaactcggacatcagtggcgtgaccggcaactcgatcacgacggagttctgc
actgctcagaagcaggcctttggcgacacggacgacttctctcagcacggtggcctggccaagatgggagcggcc
atgcagcagggtatggtcctggtgatgagtttgtgggacgactacgccgcgcagatgctgtggttggattccgac
tacccgacggatgcggaccccacgacccctggtattgcccgtggaacgtgtccgacggactcgggcgtcccatcg
gatgtcgagtcgcagagccccaactcctacgtgacctactcgaacattaagtttggtccgatcaactcgaccttc
accgcttcgtgataa

Coding sequence of *Talaromyces emersonii* CBHI fused to the alpha factor signal peptide

SEQID.NO. 07

QQAGTITAENHPRMTWKRCSGPGNCQTVQGEVVIDANWRWLHNNGQNCYEGNKWTSQCSSATDCAQRCALDGANY
QSTYGASTSGDSLTLKFVTKHEYGTNIGSRFYLMANQNKYQMFTLMNNEFAFDVDLSKVECGINSALYFVAMEED
GGMASYPSNRAGAKYGTGYCDAQCARDLKFIGGKANIEGWRPSTNDPNAGVGPMGACCAEIDVWESNAYAYAFTP
HACGSKNRYHICETNNCGGTYSDDRFAGYCDANGCDYNPYRMGNKDFYGKGKTVDTNRKFTVVSRFERNRLSQFF
VQDGRKIEVPPPTWPGLPNSADITPELCDAQFRVFDDRNRFAETGGFDALNEALTIPMVLVMSIWDDHHSNMLWL
DSSYPPEKAGLPGGDRGPCPTTSGVPAEVEAQYPDAQVVWSNIRFGPIGSTVNV

Humicola grisea CBHI (CBH-d)

SEQID.NO. 08

atgagatttccttcaatttttactgcagttttattcgcagcatcctccgcattagctgctccagtcaacactaca
acagaagatgaaacggcacaaattccggctgaagctgtcatcggttacttagatttagaaggggatttcgatgtt
gctgttttgccatttttccaacagcacaaataacgggttattgtttataaatactactattgccagcattgctgct
aaagaagaaggggtatctttggataaacgtgaggcggaagcaccctctcagcaggctggtactattactgctgag
aaccacccaagaatgacctggaagagatgctctggtccaggaaactgtcagactgttcagggcgaggttgtgatt
gacgctaattggagatggttgcacaacaacggccagaactgttacgagggtaacaagtggacctctcagtgttct
tctgctaccgactgtgctcagagatgtgctttggacggtgccaactaccagtctacctacggtgcttctacctct
ggtgactctctgaccctgaagttcgttaccaagcacgagtacggaaccaacatcggctctagattctacctgatg
gccaaccagaacaagtaccagatgttcaccctgatgaacaacgagttcgcctttgacgttgacctgtctaaggtg
gagtgcggtatcaactctgccctgtacttcgttgctatggaagaggacggtggaatggcttcttacccatctaac
agagccggtgctaagtacggtactggttactgtgacgcccagtgtgctagagacctgaagttcatcggtggaaag
gccaacattgagggttggagaccatctaccaacgacccaaacgctggtgttggtccaatgggagcttgttgtgcc
gagattgatgtgtgggagtctaacgcttacgcctacgcttttaccccacacgcttgcggttctaagaacagatac
cacatctgcgagaccaacaactgtggtggaacctactctgacgacagattcgctggatactgcgacgctaacggt

tgtgactacaacccatacagaatgggcaacaaggacttctacggcaagggaaagaccgttgacaccaacagaaag
ttcaccgtggtgtcgagattcgagagaaacagactgtcgcagttctttgtgcaggacggcagaaagattgaggtc
ccaccaccaacttggccaggattgccaaactctgccgacattaccccagagttgtgtgacgctcagttcagagtg
ttcgacgacagaaacagatttgctgagaccggtggttttgacgctttgaacgaggctctgaccattccaatggtg
ctggtgatgtctatttgggacgaccaccactctaacatgttgtggctggactcttcttacccaccagagaaggct
ggattgccaggtggtgacagaggaccatgtccaactacttcgggtgttccagctgaggttgaggctcagtaccca
gacgctcaggttgtgtggtcgaacatcagattcggcccaatcggttctaccgtgaacgtgtaa

Coding sequence of *Humicola grisea* CBHI fused to the alpha factor signal peptide

SEQID.NO. 09

heagtvtaenhpsltwqqcssggscttqngkvvidanwrwvhttsgytncytgntwdtsicpddvtcaqncaldg
adysgtygvttsgnalrlnfvtqssgknigsrlyllqddttyqifkllgqeftfdvdvsnlpcglngalyfvamd
adgnlskypgnkagakygtgycdsqcprdlkfingqanvegwqpsandpnagvgnhgsscaemdvweansistav
tphpcdtpgqtmcqgddcggtysstryagtcdtdgcdfnpyqpgnhsfygpgkivdtsskftvvtqfitddgtps
gtlteikrfyvqngkvipqsestisgvtgnsitteyctaqkaafdntgffthgglqkisgalaqgmvlvmslwdd
haanmlwldstyptdadpdtpgvargtcpttsgvpadvesqnpnsyviysnikvgpinstftan

Thermoascus auratiacus CBHI (CBH-e)

SEQID.NO. 10

atgagatttccttcaatttttactgcagttttattcgcagcatcctccgcattagctgctccagtcaacactaca
acagaagatgaaacggcacaaattccggctgaagctgtcatcggttacttagatttagaaggggatttcgatgtt
gctgttttgccatttttccaacagcacaaataacgggttattgtttataaatactactattgccagcattgctgct
aaagaagaaggggtatctttggataaacgtgaggcggaagcaccctctcacgaggccggtaccgtaaccgcagag
aatcacccttccctgacctggcagcaatgctccagcggcggtagttgtaccacgcagaatggaaaagtcgttatc
gatgcgaactggcgttgggtccataccacctctggatacaccaactgctacacgggcaatacgtgggacaccagt
atctgtcccgacgacgtgacctgcgctcagaattgtgccttggatggagcggattacagtggcacctatggtgtt
acgaccagtggcaacgccctgagactgaactttgtcacccaaagctcagggaagaacattggctcgcgcctgtac
ctgctgcaggacgacaccacttatcagatcttcaagctgctgggtcaggagtttaccttcgatgtcgacgtctcc
aatctcccttgcgggctgaacggcgccctctactttgtggccatggacgccgacggcaatttgtccaaataccct
ggcaacaaggcaggcgctaagtatggcactggttactgcgactctcagtgccctcgggatctcaagttcatcaac
ggtcaggccaacgttgaaggctggcagccgtctgccaacgacccaaatgccggcgttggtaaccacggttcctcg
tgcgctgagatggatgtctgggaagccaacagcatctctactgcggtgacgcctcacccatgcgacacccccggc
cagaccatgtgccagggagacgactgtggtggaacctactcctccactcgatatgctggtacctgcgacactgat
ggctgcgacttcaatccttaccagccaggcaaccactcgttctacggccccgggaagatcgtcgacactagctcc
aaattcaccgtcgtcacccagttcatcaccgacgacgggacaccctccggcaccctgacggagatcaaacgcttc
tacgtccagaacggcaaggtgatcccccagtcggagtcgacgatcagcggcgtcaccggcaactcaatcaccacc
gagtattgcacggcccagaaggcagccttcgacaacaccggcttcttcacgcacggcgggcttcagaagatcagt
caggctctggctcagggcatggtcctcgtcatgagcctgtgggacgatcacgccgccaacatgctctggctggac
agcacctacccgactgatgcggacccggacaccccctggcgtcgcgcgcggtacctgccccacgacctccggcgtc
ccggccgacgtggagtcgcagaaccccaattcatatgttatctactccaacatcaaggtcggacccatcaactcg
accttcaccgccaactaa

Coding sequence of *Thermoascus auratiacus* CBHI fused to the alpha factor signal peptide

SEQID.NO. 11

atgagatttccttcaatttttactgcagttttattcgcagcatcctccgcattagctgctccagtcaacactaca
acagaagatgaaacggcacaaattccggctgaagctgtcatcggttacttagatttagaaggggatttcgatgtt
gctgttttgccatttttccaacagcacaaataacgggttattgtttataaatactactattgccagcattgctgct
aaagaagaaggggtatctttggataaacgtgaggcggaagcaccctcttcagcttgtacactgcaatccgagact
catccacctttaacgtggcaaaagtgtagttctggcggaacttgtactcaacagactggtagtgtcgtgatagat
gctaactggagatggacacatgcaacgaactcctcaactaactgctacgatggtaacacctggtcttctacattg
tgtcctgacaacgaaacctgcgctaagaactgttgtcttgatggagcagcttacgcaagtacatatggtgtgact
acctctggtaacagcctttccattggttttgtaacccagtcggctcagaagaatgttggtgctagattgtacctg

atggcttcagacaccacataccaggagtttaccttgttgggaaacgagttctctttcgacgtagatgtgtctcag
ctaccatgtggattgaatggagccttgtactttgtctcaatggatgcagacggaggtgtttcaaagtaccctact
aacacagctggtgctaagtatggaactggatactgcgattctcaatgcccaagagacctgaagttcatcaacgga
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gaaatttgcgaaggtgatggttgtggtggcacttactctgataacagatacggcggaacatgtgatccagatgga
tgtgattggaacccatacagactgggtaacacttcgttttacggaccaggttcttccttcactctagacactacg
aagaagttgactgtggtcacccaatttgagacttctggtgccattaaccgatactacgtgcagaacggagttact
ttccaacagccaaacgctgaattgggtagttactcaggcaacgagcttaacgatgactactgcactgctgaagaa
gcagaatttggtggatcttccttttcggataagggtggattgacgcagttcaagaaagctacctctggtggaatg
gttctagtcatgagtctgtgggacgattactacgctaacatgctttggctggactctacttaccctacaaacgag
acatcttctactcctggtgctgtaagaggtagctgttctacatcttctggagttccagcccaagttgagagtcaa
agtccaaatgccaaggtcaccttctccaacatcaagttcggaccaattggtagcacaggtaatccttcaggtggt
aatcctccaggtggaaacagaggaacaacgacaactagaagaccagctactacaactggttcaagtccaggtcca
actcaatcacactacggtcaatgtggtggtataggttactctggtcccactgtttgtgcttctggtactacttgc
caagttctgaacccttactactcacagtgtctagcttctgcacaccatcatcatcatcattaatgataa

Coding sequence for *Trichoderma reesei* CBHI (CBH-c), including the alpha factor signal peptide and a 6x His Tag.

SEQID.NO. 12

QSACTLQSETHPPLTWQKCSSGGTCTQQTGSVVIDANWRWTHATNSSTNCYDGNTWSSTLCPDNETCAKNCCLDG
AAYASTYGVTTSGNSLSIGFVTQSAQKNVGARLYLMASDTTYQEFTLLGNEFSFDVDVSQLPCGLNGALYFVSMD
ADGGVSKYPTNTAGAKYGTGYCDSQCPRDLKFINGQANVEGWEPSSNNANTGIGGHGSCCSEMDIWEANSISEAL
TPHPCTTVGQEICEGDGCGGTYSDNRYGGTCDPDGCDWNPYRLGNTSFYGPGSSFTLDTTKKLTVVTQFETSGAI
NRYYVQNGVTFQQPNAELGSYSGNELNDDYCTAEEAEFGGSSFSDKGGLTQFKKATSGGMVLVMSLWDDYYANML
WLDSTYPTNETSSTPGAVRGSCSTSSGVPAQVESQSPNAKVTFSNIKFGPIGSTGNPSGGNPPGGNRGTTTTRRP
ATTTGSSPGPTQSHYGQCGGIGYSGPTVCASGTTCQVLNPYYSQCL

Trichoderma reesei CBHI (CBH-c)

SEQID.NO. 13

atgagatttccttcaatttttactgcagttttattcgcagcatcctccgcattagctgctccagtcaacactaca
acagaagatgaaacggcacaaattccggctgaagctgtcatcggttacttagatttagaaggggatttcgatgtt
gctgttttgccatttttccaacagcacaaataacgggttattgtttataaatactactattgccagcattgctgct
aaagaagaaggggtatctttggataaacgtgaggcggaagcaccctctcaatctgcttgcaccttgcagtctgaa
actcacccaccattgacctggcagaagtgttcttctggcggtacttgtactcagcagaccggttctgttgttatc
gacgccaactggagatggactcacgctaccaactcttctaccaactgctacgacggtaacacttggtcgtctacc
ttgtgtccagacaacgagacctgtgccaagaactgttgtttggacggtgctgcttacgcttctacctacggtgtt
accacctctggtaactcgctgtctatcggtttcgttacccagtctgcccagaaaaatgttggtgccagactgtac
ttgatggcttctgacaccacctaccaagagtttaccctgctgggtaacgagttctctttcgacgtggacgtttct
caactgccatgtggactgaacggtgccctgtacttcgtttctatggacgctgacggtggtgtttctaagtaccca
accaacaccgctggtgctaaatacggaaccggttactgcgattctcagtgcccaagagacctgaagttcatcaac
ggacaggctaacgttgaaggatgggagccatcttctaacaacgccaacaccggtattggtggtcacggttcttgc
tgttctgagatggacatctgggaggccaactctatttctgaggctttgaccccacacccatgtactactgtgggt
caagagatctgtgagggtgatggttgtggtggtacttactcggacaacagatacggtggtacttgtgacccagac
ggttgtgattgggacccatacagactgggtaacacctctttctacggtccaggatcttctttttaccctggacacc
accaagaagttgaccgttgttacccagtttgagacctctggtgccatcaacagatactacgtgcagaacggtgtt
actttccagcagccaaacgctgaactgggatcttactctggtaacggactgaacgacgactactgtactgctgag
gaagctgagttcggtggttcttctttctctgacaagggtggactgacccagtttaagaaggctacctctggcgga
atggtgctggttatgtctttgtgggacgactactacgctaacatgctgtggcttgactctacctacccaactaac
gagacctcttctaccccaggtgctgttagaggatcttgctctacctcttctggtgttccagctcaggttgagtct
cagtctccaaacgccaaggtgaccttctctaacatcaagttcggtccaatcggttctactggtgacccatctggt
ggtaacccaccaggtggaaacccacctggtactaccactaccagaagaccagctaccaccactggttcttctcca
ggtccaacccaatctcactacggtcagtgtggtggtattggttactctggtccaaccgtttgtgcttctggaacc
acctgtcaggttctgaacccatactactcgcagtgcctgtaa

Coding sequence for *Trichoderma viride* CBHI, including the alpha factor signal peptide.

SEQID.NO. 14

QSACTLQSETHPPLTWQKCSSGGTCTQQTGSVVIDANWRWTHATNSSTNCYDGNTWSSTLCPDNETCAKNCCLDG
AAYASTYGVTTSGNSLSIGFVTQSAQKNVGARLYLMASDTTYQEFTLLGNEFSFDVDVSQLPCGLNGALYFVSMD
ADGGVSKYPTNTAGAKYGTGYCDSQCPRDLKFINGQANVEGWEPSSNNANTGIGGHGSCCSEMDIWEANSISEAL
TPHPCTTVGQEICEGDGCGGTYSDNRYGGTCDPDGCDWDPYRLGNTSFYGPGSSFTLDTTKKLTVVTQFETSGAI
NRYYVQNGVTFQQPNAELGSYSGNGLNDDYCTAEEAEFGGSSFSDKGGLTQFKKATSGGMVLVMSLWDDYYANML
WLDSTYPTNETSSTPGAVRGSCSTSSGVPAQVESQSPNAKVTFSNIKFGPIGSTGDPSGGNPPGGNPPGTTTTRR
PATTTGSSPGPTQSHYGQCGGIGYSGPTVCASGTTCQVLNPYYSQCL

Trichoderma viride CBHI (CBH-f)

SEQID.NO. 15

atgagatttccttcaatttttactgcagttttattcgcagcatcctccgcattagctgctccagtcaacactaca
acagaagatgaaacggcacaaattccggctgaagctgtcatcggttacttagatttagaaggggatttcgatgtt
gctgttttgccatttccaacagcacaaataacgggttattgtttataaatactactattgccagcattgctgct
aaagaagaaggggtatctttggataaacgtgaggcggaagcatgctcgcagcaggctggtacaattactgctgag
aaccatccaagaatgacgtggaagagatgtagtggtccaggaaactgtcagactgttcagggtgaggtcgtgata
gatgctaactggagatggttgcataacaacggccagaactgctacgagggtaacaagtggacctctcagtgttct
tctgctaccgactgcgctcagagatgtgctcttgatggagcaaactaccagagtacatatggtgcttctacctct
ggtgacagccttaccctgaagtttgtaaccaagcacgagtacggaaccaatatcggttctagattctacctgatg
gctaaccagaacaagtaccagatgtttaccttgatgaacaacgagttcgccttcgacgtagatctgtctaaggtg
gagtgtggaatcaattctgccttgtactttgtcgctatggaagaggacggaggtatggcttcttacccttctaac
agagctggtgctaagtatggaactggatactgcgatgcccaatgcgctagagacctgaagttcatcggtggaaag
gctaacattgaaggttggagaccttctaccaacgacccaaacgctggagttggtccaatgggtgcttgctgtgcc
gagattgacgtgtgggaatctaacgcttacgcctacgcttttactccacatgcttgcggttctaagaacagatac
cacatttgcgaaaccaacaactgtggtggcacttactctgatgacagattcgctggatactgtgatgctaacgga
tgtgattacaacccatacagaatgggtaacaaggacttttacggaaagggtaagactgttgacactaacagaaag
ttcactgtggtctcgagatttgagagaaacagactgtcgcagttctttgtgcaggacggaagaaagattgaggtc
ccaccaccaacttggccaggattgccaaactctgccgacattaccccagagttgtgcgacgctcagttcagagtg
tttgacgacagaaacagatttgctgagaccggtggatttgacgctttgaacgaggctctgaccattccaatggtt
ctagtcatgagtatttgggacgatcaccactctaacatgctttggctggactcttcttaccctccagagaaggct
ggattgcctggtggtgacagaggtccatgtccaacaacttctggagttccagccgaggttgaggctcaataccca
gacgcccaggtcgtgtggtccaacatcagattcggaccaattggaagcttaacaggtaatccttcaggtggtaat
cctccaggtggaaacagaggaacaacgacaactagaagaccagctactacaactggttcaagtccaggtccaact
caatcacactacggtcaatgtggtggtataggttactctggtcccactgtttgtgcttctggtactacttgccaa
gttctgaaccccttactactcacagtgtctagcttctgcacaccatcatcatcatcattaa

Coding Sequence for *Humicola grisea* CBHI- *Trichoderma reesei* CBHI cellulose binding domain fusion protein including the alpha factor signal peptide and a 6x His Tag.

SEQID.NO. 16

qqagtitaenhprmtwkrcsgpgncqtvqgevvidanwrwlhnngqncyegnkwtsqcssatdcaqrcaldgany
qstygastsgdsltlkfvtkheygtnigsrfylmanqnkyqmftlmnnefafdvdlskvecginsalyfvameed
ggmasypsnragakygtgycdaqcardlkfiggkaniegwrpstndpnagvgpmgaccaeidvwesnayayaftp
hacgsknryhicetnncggtysddrfagycdangcdynpyrmgnkdfygkgktvdtnrkftvvsrfernrlsqff
vqdgrkievppptwpglpnsaditpelcdaqfrvfddrnrfaetggfdalnealtipmvlvmsiwddhhsnmlwl
dssyppekaglpggdrgpcpttsgvpaeveaqypdaqvvwsnirfgpigsltgnpsggnppggnrgttttrrpat
ttgsspgptqshygqcggigysgptvcasgttcqvlnpyysqclasahhhhhh

Humicola grisea CBHI- *Trichoderma reesei* CBHI cellulose binding domain fusion protein including a 6x His Tag (CBH-g)

SEQID.NO. 17

atgagatttccttcaatttttactgcagttttattcgcagcatcctccgcattagctgctccagtcaacactaca
acagaagatgaaacggcacaaattccggctgaagctgtcatcggttacttagatttagaaggggatttcgatgtt
gctgttttgccatttccaacagcacaaataacgggttattgtttataaatactactattgccagcattgctgct
aaagaagaaggggtatctttggataaacgtgaggcggaagcatgctcgcagcaggccggcacggcgacggcagag
aaccacccgcccctgacatggcaggaatgcaccgcccctgggagctgcaccacccagaacggggcggtcgttctt
gatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgctacacgggcaatacctgggaccccacg
tactgccctgacgacgaaacctgcgcccagaactgtgcgctggacggcgcggattacgagggcacctacggcgtg
acttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaacgtcggatcccgtctctacctgctgcag
gacgactcgacctatcagatcttcaagctcctgaaccgcgagttcagctttgacgtcgatgtctccaatcttccg
tgcggattgaacggcgctctgtactttgtcgccatggacgccgacggcggcgtgtccaagtacccgaacaacaag
gctggtgccaagtacggaaccgggtattgcgactcccaatgcccacgggacctcaagttcatcgacggcgaggcc
aacgtcgagggctggcagccgtcttcgaacaacgccaacaccggaattggcgaccacggctcctgctgtgcggag
atggatgtctgggaagcaaacagcatctccaatgcggtcactccgcacccgtgcgacacgccaggccagacgatg
tgctctggagatgactgcggtggcacatactctaacgatcgctacgcgggaacctgcgatcctgacggctgtgac
ttcaaccttaccgcatgggcaacacttctttctacgggcctggcaagatcatcgataccaccaagcccttcact
gtcgtgacgcagttcctcactgatgatggtacggatactggaactctcagcgagatcaagcgcttctacatccag
aacagcaacgtcattccgcagcccaactcggacatcagtggcgtgaccggcaactcgatcacgacggagttctgc
actgctcagaagcaggcctttggcgacacggacgacttctctcagcacggtggcctggccaagatgggagcggcc
atgcagcagggtatggtcctggtgatgagtttgtgggacgactacgccgcgcagatgctgtggttggattccgac
tacccgacggatgcggaccccacgacccctggtattgcccgtggaacgtgtccgacggactcgggcgtcccatcg
gatgtcgagtcgcagagccccaactcctacgtgacctactcgaacattaagtttggtccgatcggtagcacaggt
aatccttcaggtggtaatcctccaggtggaaacagaggaacaacgacaactagaagaccagctactacaactggt
tcaagtccaggtccaactcaatcacactacggtcaatgtggtggtataggttactctggtcccactgtttgtgct
tctggtactacttgccaagttctgaacccttactactcacagtgtctagcttctgcacatcatcaccaccaccat
taatgataa

Coding sequence for *Talaromyces emersonii* CBHI / *Trichoderma reesei* -CBD fusion including the alpha factor signal peptide and a 6x His Tag.

SEQID.NO. 18

QQAGTATAENHPPLTWQECTAPGSCTTQNGAVVLDANWRWVHDVNGYTNCYTGNTWDPTYCPDDETCAQNCALDG
ADYEGTYGVTSSGSSLKLNFVTGSNVGSRLYLLQDDSTYQIFKLLNREFSFDVDVSNLPCGLNGALYFVAMDADG
GVSKYPNNKAGAKYGTGYCDSQCPRDLKFIDGEANVEGWQPSSNNANTGIGDHGSCCAEMDVWEANSISNAVTPH
PCDTPGQTMCSGDDCGGTYSNDRYAGTCDPDGCDFNPYRMGNTSFYGPGKIIDTTKPFTVVTQFLTDDGTDTGTL
SEIKRFYIQNSNVIPQPNSDISGVTGNSITTEFCTAQKQAFGDTDDFSQHGGLAKMGAAMQQGMVLVMSLWDDYA
AQMLWLDSDYPTDADPTTPGIARGTCPTDSGVPSDVESQSPNSYVTYSNIKFGPIGSTGNPSGGNPPGGNRGTTT
TRRPATTTGSSPGPTQSHYGQCGGIGYSGPTVCASGTTCQVLNPYYSQCLASAHHHHHH

Mature Sequence of *Talaromyces emersonii* CBHI / *Trichoderma reesei* -CBD fusion with 6x-His tag (CBH-ah)

SEQID.NO 19

atggccagcgatctggcacagcaggctggtacaattactgctgagaaccatccaagaatgacgtggaagagatgt
agtggtccaggaaactgtcagactgttcagggtgaggtcgtgatagatgctaactggagatggttgcataacaac
ggccagaactgctacgagggtaacaagtggacctctcagtgttcttctgctaccgactgcgctcagagatgtgct
cttgatggagcaaactaccagagtacatatggtgcttctacctctggtgacagccttaccctgaagtttgtaacc
aagcacgagtacggaaccaatatcggttctagattctacctgatggctaaccagaacaagtaccagatgtttacc
ttgatgaacaacgagttcgccttcgacgtagatctgtctaaggtggagtgtggaatcaattctgccttgtacttt
gtcgctatggaagaggacggaggtatggcttcttacccttctaacagagctggtgctaagtatggaactggatac
tgcgatgcccaatgcgctagagacctgaagttcatcggtggaaaggctaacattgaaggttggagaccttctacc
aacgacccaaacgctggagttggtccaatgggtgcttgctgtgccgagattgacgtgtgggaatctaacgcttac
gcctacgcttttactccacatgcttgcggttctaagaacagataccacatttgcgaaaccaacaactgtggtggc
acttactctgatgacagattcgctggatactgtgatgctaacggatgtgattacaacccatacagaatgggtaac
aaggacttttacggaaagggtaagactgttgacactaacagaaagttcactgtggtctcgagatttgagagaaac
agactgtcgcagttctttgtgcaggacggaagaaagattgaggtcccaccaccaacttggccaggattgccaaac
tctgccgacattaccccagagttgtgcgacgctcagttcagagtgtttgacgacagaaacagatttgctgagacc
ggtggatttgacgctttgaacgaggctctgaccattccaatggttctagtcatgagtatttgggacgatcaccac
tctaacatgctttggctggactcttcttaccctccagagaaggctggattgcctggtggtgacagaggtccatgt

ccaacaacttctggagttccagccgaggttgaggctcaatacccagacgcccaggtcgtgtggtccaacatcaga
ttcggaccaattggtagcacagtgaatgtggcttctgcacaccatcatcatcatcattga

Alternative coding sequence of *Humicola grisea* CBHI with signal sequence

SEQID NO 42 [P]

LQACTATAENHPPLTWQECTAPGSCTTRNGAVVLDANWRWVHDVNGYTNCYTGNTWDPTYCPDDVTCAQNCCLDG
ADYEGTYGVTSSGSSLKLNFVTGSNVGSRLYLLQDDSTYQIFKLLNREFSFDVDVSNLPCGLNGALYFVAMDADG
GVSKYPNNKAGAKYGTGYCDSQCPRDLKFINGMANVEGWQPSSNNANTGIGDHGSCCAEMDVWEANSISNAVTLH
PCDTPGQTMCSGDDCGGTYSNDRYAGTCDPDGCDFNPYRMGNTSFYGPGKIIDTTKPFTVVTQFLTDDGTDTGTL
SEIKRFYIQNGNVIPQPNSIISGVTGNSITTEFCTAQKQAFGDTDEFSKHGGLAKMGAAMQQGMVLVMSLWDDYA
AQMLWLDSDYPTDADPTVPGIARGTCPTDSGVPSDVESQSPNSYVTFSNIKFGPINSTVPGLDGSTPSNPTATVA
PPTSTTTSVRSSTTQISTPTSQPGGCTTQKWGQCGGIGYTGCTNCVAGTTCTELNPWYSQCLASAHHHHHH

Talaromyces emersonii CBHI Mutant with *Chaetomium thermophilum* cellobiohydrolase I CBD with 6x His-TAG

SEQID NO 43 [N]

ctgcaggcctgcacggcgacggcagagaaccacccgcccctgacatggcaggaatgcaccgcccctgggagctgc
accaccaggaacggggcggtcgttcttgatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgc
tacacgggcaatacctgggaccccacgtactgccctgacgacgtaacctgcgcccagaactgttgcctggacggc
gcggattacgagggcacctacggcgtgacttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaac
gtcggatcccgtctctacctgctgcaggacgactcgacctatcagatcttcaagctcctgaaccgcgagttcagc
tttgacgtcgatgtctccaatcttccgtgcggattgaacggcgctctgtactttgtcgccatggacgccgacggc
ggcgtgtccaagtacccgaacaacaaggctggtgccaagtacggaaccgggtattgcgactcccaatgcccacgg
gacctcaagttcatcaacggcatggccaacgtcgagggctggcagccgtcatcgaacaacgccaacaccggaatt
ggcgaccacggctcctgctgtgcggagatggatgtctgggaagcaaacagcatctccaatgcggtcactctgcac
ccgtgcgacacgccaggccagacgatgtgctctggagatgactgcggtggcacatactctaacgatcgctacgcg
ggaacctgcgatcctgacggctgtgacttcaacccttaccgcatgggcaacacttctttctacgggcctggcaag
atcatcgataccaccaagcccttcactgtcgtgacgcagttcctcactgatgatggtacggatactggaactctc
agcgagatcaagcgcttctacatccagaacggcaacgtcattccgcagcccaactcgatcatcagtggcgtgacc
ggcaactcgatcacgacggagttctgcactgctcagaagcaggcctttggcgacacggacgaattctctaagcac
ggtggcctggccaagatgggagcggccatgcagcagggtatggtcctggtgatgagtttgtgggacgactacgcc
gcgcagatgctgtggttggattccgactacccgacggatgcggaccccacggtccctggtattgcccgtggaacg
tgtccgacggactcgggcgtcccatcggatgtcgagtcgcagagccccaactcctacgtgaccttctcgaacatt
aagtttggtccgatcaactcgaccgtccctggcctcgacggcagcacccccagcaacccgaccgccaccgttgct
cctcccacttctaccaccaccagcgtgagaagcagcactactcagatttccaccccgactagccagcccggcggc
tgcaccacccagaagtggggccagtgcggtggtatcggctacaccggctgcactaactgcgttgctggcactacc
tgcactgagctcaacccctggtacagccagtgcctggcttctgctcatcatcaccatcaccac

Coding Sequence for Talaromyces emersonii CBHI Mutant with *Chaetmium thermophilum cellobiohydrolase* I CBD with 6x His-TAG

SEQID NO 44 [P]

LQACTATAENHPPLTWQECTAPGSCTTRNGAVVLDANWRWVHDVNGYTNCYTGNTWDPTYCPDDVTCAQNCCLDG
ADYEGTYGVTSSGSSLKLNFVTGSNVGSRLYLLQDDSTYQIFKLLNREFSFDVDVSNLPCGLNGALYFVAMDADG
GVSKYPNNKAGAKYGTGYCDSQCPRDLKFINGMANVEGWQPSSNNANTGIGDHGSCCAEMDVWEANSISNAVTLH
PCDTPGQTMCSGDDCGGTYSNDRYAGTCDPDGCDFNPYRMGNTSFYGPGKIIDTTKPFTVVTQFLTDDGTDTGTL
SEIKRFYIQNGNVIPQPNSIISGVTGNSITTEFCTAQKQAFGDTDEFSKHGGLAKMGAAMQQGMVLVMSLWDDYA
AQMLWLDSDYPTDADPTVPGIARGTCPTDSGVPSDVESQSPNSYVTFSNIKFGPINSTYTGTVSSSSVSSSHSST
STSSSHSSSSTPPTQPTGVTVPQWGQCGGIGYTGSTTCASPYTCHVLNPYYSQCYASAHHHHHH

Talaromyces emersonii CBHI Mutant with *Phanerochaete chrysosporium* cellobiohydrolase CBD with 6x His-TAG

SEQID NO 45 [N]

ctgcaggcctgcacggcgacggcagagaaccacccgcccctgacatggcaggaatgcaccgcccctgggagctgc
accaccaggaacggggcggtcgttcttgatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgc
tacacgggcaatacctgggaccccacgtactgccctgacgacgtaacctgcgcccagaactgttgcctggacggc
gcggattacgagggcacctacggcgtgacttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaac
gtcggatcccgtctctacctgctgcaggacgactcgacctatcagatcttcaagctcctgaaccgcgagttcagc
tttgacgtcgatgtctccaatcttccgtgcggattgaacggcgctctgtactttgtcgccatggacgccgacggc
ggcgtgtccaagtacccgaacaacaaggctggtgccaagtacggaaccgggtattgcgactcccaatgcccacgg
gacctcaagttcatcaacggcatggccaacgtcgagggctggcagccgtcatcgaacaacgccaacaccggaatt
ggcgaccacggctcctgctgtgcggagatggatgtctgggaagcaaacagcatctccaatgcggtcactctgcac
ccgtgcgacacgccaggccagacgatgtgctctggagatgactgcggtggcacatactctaacgatcgctacgcg
ggaacctgcgatcctgacggctgtgacttcaacccttaccgcatgggcaacacttctttctacgggcctggcaag
atcatcgataccaccaagcccttcactgtcgtgacgcagttcctcactgatgatggtacggatactggaactctc
agcgagatcaagcgcttctacatccagaacggcaacgtcattccgcagcccaactcgatcatcagtggcgtgacc
ggcaactcgatcacgacggagttctgcactgctcagaagcaggcctttggcgacacggacgaattctctaagcac
ggtggcctggccaagatgggagcggccatgcagcagggtatggtcctggtgatgagtttgtgggacgactacgcc
gcgcagatgctgtggttggattccgactacccgacggatgcggaccccacggtccctggtattgcccgtggaacg
tgtccgacggactcgggcgtcccatcggatgtcgagtcgcagagccccaactcctacgtgaccttctcgaacatt
aagtttggtccgatcaactcgacctacactggaactgtttcttcatcctccgtttcatcttctcactcctccact
tctacttcatcttcccattcctcatcttccactccaccaactcaaccaactggtgttactgttccacaatgggga
caatgtggtggtattggttacactggttccactacttgtgcttccccatacacttgtcacgttttgaacccatac
tactcccaatgttacgcttctgctcatcatcaccatcaccactaa

Coding Sequence for *Talaromyces emersonii CBHI Mutant with Phanerochaete chrysosporium cellobiohydrolase CBD* with 6x His-TAG

SEQID NO 46 [P]

lqactataenhppltwqectapgscttrngavvldanwrwvhdvngytncytgntwdptycpddvtcaqnccldg
adyegtygvtssgsslklnfvtgsnvgsrlyllqddstyqifkllnrefsfdvdvsnlpcglngalyfvamdadg
gvskypnnkagakygtgycdsqcprdlkfingmanvegwqpssnnantgigdhgsccaemdvweansisnavtlh
pcdtpgqtmcsgddcggtysndryagtcdpdgcdfnpyrmgntsfygpgkiidttkpftvvtqfltddgtdtgtl
seikrfyiqngnvipqpnsiisgvtgnsittefctaqkqafgdtdefskhgglakmgaamqqgmvlvmslwddya
aqmlwldsdyptdadptvpgiargtcptdsgvpsdvesqspnsyvtfsnikfgpinstftggttsssstttttsk
ststsssskttttsvtttttssgssgtgaahwaqcggngwtgpttcvspytctkqndwysqclasahhhhhh

Talaromyces emersonii CBHI Mutant with Penicillium janthinellum cellobiohydrolase CBD with 6x His-TAG

SEQID NO 47 [N]

ctgcaggcctgcacggcgacggcagagaaccacccgcccctgacatggcaggaatgcaccgcccctgggagctgc
accaccaggaacggggcggtcgttcttgatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgc
tacacgggcaatacctgggaccccacgtactgccctgacgacgtaacctgcgcccagaactgttgcctggacggc
gcggattacgagggcacctacggcgtgacttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaac
gtcggatcccgtctctacctgctgcaggacgactcgacctatcagatcttcaagctcctgaaccgcgagttcagc
tttgacgtcgatgtctccaatcttccgtgcggattgaacggcgctctgtactttgtcgccatggacgccgacggc
ggcgtgtccaagtacccgaacaacaaggctggtgccaagtacggaaccgggtattgcgactcccaatgcccacgg
gacctcaagttcatcaacggcatggccaacgtcgagggctggcagccgtcatcgaacaacgccaacaccggaatt
ggcgaccacggctcctgctgtgcggagatggatgtctgggaagcaaacagcatctccaatgcggtcactctgcac
ccgtgcgacacgccaggccagacgatgtgctctggagatgactgcggtggcacatactctaacgatcgctacgcg
ggaacctgcgatcctgacggctgtgacttcaacccttaccgcatgggcaacacttctttctacgggcctggcaag
atcatcgataccaccaagcccttcactgtcgtgacgcagttcctcactgatgatggtacggatactggaactctc
agcgagatcaagcgcttctacatccagaacggcaacgtcattccgcagcccaactcgatcatcagtggcgtgacc
ggcaactcgatcacgacggagttctgcactgctcagaagcaggcctttggcgacacggacgaattctctaagcac
ggtggcctggccaagatgggagcggccatgcagcagggtatggtcctggtgatgagtttgtgggacgactacgcc
gcgcagatgctgtggttggattccgactacccgacggatgcggaccccacggtccctggtattgcccgtggaacg
tgtccgacggactcgggcgtcccatcggatgtcgagtcgcagagccccaactcctacgtgaccttctcgaacatt
aagtttggtccgatcaactcgaccttcactggtggtactacttcatcctcctccactactactacaacttccaag
tccacttccacttcatcttcatccaagactacaactacttccgttacaactactactacttcctctggttcttct
ggtactggtgctgctcattgggctcaatgtggtggtaatggatggactggtccaactacttgtgtttccccatac
acttgtactaagcagaacgactggtactctcaatgtttggcttctgctcatcatcaccatcaccac

Coding Sequence for Talaromyces emersonii CBHI Mutant with Penicillium janthinellum cellobiohydrolase CBD with 6x His-TAG

SEQID NO 48 [P]

lqactataenhppltwqectapgscttrngavvldanwrwvhdvngytncytgntwdptycpddvtcaqnccldg
adyegtygvtssgsslklnfvtgsnvgsrlyllqddstyqifkllnrefsfdvdvsnlpcglngalyfvamdadg
gvskypnnkagakygtgycdsqcprdlkfingmanvegwqpssnnantgigdhgsccaemdvweansisnavtlh
pcdtpgqtmcsgddcggtysndryagtcdpdgcdfnpyrmgntsfygpgkiidttkpftvvtqfltddgtdtgtl
seikrfyiqngnvipqpnsiisgvtgnsittefctaqkqafgdtdefskhgglakmgaamqqgmvlvmslwddya
aqmlwldsdyptdadptvpgiargtcptdsgvpsdvesqspnsyvtfsnikfgpinstftgtgstspsspagpvs
sstsvasqptqpaqgtvaqwgqcggtgftgptvcaspftchvvnpyysqcyasahhhhhh

Talaromyces emersonii CBHI Mutant with Irpex lacteus cellobiohydrolase CBD with 6x His-TAG

SEQID NO 49 [N]

ctgcaggcctgcacggcgacggcagagaaccacccgcccctgacatggcaggaatgcaccgcccctgggagctgc
accaccaggaacggggcggtcgttcttgatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgc
tacacgggcaatacctgggaccccacgtactgccctgacgacgtaacctgcgcccagaactgttgcctggacggc
gcggattacgagggcacctacggcgtgacttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaac
gtcggatcccgtctctacctgctgcaggacgactcgacctatcagatcttcaagctcctgaaccgcgagttcagc
tttgacgtcgatgtctccaatcttccgtgcggattgaacggcgctctgtactttgtcgccatggacgccgacggc
ggcgtgtccaagtacccgaacaacaaggctggtgccaagtacggaaccgggtattgcgactcccaatgcccacgg
gacctcaagttcatcaacggcatggccaacgtcgagggctggcagccgtcatcgaacaacgccaacaccggaatt
ggcgaccacggctcctgctgtgcggagatggatgtctgggaagcaaacagcatctccaatgcggtcactctgcac
ccgtgcgacacgccaggccagacgatgtgctctggagatgactgcggtggcacatactctaacgatcgctacgcg
ggaacctgcgatcctgacggctgtgacttcaacccttaccgcatgggcaacacttctttctacgggcctggcaag
atcatcgataccaccaagcccttcactgtcgtgacgcagttcctcactgatgatggtacggatactggaactctc
agcgagatcaagcgcttctacatccagaacggcaacgtcattccgcagcccaactcgatcatcagtggcgtgacc
ggcaactcgatcacgacggagttctgcactgctcagaagcaggcctttggcgacacggacgaattctctaagcac
ggtggcctggccaagatgggagcggccatgcagcagggtatggtcctggtgatgagtttgtgggacgactacgcc
gcgcagatgctgtggttggattccgactacccgacggatgcggaccccacggtccctggtattgcccgtggaacg
tgtccgacggactcgggcgtcccatcggatgtcgagtcgcagagccccaactcctacgtgaccttctcgaacatt
aagtttggtccgatcaactcgaccttcactggtactggttctacttctccatcttctccagctggtccagtttct
tcttccacttccgttgcttcccaaccaactcaaccagctcaaggtactgttgctcaatggggacaatgtggtggt
actggtttcactggtccaactgtttgtgcttccccattcacttgtcacgttgttaacccatactactcccagtgt
tacgcttctgctcatcatcatcaccatcac

Coding Sequence for Talaromyces emersonii CBHI Mutant with Irpex lacteus cellobiohydrolase CBD with 6x His-TAG

SEQID NO 50 [P]

lqactataenhppltwqectapgscttrngavvldanwrwvhdvngytncytgntwdptycpddvtcaqnccldg
adyegtygvtssgsslklnfvtgsnvgsrlyllqddstyqifkllnrefsfdvdvsnlpcglngalyfvamdadg
gvskypnnkagakygtgycdsqcprdlkfingmanvegwqpssnnantgigdhgsccaemdvweansisnavtlh
pcdtpgqtmcsgddcggtysndryagtcdpdgcdfnpyrmgntsfygpgkiidttkpftvvtqfltddgtdtgtl
seikrfyiqngnvipqpnsiisgvtgnsittefctaqkqafgdtdefskhgglakmgaamqqgmvlvmslwddya
aqmlwldsdyptdadptvpgiargtcptdsgvpsdvesqspnsyvtfsnikfgpigstgnpsggnpsggdggttt
trrpatttgsspgptqslygqcggigysgpticasgttcqvlnpyysqclasahhhhhh

Talaromyces emersonii CBHI Mutant with mutated Trichoderma reesei CBD with 6x His-TAG

SEQID NO 51 [N]

ctgcaggcctgcacggcgacggcagagaaccacccgcccctgacatggcaggaatgcaccgccctgggagctgc
accaccaggaacggggcggtcgttcttgatgcgaactggcgttgggtgcacgatgtgaacggatacaccaactgc
tacacgggcaatacctgggaccccacgtactgccctgacgacgtaacctgcgcccagaactgttgcctggacggc
gcggattacgagggcacctacggcgtgacttcgtcgggcagctccttgaaactcaatttcgtcaccgggtcgaac
gtcggatcccgtctctacctgctgcaggacgactcgacctatcagatcttcaagctcctgaaccgcgagttcagc
tttgacgtcgatgtctccaatcttccgtgcggattgaacggcgctctgtactttgtcgccatggacgccgacggc
ggcgtgtccaagtacccgaacaacaaggctggtgccaagtacggaaccgggtattgcgactcccaatgcccacgg
gacctcaagttcatcaacggcatggccaacgtcgagggctggcagccgtcatcgaacaacgccaacaccggaatt
ggcgaccacggctcctgctgtgcggagatggatgtctgggaagcaaacagcatctccaatgcggtcactctgcac
ccgtgcgacacgccaggccagacgatgtgctctggagatgactgcggtggcacatactctaacgatcgctacgcg
ggaacctgcgatcctgacggctgtgacttcaacccttaccgcatgggcaacacttctttctacgggcctggcaag
atcatcgataccaccaagcccttcactgtcgtgacgcagttcctcactgatgatggtacggatactggaactctc
agcgagatcaagcgcttctacatccagaacggcaacgtcattccgcagcccaactcgatcatcagtggcgtgacc
ggcaactcgatcacgacggagttctgcactgctcagaagcaggcctttggcgacacggacgaattctctaagcac
ggtggcctggccaagatgggagcggccatgcagcagggtatggtcctggtgatgagtttgtgggacgactacgcc
gcgcagatgctgtggttggattccgactacccgacggatgcggaccccacggtccctggtattgcccgtggaacg
tgtccgacggactcgggcgtcccatcggatgtcgagtcgcagagccccaactcctacgtgaccttctcgaacatt
aagtttggtccgatcggtagcacaggtaatccttcaggtggtaatccttcaggtggagacggcggaacaacgaca
actagaagaccagctactacaactggttcaagtccaggtccaactcaatcactatacggtcaatgtggtggtata
ggttactctggtcccactatttgtgcttctggtactacttgccaagttctgaacccttactactcacagtgtcta
gcttctgcacatcatcaccaccaccat

Coding Sequence for Talaromyces emersonii CBHI Mutant with mutated Trichoderma reesei CBD with 6x His-TAG

Claims

1. A polypeptide having cellobiohydrolase activity, wherein the polypeptide comprises an amino acid sequence having at least 60 % sequence identity to SEQ ID NO: 5 over a sequence length of 437 positions, and wherein the polypeptide maintains 50 % of its maximum substrate conversion capacity when the conversion is done for 60 minutes at a temperature of 62 °C or higher.

2. The polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence having at least 80 % sequence identity to SEQ ID NO:5 over a sequence length of 437 amino acid residues

3. The polypeptide according to claim 1 or 2, wherein one or more of the amino acid residues of the sequence defined by SEQ ID NO: 5 are modified by substitution or deletion at one or more positions preferably selected from Q1, Q2, G4, A6, T7, A8, N10, P12, T15, A21, G23, S24, T26, T27, Q28, N29, G30, A31, V32, N37, W40, V41, G46, Y47, T48, N49, C50, T52, N54, D57, T59, Y60, D64, E65, A68, Q69, A72, V84, S86, S89, S90, K92, S99, Q109, D110, D111, I116, F117, K118, L119, L120, D129, V130, G139, A145, M146, V152, K154, Y155, N157, N158, K159, K163, G167, Q172, F179, I180, D181, E183, E187, G188, Q190, S192, S193, N194, I200, D202, H203, D211, V212, A221, P224, D228, T229, G231, T233, M234, S236, T243, Y244, S245, N246, D247, G251, F260, G266, K275, I276, I277, T280, L290, D293, G294, T295, T297, T299, S301, K304, F306, N310, S311, V313, I314, N318, D320, I321, T325, N327, T335, A340, F341, D343, T344, D345, D346, Q349, H350, A354, K355, A358, Q361, Q362, G363, M364, V367, D373, Y374, A375, A376, P386, T387, D390, T392, T393, P394, T400, P402, T403, D404, D410, N417, S418, T421, Y422 and/or one or more insertions after positions G151, K159,

   and in a more preferred embodiment are modified by substitution or deletion at one or more positions selected from Q1, Q2, G4, A6, T7, A8, N10, A21, S24, T26, T27, Q28, N29, G30, W40, Y47, D64, E65, A68, Q69, A72, S86, K92, K118, Y155, D181, E183, Q190, S192, N194, D202, H203, P224, T229, G231, M234, S236, T243, D247, S311, N318, D320, T335, A340, T344, D346, Q349, K355, Y374, A375, T387, D390, T392, T393, Y422 and/or one or more insertion of 1-8 amino acids after positions G151, K159

   are modified by substitution or deletion at one or more positions selected from Q1, Q2, G4, A6, T7, A8, N10, Q28, E65, A72, S86, D181, E183, D202, P224, S311, N318, D320, T335, D346, Q349, T392, T393, Y422 and/or insertions at one or more after positions and/or one or more insertion of 5 amino acids after positions G151, K159 of

   of amino acids 1 to 437 of SEQ ID NO: 5.

4. A polypeptide according to any one of the preceding claims, wherein the polypeptide comprises an amino acid sequence having at least 85 % sequence identity to SEQ ID NO: 5 over a sequence length of 437 amino acid residues.

5. A polypeptide according to any one of the preceding claims, wherein the polypeptide comprises an amino acid sequence having at least 85 % sequence identity to SEQ ID NO: 2 over a sequence length of 500 amino acid residues.

6. The polypeptide according to claim 5, wherein the polypeptide comprises an amino acid sequence having at least 90 %, preferably at least 95 %, more preferably at least 99 % sequence identity to SEQ ID NO: 2 over a sequence length of 500 amino acid residues.

7. The polypeptide according to one or more of the preceding claims, wherein the amino acid sequence of the polypeptide has a sequence as defined by SEQ ID NO: 2 wherein 1 to 75 amino acid residues, more preferably 1 to 35 amino acid residues are substituted, deleted, or inserted.

8. The polypeptide according to claim 7, wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 2 are preferably modified by substitution or deletion at positions Q1, Q2, G4, A6, T7, A8, N10, P12, T15, A21, G23, S24, T26, T27, Q28, N29, G30, A31, V32, N37, W40, V41, G46, Y47, T48, N49, C50, T52, N54, D57, T59, Y60, D64, E65, A68, Q69, A72, V84, S86, S89, S90, K92, S99, Q109, D110, D111, I116, F117, K118, L119, L120, D129, V130, G139, A145, M146, V152, K154, Y155, N157, N158, K159, K163, G167, Q172, F179, I180, D181, E183, E187, G188, Q190, S192, S193, N194, I200, D202, H203, D211, V212, A221, P224, D228, T229, G231, T233, M234, S236, T243, Y244, S245, N246, D247, G251, F260, G266, K275, I276, I277, T280, L290, D293, G294, T295, T297, T299, S301, K304, F306, N310, S311, V313, I314, N318, D320, I321, T325, N327, T335, A340, F341, D343, T344, D345, D346, Q349, H350, A354, K355, A358, Q361, Q362, G363, M364, V367, D373, Y374, A375, A376, P386, T387, D390, T392, T393, P394, T400, P402, T403, D404, D410, N417, S418, T421, Y422, F427, P429, I430, G431, T433, G434, N435, P436, S437, G439, N440, P441, P442, G443, N445, R446, T448, T449, T450, T451, R453, P454, A455, T456, T457, G459, S460, S461, P462, G463, P464, T465, S467, H468, G470, C472, G474, G476, Y477, S478, P480, V482, C483, S485, G486, T488, C489, Q490, V491, L492, N493, Y495, Y496, Q498, C499, L500 and/or by one or more insertions after positions G151, K159, G434, A455 or P464

and in a more preferred embodiment are modified by substitution or deletion at one or more positions selected from Q1, Q2, G4, A6, T7, A8, N10, A21, S24, T26, T27, Q28, N29, G30, W40, Y47, D64, E65, A68, Q69, A72, S86, K92, K118, Y155, D181, E183, Q190, S192, N194, D202, H203, P224, T229, G231, M234, S236, T243, D247, S311, N318, D320, T335, A340, T344, D346, Q349, K355, Y374, A375, T387, D390, T392, T393, Y422, P436, P442, N445, R446, T448, T451, R453, P462, G463, H468, P480, V482, S485, and/or by one or more insertion of 1-8 amino acids after positions G151, K159, G434, A455 or P464

and in an even more preferred embodiment are modified by substitution or deletion at one or more positions selected from Q1, Q2, G4, A6, T7, A8, N10, Q28, E65, A72, S86, D181, E183, D202, P224, S311, N318, D320, T335, D346,

Q349, T392, T393, Y422, P442, N445, R446, H468, V482, and/or by insertions at one or more after positions and/or one or more insertion of 5 amino acids after positions G151, K159, G434, A455 or P464

of amino acids 1 to 500 of SEQ ID NO: 2.

9. The polypeptide according to claim 8, wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 2 are modified as follows:

Position	Preferred	More Preferred	Most Preferred
Q1	L	L	L
Q2	P,S	P,S	S
G4	C	C	C
A6	G,L,V	G,L,V	L
T7	Q	Q	Q
A8	S	S	S
N10	T,D	T,D	T,D
P12	Q		
T15	S		
A21	S,T,C	S,T,C	
G23	A,D,N		
S24	T,C,N	T,C,N	
T26	I,N	I,N	
T27	S,Q	S,Q	
Q28	L,K,R,N	L,K,R,N	K,R
N29	T,Y	T,Y	
G30	A	A	
A31	S		
V32	G		
N37	S		
W40	R	R	
V41	T		
G46	S		
Y47	S,F	S,F	
T48	A		
N49	S		
C50	S		
T52	D		
N54	S		
D57	S		
T59	M		
Y60	H		
D64	N	N	
E65	V,M,K	V,M,K	V,M,K
A68	T	T	
Q69	K,R	K,R	
A72	V,C	V,C	C
V84	A		
S86	T	T	T
S89	N		
S90	T,F		

K92	R	R	
S99	T		
Q109	R		
D110	G,S,N		
D111	H,E		
I116	V,K,E		
F117	Y		
K118	A,T,Q	A,T,Q	
L119	L,I		
L120	P,M		
D129	N		
V130	I		
G139	S		
A145	T		
M146	C		
G151	GCGRSG	GCGRSG	GCGRSG
V152	A,E		
K154	R		
Y155	S,C,H	S,C,H	
N157	S		
N158	D		
K159	E, KCGRNK	KCGRNK	KCGRNK
K163	C		
G167	C		
Q172	Q		
F179	I		
I180	N		
D181	N	N	N
E183	V,M,K	V,M,K	V,M,K
E187	K		
G188	C		
Q190	L,K	L,K	
S192	L,I,P,T,M	L,I,P,T,M	
S193	L,P,T		
N194	G,L,I,V,S,C,K,R,D,Q,Y	G,L,I,V,S,C,K,R,D,Q,Y	
I200	N,F		
D202	G,I,V,N,F,Y	G,I,V,N,F,Y	G,I,V,N,F,Y
H203	R	R	
D211	G		
V212	L		
A221	V		
P224	L	L	L
D228	N		
T229	A,S,M	A,S,M	
G231	D	D	
T233	S		
M234	L,I,V,T,K	L,I,V,T,K	
S236	F,Y	F,Y	
T243	G,A,L,I,V,P,S,C,M,R,D,Q,F,Y,W	G,A,L,I,V,P,S,C,M,R,D,Q,F,Y,W	
Y244	H,F		
S245	T		
N246	S,K,D		
D247	N	N	
G251	R		
F260	C		
G266	S		

K275	E		
I276	V		
I277	V		
T280	A		
L290	H		
D293	R,H		
G294	A		
T295	S		
T297	N		
T299	I,S		
S301	C		
K304	R		
F306	L,Y		
N310	D,E		
S311	G,D,N	G,D,N	G,D,N
V313	I		
I314	F		
N318	I,H,D,Y	I,H,D,Y	I,D,Y
D320	I,V,E,N	I,V,E,N	I,V,N
I321	N		
T325	A,I		
N327	Y		
T335	I	I	I
A340	G,S,T	G,S,T	
F341	C		
D343	A		
T344	M	M	
D345	E		
D346	G,A,V,E	G,A,V,E	G,A,V,E
Q349	K,R	K,R	K,R
H350	Y		
A354	T		
K355	Q	Q	
A358	E		
Q361	R		
Q362	G,R,H		
G363	P		
M364	L,S		
V367	A		
D373	E		
Y374	A,P,S,C,R,H,D	A,P,S,C,R,H,D	
A375	G,L,V,T,C,M,R,D,E,N,Q,Y	G,L,V,T,C,M,R,D,E,N,Q,Y	
A376	T		
P386	L,S		
T387	A,S	A,S	
D390	G,E	G,E	
T392	S,M,K	S,M,K	M
T393	A,I,V,S	A,I,V,S	A,I,V
P394	C		
T400	S		
P402	S		
T403	K		
D404	N		
D410	G		
N417	Y		
S418	P		

T421	I		
Y422	F	F	F
F427	Y		
P429	C		
I430	L		
G431	D		
T433	S,E		
G434	S,GAAATG	GAAATG	GAAATG
N435	Q		
P436	S	S	
S437	P		
G439	V,D		
N440	E		
P441	A,L,S		
P442	S,Q,del	S,Q	S
G443	D		
N445	S,D	S,D	D
R446	G,S	G,S	G,S
T448	A	A	
T449	A		
T450	I		
T451	A,S	A,S	
R453	G,S,K	G,S,K	
P454	S		
A455	V,T, AAAAPA	AAAAPA	AAAAPA
T456	A,I		
T457	P		
G459	D		
S460	P		
S461	R		
P462	L,del	L	
G463	V,D	V,D	
P464	L,Q, PTHAAA	PTHAAA	PTHAAA
T465	I,S		
S467	T		
H468	L,R,Q	L,R,Q	L,R,Q
G470	D		
C472	R		
G474	S		
G476	D		
Y477	Y		
S478	Y		
P480	S	S	
V482	A,I,T	A,I,T	A,I,T
C483	R		
S485	T	T	
G486	S,D		
T488	I		
C489	R		
Q490	L		
V491	I		
L492	Q		
N493	D		
Y495	C		
Y496	F		
Q498	K		

C499 G
L500 I

10. The polypeptide according to one or more of the preceding claims, wherein the polypeptide has an amino acid sequence selected from the list of the following mutations of SEQ ID NO: 2:

Consecutive Number	Mutation Pattern with respect to Seq. ID NO:2
1	G4C, A72C, Q349K
2	G4C, A72C, T344M, Q349K
3	G4C, A72C, T344M, D346G, Q349R
4	G4C, A72C, D320V, Q349K
5	G4C, A72C, P224L, F306Y, Q349R
6	G4C, A72C
7	A72V, D346A, T393A
8	G4C, A72C, Q349R, R446S, T456A
9	G4C, W40R, A72C, T344M, Q349K
10	A72V, D320V, D346A
11	G4C, A72C, N194Y, T243L, Q349R, Y374S, A375R
12	G4C, A72C, Q349K, T448A, T449A
13	G4C, E65V, A72C, Y244H, Q349R
14	G4C, A72C, D202G, D320N, Q349R, A358E
15	G4C, A72C, D320V, Q349R
16	G4C, A72C, Q349K, S86T
17	A72V, T335I, D346A, T393A, P436S
18	G4C, A72C, E183V, K304R, Q349K
19	G4C, A72C, T243G, Q349R, Y374P, A375M
20	G4C, A72C, Q349R, T465I
21	G4C, A72C, Q349R
22	G4C, A72C, N194V, T243M, Q349R, Y374A, A375T
23	G4C, D64N, A72C, Q349R, A358E, P464Q
24	G4C, A72C, Q349K, Q28R, S193T, Q490L
25	G4C, A72C, E183K, Q349K
26	G4C, A72C, S311N, Q349K, A455T
27	G4C, A72C, N194K, Q349R, Y374P, A375Q
28	G4C, A72C, D181N, Q349K
29	W40R, D320V, Q349K, T393A, N445D
30	W40R, T335I, D346A, T393A
31	Q1L, G4C, A72C, D181N, E183K, N327Y, Q349R
32	A72C, L119L, T335I, Q349R, G486D
33	G4C, A72C, N194K, T243P, Q349R, Y374H, A375E
34	G4C, A72V, Q349R, P462del
35	G4C, A72C, S236Y, Q349R
36	G4C, A72C, S311G, Q349K
37	A72V, D320V, T335I, D346A, T393A, N445D

38	G4C, A72C, S86T, M234V, Q349K
39	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
40	G4C, A72C, G251R, Q349R
41	G4C, A72C, Q349K, D320V
42	A72V, T335I, D346A, T393A
43	G4C, A72C, E183K, Q349R
44	Q1L, G4C, A72C, H203R, Q349K, P442S
45	G4C, A72C, Q349K, G434S, G470D
46	G4C, W40R, A72C, Q349K
47	G4C, A72C, Q349R, V367A
48	Q1L, G4C, A6V, C50S, A72C, I180N, D181N, E183K, Q349R, T457P, C472R, C499G
49	G4C, A72C, S311G, D320V, Q349K
50	W40R, T335I, D346A, T393A, P436S
51	Q1L, G4C, A72C, D181N, E183K, T243S, Q349R, P386S
52	A72V, D346A, T393A, N445D
53	Q1L, G4C, A72C, K154R, Q349K, T393I
54	G4C, A72C, N194G, T243F, Q349R, Y374P, A375R
55	A72V, D320V, D346A, T393A, N445D
56	A72C, L119L, Q172Q, Q349K, T488I
57	G4C, A72C, E183V, Q349K
58	G4C, A72C, E183K, N318Y, Q349K
59	W40R, A221V, T449A, C483R
60	G4C, A72C, K92R, Q349K, N493D
61	Q1L, G4C, A72C, S90T, D181N, E183K, Q349R
62	G4C, A72C, Q349R, G459D
63	G4C, A72C, Q349R, Y422F
64	G4C, T48A, A72C, Q349R, P480S
65	E187K, D320V, P442del
66	G4C, S24N, E65K, A72C, Q349R, I430L, G439D
67	A72V, D320V, T335I, D346A, T393A, P436S
68	Q1L, G4C, A72C, S193P, Q349K, V482I
69	G4C, A72C, D320V, Q349K, G443D, L492Q
70	Q1L, G4C, A72C, DV152-K159, D181N, E183K, Q349R
71	Q1L, G4C, A72C, Q349K
72	Q1L, G4C, A72C, D181N, E183K, M234L, V313I, Q349R, H468R
73	Q1L, G4C, A72C, D181N, E183K, I200N, Q349R
74	G4C, A72C, N194K, T243Y, Q349R, A375N
75	Q1L, G4C, Q28R, A72C, Q349K, H468L
76	G4C, E65V, A72C, Q349R
77	D320V, Q349K
78	Q1L, G4C, A72C, S311G, Q349K, H468R

79	G4C, A72C, T243Q, Q349R, Y374P, A375M
80	Q1L, G4C, A72C, D320V, Q349R
81	Q1L, G4C, T15S, A72C, Y244F, Q349K
82	G4C, A72C, E183K, D346E, Q349R
83	Q1L, G4C, A72C, Q349K, T392M
84	G4C, A72C, D202N, S311N, Q349R, N493D
85	G4C, A72C, N194D, T243A, Q349R, Y374P, A375Y
86	G4C, A72C, N194Y, T243V, Q349R, Y374P
87	Q1L, G4C, A72C, Q349R
88	G4C, Q28R, E65K, A72C, S86T, D202N, H203R, S311N, D320I, A340G, D346A, Q349K, T393A, Y422F, P442S, R446S, H468L, V482A
89	G4C, A72C, D202N, Q349R
90	G4C, A72C, P224L, Q349R
91	Q1L, G4C, A72C, D181N, E183K, T229M, A340T, Q349R, V491I
92	Q1L, G4C, A72C, D181N, Q349R
93	G4C, A72C, D320V, D346V, Q349K
94	Q1L, G4C, A72C, V152A, Q349K
95	Q1L, G4C, Q28R, A72C, Q349K
96	Q1L, G4C, A72C, Q349K, Y422F
97	G4C, A72C, D202V, D320V, Q349K
98	Q1L, G4C, A72C, Y155S, D181N, E183K, Q349R
99	Q1L, G4C, A72C, D181N, D247N, Q349K
100	Q1L, G4C, A68T, A72C, Q349K, G439D, R453S
101	Q1L, G4C, A72C, Q349K, H468R
102	Q1L, G4C, D64N, A72C, Q349K
103	G4C, A72C, E183K, Q349R, P464L
104	G4C, A72C, D181N, P224L, Q349K
105	G4C, A72C, N194I, T243Y, Q349R, Y374P, A375R
106	Q1L, G4C, A72C, Q349K, P462L
107	Q1L, G4C, A72C, E183K, Q349R
108	G4C, A72C, S311G, Q349R
109	Q1L, G4C, A72C, S311N, Q349K, G463D
110	Q1L, G4C, A72C, S86T, Q349R
111	Q1L, G4C, A72C, D181N, E183K, G231D, Q349R
112	Q1L, G4C, A72C, S89N, D181N, E183K, Q349R
113	Q1L, G4C, E65K, A72C, Q349K
114	Q1L, Q2P, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F, R446G
115	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
116	G4C, A72C, E183K, D202Y, N310D, Q349R
117	G4C, A72C, N194I, T243D, Q349R, Y374P, A375Y
118	Q1L, G4C, A72C, D181N, E183K, Q349R, T456I
119	G4C, Q28R, A72C, S86T, E183K, P224L, S311N,

	N318Y, T335I, D346G, Q349R, T393I, P441A, P442S, R446G, H468L, V482I
120	Q1L, G4C, A72C, D181N, Q349K, T451S
121	Q1L, G4C, A72C, D181N, E183K, T243I, N246D, Q349R, T488I
122	Q1L, G4C, G23N, A72C, D110G, I116V, L119I, D181N, E183K, D211G, D293R, N310D, Q349R, Q362R, G363P, M364S
123	G439V, N440E, P441S, P442Q
124	G431D, S431V, T433E, G434S, N435Q
125	Q1L, G4C, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
126	Q1L, G4C, A72C, S86T, D181N, E183K, Q349R, T393S
127	Q1L, G4C, A72C, D181N, E183K, Q349R, S485T
128	Q1L, G4C, G23N, A72C, V84A, D110G, D111H, I116E, F117Y, K118A, D181N, E183K, D293R, T295S, Q349R, M364L
129	Q1L, G4C, A72C, D181N, E183K, Q349R, R453K
130	Q1L, G4C, A72C, A145T, H203R, Q349K, T403K
131	Q1L, G4C, A72C, D181N, E183K, Q349R, N445S
132	Q1L, G4C, A72C, D181N, E183K, M234I, Q349R
133	Q1L, G4C, A72C, D181N, E183K, Q349R, T465S
134	Q1L, G4C, A72C, D181N, E183K, T297N, Q349R
135	Q1L, G4C, A72C, S311G, Q349K
136	G4C, Q28R, E65M, A72C, S86T, E183K, S192I, H203R, S311N, D346E, Q349K, T392M, T393A, Y422F, N445D, R446S
137	Q1L, G4C, A72C, D202N, Q349K, G486D
138	Q1L, G4C, A72C, S99T, D181N, E183K, Q349R, T450I
139	Q1L, G4C, A72C, I200F, Q349K, L500I
140	Q1L, G4C, A72C, D181N, E183K, Q349R, G434S
141	Q1L, G4C, A31S, A72C, D181N, E183K, Q349R
142	Q1L, G4C, Q28L, A72C, D181N, E183K, Q349R
143	Q1L, G4C, A72C, D181N, E183K, Q349R, P436S
144	Q1L, G4C, A72C, D181N, E183K, T233S, Q349R
145	Q1L, G4C, A72C, D202N, Q349K
146	Q1L, G4C, A68T, A72C, Q349K
147	Q1L, G4C, A21T, A72C, D181N, E183K, Q349R, P454S
148	Q1L, G4C, A72C, D346V, Q349K
149	Q1L, G4C, Y47F, A72C, D181N, E183K, Q349R, P436S, S461R
150	Q1L, G4C, A72C, D181N, E183K, M234T, Q349R
151	Q1L, G4C, A72C, N157S, D181N, E183K, Q349R
152	Q1L, G4C, A72C, D181N, E183K, Q349R
153	G4C, A72C, N194Q, T243V, Q349R, Y374P, A375Y
154	Q1L, G4C, A72C, D181N, E183K, I314F, Q349R, N445D

155	Q1L, G4C, A72C, Q349K, T392K
156	Q1L, G4C, A72C, D181N, E183K, Q349R, T451A
157	Q1L, G4C, A72C, D181N, E183K, M234V, Q349R
158	Q1L, G4C, A21S, A72C, D181N, E183K, Q349R
159	Q1L, G4C, A72C, D181N, E183K, Q349R, N493D
160	Q1L, G4C, A72C, S311N, Q349K
161	Q1L, G4C, Q28R, E65V, A72C, D181N, E183V, D228N, S311N, N318Y, D346E, Q349R, Y422F, P442S, N445D, R446G, H468L, V482T
162	G4C, A72C, N194C, Q349R, Y374C
163	Q1L, G4C, A72C, D181N, E183K, Q349R, A455V
164	Q1L, G4C, A72C, D181N, E183K, Q349R, T400S
165	Q1L, G4C, T26I, A72C, D181N, E183K, Q349R
166	Q1L, G4C, A72C, D181N, E183K, N310D, Q349R, T392S, G463D
167	Q1L, G4C, A72C, D129N, D181N, E183K, Q190L, G266S, I276V, Q349R, P386L, F427Y
168	Q1L, G4C, A72C, D181N, E183K, D202N, Q349R
169	Q1L, G4C, A72C, Y155C, D181N, E183K, Q349R
170	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454PATAAA, H468L, V482I
171	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
172	Q1L, G4C, A72C, D181N, E183K, N246K, Q349R
173	G4C, W40R, E65V, A72C, S86T, D181N, E183K, D202I, H203R, S311D, D320N, D346V, Q349R, T392M, T393A, Y422F, P442S, H468Q, V482A
174	Q1L, G4C, A72C, Y155C, Q349K
175	Q1L, G4C, A68T, A72C, D181N, E183K, Q349R
176	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, T448A, R453G, H468L, P480S, V482I
177	Q1L, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F, R446G
178	Q1L, G4C, A72C, S86T, D181N, E183K, D320V, Q349R
179	G4C, Q28K, A72C, S86T, E183M, D202N, P224L, S311G, N318Y, D320N, D346A, Q349R, T392M, T393I, P442S, H468L, V482I
180	Q1L, Q2P, G4C, Q28R, W40R, E65K, A72C, D181N, S192L, D202I, H203R, P224L, S311G, D320I, D343A, D346A, Q349K, P442S, N445D, R446G, V482A
181	Q1L, G4C, Q28R, E65K, A72C, E183M, D202I, P224L, D320N, D346V, Q349K, T392M, T393V, Y422F, N445D, R446G, H468L, V482T
182	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202V, S311G, N318Y, D320I, D346G, Q349K,

	T393V, Y422F, N445D, R446S, H468Q, V482T
183	Q1L, G4C, W40R, E65M, A72C, D181N, E183K, S192P, D202N, P224L, S311D, N318Y, D320V, D346G, Q349K, T392M, N445D, R446G, H468L, V482T
184	Q1L, G4C, E65V, A72C, D181N, E183K, P224L, S311G, D320N, D346G, Q349R, T392M, T393I, R446G, H468L, V482I
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186	Q1L, G4C, E65M, A72C, D181N, E183M, D202Y, P224L, S311D, N318Y, D320I, T335I, D346A, Q349K, T392M, T393I, N445D, R446G, T448A, H468Q, V482A
187	Q1L, G4C, G23A, A72C, D110S, D111H, I116V, F117Y, K118A, L120M, D181N, E183K, D293H, G294A, N310E, Q349R, Q362G, M364S
188	Q1L, G4C, A72C, D181N, E183K, Q349R, T421I, G439D
189	G4C, Q28K, E65M, A72C, S86T, V152A, D181N, E183V, S192L, D202N, S311N, D320N, D346E, Q349R, T387A, T392M, T393I, Y422F, P442S, R446S, H468L, G476D, V482I
190	Q1L, G4C, W40R, E65V, A72C, S86T, E183V, G188C, S192T, D202Y, H203R, P224L, S311N, D320V, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
191	Q1L, G4C, E65M, A72C, S86T, E183M, D202N, P224L, T335I, D346G, Q349K, T392M, T393A, P442S, N445D, R446G, H468Q, V482A
192	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F, P442S, N445D, R446G, H468L, P480S, V482I
193	G4C, W40R, A72C
194	Q1L, G4C, W40R, E65K, A72C, S86T, E183K, S192L, D202Y, P224L, D320I, D346E, Q349R, P442S, R446G, H468R, V482T
195	Q1L, G4C, A21T, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, D202N, P224L, S311G, N318Y, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, P480S, V482I
196	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
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198	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
199	Q1L, G4C, T7Q, A8S, N10T, S24T, T27Q, Q28R, N29T, V41T, G46S, Y47S, T52D, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D,

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200	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
201	Q1L, G4C, Q28K, W40R, E65V, A72C, D181N, E183V, S192P, D202V, H203R, S311G, D320N, D346E, Q349K, T392M, T393A, Y422F, V482I
202	Q1L, G4C, Q28R, E65V, A72C, G139S, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
203	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I
204	Q1L, G4C, Q28R, E65K, A72C, D181N, S311N, N318Y, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
205	Q1L, G4C, W40R, A72C, S192L, D202N, H203R, P224L, S311N, D320I, T335I, D346V, Q349R, T393I, N445D, R446G, H468Q, V482T
206	Q1L, G4C, Q28K, E65K, A72C, E183M, D202N, P224L, T229S, S311G, D320I, T335I, D346V, Q349R, T393V, H468Q, V482A
207	Q1L, G4C, Q28R, G30A, E65M, A72C, D181N, D202N, P224L, S311D, N318Y, D346E, Q349K, T392M, T393V, Y422F, P442S, N445D, R446S
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209	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
210	T243C, A375C, N194C, Y374C
211	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, S311G, D346V, Q349R, T392M, T393V, Y422F, P442S, N445D, R446G, H468L, S478Y, V482I
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217	Q1L, G4C, Q28K, E65V, A72C, D202N, H203R, S311G, T335I, D346V, Q349K, T393A, P442S, R446G, H468L, V482I

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219	Q1L, G4C, Q28R, E65K, A72C, D181N, D202N, H203R, P224L, S311D, D346G, Q349K, P442S, R446S, H468Q, V482T
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224	Q1L, G4C, Q28N, E65K, A72C, D181N, E183M, D202N, H203R, S311G, N318Y, D320N, Q349R, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
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227	Q1L, G4C, Q28R, W40R, A72C, S86T, D181N, S192T, D202N, P224L, S311G, N318Y, D320V, D346E, Q349K, T392M, T393I, P442S, N445D, R446G, H468Q, V482I
228	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, T229M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
229	Q1L, G4C, Q28K, W40R, A72C, S86T, D181N, E183M, S192I, D202Y, T299S, S311N, N318Y, D320I, D346V, Q349R, T393I, P442S, H468L
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232	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, G463V, H468L, V482I
233	Q1L, G4C, Q28R, E65K, A72C, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S,

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234	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
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237	Q1L, G4C, Q28K, E65K, A72C, D181N, H203R, P224L, S311G, D320V, D346G, Q349K, T392M, T393I, P442S, N445D, R446G, H468L, V482A
238	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
239	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, S311G, N318Y, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
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242	G4C, Q28R, E65K, A72C, S86T, D181N, E183M, S192L, D202N, H203R, P224L, S311D, D346E, Q349R, T392M, T393A, Y422F, P442S, N445D, R446G, P462L, H468L, V482T
243	Q1L, G4C, W40R, E65K, A72C, Q109R, D181N, E183M, S192I, D202I, H203R, S245T, D346A, Q349R, T393A, Y422F, P442S, N445D, R446G, H468R, V482A
244	Q1L, G4C, Q28K, E65M, A72C, D181N, D202N, S311N, T335I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482I
245	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349R, T393V, N417Y, Y422F, P442S, N445D, R446G, H468L, V482I
246	Q1L, G4C, Q28R, W40R, E65V, A72C, D202Y, H203R, P224L, T299I, N318Y, D320V, D346A, Q349K, T392M, T393A, P442S, N445D, R446G, H468R, V482T
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253	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
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256	Q1L, G4C, T7Q, A8S, N10T, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
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265	Q1L, G4C, E65V, A72C, D181N, E183K, D202G, Q349R
266	Q1L, G4C, Q28R, E65K, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
267	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, F306L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
268	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T

269	Q1L, G4C, Q28K, E65K, A72C, D181N, E183K, S192P, P224L, S311G, N318Y, D320V, D346E, Q349R, T392M, T393I, Y422F, P442S, H468Q
270	Q1L, G4C, Q28K, E65M, A72C, S86T, E183M, H203R, S311D, D320V, T335I, D346E, Q349R, T393A, N445D, R446G, H468Q, V482A
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272	Q1L, G4C, Q28K, W40R, E65K, A72C, S86T, D181N, E183K, S192L, D202I, H203R, S311N, D320N, D346V, Q349K, T392M, T393A, Y422F, N445D, R446S
273	G4C, E65V, A72C, S86T, Y155H, D181N, E183V, Q190K, P224L, S311N, D320V, D346V, Q349K, T392M, T393V, Y422F, P442S, N445D, R446G, H468L, V482A
274	Q1L, G4C, Q28R, E65M, A72C, S86T, E183M, D202N, S311D, N318Y, D320N, T335I, D346A, Q349R, T392M, T393I, Y422F, P442S, N445D, R446G, H468L, V482A
275	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311N, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
276	Q1L, G4C, Q28R, E65K, A72C, S86T, D181N, D202N, S311G, D346E, Q349K, T393I, Y422F, N445D, R446G, H468L, V482I
277	Q1L, G4C, Q28R, E65K, A72C, D181N, D202N, S311N, N318Y, D320I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468L, V482T
278	Q1L, G4C, T7Q, A8S, N10T, S24T, T27Q, Q28R, N29T, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
279	Q1L, G4C, Q28R, E65K, A72C, S86T, D202N, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468L, V482I
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282	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
283	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, S311N, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
284	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
285	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
286	Q1L, G4C, E65M, A72C, S86T, E183K, D202Y, S311G, D320N, T335I, D346A, Q349K, T393V, Y422F, R446G, H468Q, V482T
287	Q1L, G4C, Q28R, E65V, A72C, S86T, E183M,

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288	Q1L, G4C, Q28K, E65K, A72C, S86T, D181N, E183M, H203R, P224L, S311D, D320I, D346E, Q349R, T392M, Y422F, R446G, H468L
289	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
290	Q1L, G4C, Q28K, N29Y, E65K, A72C, D181N, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
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292	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, D202N, S311N, N318Y, D320N, T335I, D346A, Q349K, T392M, T393V, P442S, N445D, R446G, H468Q
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296	Q1L, G4C, S24T, Q28R, E65K, A72C, D202N, S311G, T335I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T
297	Q1L, G4C, A72C, S86T, D181N, S192L, D202N, P224L, S311G, N318Y, D320V, T335I, D346G, Q349K, T393I, R446G, H468Q
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299	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, D202N, P224L, S311G, D346A, Q349K, T393I, Y422F, P442S, N445D, R446G, H468L, V482T
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302	Q1L, G4C, Q28K, A72C, D181N, D202I, S311D, N318Y, T335I, D346E, Q349K, T392M, Y422F, R446G, H468L
303	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320N, D346E, Q349K, T393V, Y422F, T433S, P442S, N445D, R446G, H468L, V482I
304	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, S311G, N318Y, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I

305	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, S311G, N318Y, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T
306	Q1L, G4C, Q28R, E65K, A72C, S86T, E183M, D202N, D320I, T335I, D346A, Q349K, T392M, Y422F, N445D, R446G, H468L, V482T
307	Q1L, G4C, Q28K, E65M, A72C, S86T, E183M, S311N, N318Y, D320I, T335I, D346E, Q349K, T393I, Y422F, P442S, H468Q, V482I
308	Q1L, G4C, E65M, A72C, S86T, E183V, S192L, D202I, H203R, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468R, V482A
309	Q1L, G4C, T7Q, A8S, N10T, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
310	Q1L, G4C, E65K, A72C, S86T, D202V, S311N, D320V, T335I, D346V, Q349R, T392M, Y422F, N445D, R446G, H468L
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312	Q1L, G4C, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
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314	Q1L, G4C, Q28K, E65V, A72C, D181N, D202N, S311N, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482I
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317	G434GAAATG, T457TAAATT, Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
318	G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202Y, P224L, S311N, D346A, Q349K, T393I, Y422F, N445D, R446S, H468Q, V482A
319	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482T
320	Q1L, G4C, T27S, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
321	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, P224L, S311G, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T

322	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
323	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
324	Q1L, G4C, Q28K, E65V, A72C, E183M, D202N, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
325	Q1L, G4C, Q28R, E65K, A72C, D181N, P224L, S311N, N318Y, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I
326	Q1L, G4C, Q28R, E65M, A72C, S90F, D181N, P224L, S311G, N318Y, D346E, Q349K, T393I, Y422F, P442S, N445D, R446G, H468Q, V482I
327	G4C, Q28R, A72C, S86T, D181N, E183V, S192L, D202V, N246S, S311D, N318Y, D320V, D346A, Q349K, T393V, P442S, N445D, H468L, V482A
328	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311N, N318Y, D320I, T335I, D346A, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T
329	Q1L, G4C, Q28R, A72C, S86T, E183M, S192L, H203R, S311D, D320V, T335I, D346V, Q349K, N445D, H468Q, V482A
330	Q1L, G4C, Q28R, T59M, E65K, A68T, A72C, S86T, D181N, S192L, D202N, H203R, S311D, D320V, T335I, Q349R, T393A, P442S, N445D, R446G, H468L, V482A
331	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
332	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, K355Q, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
333	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, N318Y, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
334	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T448A, R453G, H468L, V482I
335	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
336	Q1L, G4C, E65M, A72C, E183M, D202I, P224L, S311D, N318Y, D320V, T335I, D346A, Q349K, T393A, Y422F, P442S, N445D, R446G, R453G, H468Q, V482I
337	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
338	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, S311G, N318Y, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
339	Q1L, G4C, S24T, T27Q, Q28R, N29T, E65V, A72C,

	D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
340	Q1L, G4C, E65V, A72C, D181N, E183M, S192T, P224L, S311G, D320V, T335I, D346G, Q349K, T393A, Y422F, P442S, N445D, R446G, H468L, V482T
341	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
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346	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
347	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, S311N, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
348	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482T
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352	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P462L, H468L, V482I
353	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468L, V482I
354	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, T280A, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
355	Q1L, G4C, Q28R, E65V, Q69R, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I

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357	Q1L, G4C, Q28K, E65V, A72C, E183K, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
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366	Q1L, G4C, S24C, Q28R, G30A, E65V, A72C, Y155C, D181N, Q190K, D202N, P224L, S311G, T335I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, R453G, H468Q, P480S, V482I
367	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, P402S, Y422F, P442S, N445D, R446G, H468L, V482I
368	Q1L, G4C, Q28R, E65K, A72C, E183M, D202N, P224L, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
369	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A72C, Y155C, D181N, D202N, P224L, M234T, S311G, D320I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
370	Q1L, G4C, Q28R, E65K, A72C, S86T, D202N, P224L, S311D, D320N, T335I, D346V, Q349K, T392M, T393V, Y422F, P442S, R446S, H468L
371	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202N, S311G, N318Y, D320I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
372	Q1L, G4C, W40R, E65M, A72C, S86T, E183V, S192L, D202I, H203R, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468R, V482A

373	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
374	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, T457TAAATT, H468L, V482I
375	Q1L, G4C, Q28R, E65V, A72C, K118Q, D181N, E183M, P224L, D247N, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
376	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
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383	Q1L, G4C, Q28R, G30A, E65V, A68T, A72C, D181N, E183M, D202N, P224L, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, V482I
384	Q1L, G4C, Q28R, E65V, A72C, K92R, L120P, D181N, E183M, D202N, S236F, T280A, S311G, D346E, Q349K, K355Q, T387S, T393V, P402S, D404N, Y422F, N445D, R446G, T451S, G463V, H468Q, V482I, S485T
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387	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, D202N, S311G, D320I, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, H468Q, V482I
388	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, S311G, T335I, D346A, Q349K, T393I, Y422F, P442S, N445D, R446G, H468L, V482I

389	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, D247N, S311G, D320I, D346E, Q349K, T387S, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
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391	Q1L, G4C, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, S236F, S311N, N318I, D346E, Q349K, K355Q, T387S, T393V, D404N, Y422F, N445D, R446G, H468Q, V482I
392	Q1L, G4C, T27S, Q28R, E65V, Q69R, A72C, K118Q, D181N, E183M, D202N, D247N, I277V, S311G, T335I, D346E, Q349K, K355Q, T393V, Y422F, N445D, R446G, H468Q, V482T
393	Q1L, G4C, Q28R, G30A, E65V, A72C, Y155C, D181N, E183M, D202N, M234T, S311G, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, V482T
394	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, H468L, V482I
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397	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, K92R, K118Q, D181N, E183M, D202N, S311G, T335I, D346E, Q349K, T387S, T393V, Y422F, N445D, R446G, P462L, H468Q, V482T, S485T
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400	Q1L, G4C, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, M234T, S311G, D320I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
401	Q1L, G4C, Q28K, E65V, A72C, S86T, E183K, S192L, D202N, D320N, T335I, D346A, Q349R, T393A, Y422F, P442S, R446G, H468R, V482A
402	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S236F, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
403	Q1L, G4C, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, D202N, M234T, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
404	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A72C, Y155C, D181N, E183M, D202N, P224L, M234T,

	S311G, D320I, T335I, A340S, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, P480S, V482I
405	Q1L, G4C, Q28R, E65K, A72C, D202I, P224L, S311G, N318Y, D320V, T335I, D346A, Q349R, T392M, T393A, N445D, R446G, H468L
406	Q1L, G4C, E65M, A72C, S86T, E183V, D202I, P224L, S311G, N318Y, D320V, D346A, Q349K, P442S, N445D, R446G, H468L, V482A
407	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, D181N, E183M, D202N, S311G, D346E, Q349K, T387S, T393V, Y422F, N445D, R446G, T451S, P462L, H468Q, V482T
408	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, E65M, A72C, S86T, E183M, D202N, P224L, S311G, D320I, T335I, (DeletionS437-P441), D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
409	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, T26I, Q28R, N29Y, G30A, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
410	Q1L, G4C, Q28R, E65V, A72C, K92R, D181N, E183M, P224L, I277V, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
411	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
412	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454PVRPQP, H468L, V482I
413	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P464THAAA, H468L, V482I
414	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P464PTHAAA, H468L, V482I
415	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, G151GCGRSG, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
416	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, K159KCGRNK, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
417	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, P454ATAAA, H468L, V482I
418	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, E65K, A72C, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
419	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, E65V, A72C, E183M, D202N, P224L, S311G, T335I,

	D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
420	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65M, A72C, S86T, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482I
421	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65M, A72C, E183M, S311G, N318Y, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
422	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
423	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, E183M, P224L, S311G, N318Y, T335I, D346A, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482T
424	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F, N445D, R446G, H468Q, V482I
425	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65K, A72C, S311N, N318Y, D346E, Q349K, T393V, Y422F, (DeletionbeiG439-G444), N445D, R446G, H468Q, V482I
426	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, N29Y, E65K, A72C, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
427	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
428	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, N445D, R446G, T448A, R453G, H468L, P480S, V482I, Y422F, P442S
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431	Q1L, G4C, A72C, S86T, D181N, E183K, D202V, P224L, S311G, D320V, D346E, Q349R, T393A, Y422F, P442S, N445D, R446G, H468L
432	Q1L, G4C, Q28R, E65V, A72C, K159CGRNKE183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
433	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, Q28R, E65K, A72C, D202N, S311G, T335I, D346E, Q349K, T393I, Y422F, N445D, R446G, H468Q, V482T
434	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65M,

	A72C, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
435	Q1L, G4C, Q28K, E65M, A72C, S86T, E183M, D202N, P224L, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F, (S437-P441), N445D, R446G, H468Q, V482T
436	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
437	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
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442	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I, Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
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445	Q1L, G4C, Q28R, E65K, A72C, S311N, N318Y, D346E, Q349K, T393V, Y422F, (DG439-G444)N445D, R446G, H468Q, V482I
446	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
447	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, N445D, R446G, T448A, R453G, H468L, P480S, V482I, Y422F, P442S
448	Q1L, G4C, A21T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, D181N, Q190K, D202N, T229M,

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449	Q1L, G4C, N10D, T27S, Q28R, E65V, A72C, K92R, K118Q, D181N, D202N, S236F, I277V, S311G, D346E, Q349K, K355Q, T387S, T393V, D404N, N417Y, Y422F, N445D, R446G, P462L, H468Q, V482I, S485T
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451	Q1L, G4C, N10D, T27S, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, D247N, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T
452	Q1L, G4C, T26I, Q28R, G30A, E65V, A72C, Y155C, D181N, D202N, T229M, G231D, S311G, T335I, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, V482T
453	Q1L, G4C, S24R, T26I, Q28R, G30A, E65V, A72C, D181N, E183M, D202N, P224L, S311N, T335I, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, H468Q, V482T
454	Q1L, G4C, N10D, T27S, Q28R, E65V, Q69R, A72C, D181N, E183M, D202N, S236F, D247N, I277V, S311N, T335I, D346E, Q349K, T387S, T393V, N417Y, Y422F, T433S, N445D, R446G, P462L, H468Q, V482I
455	Q1L, G4C, A21T, Q28R, E65V, A72C, Y155C, D181N, D202N, P224L, S311G, N318Y, D346E, Q349K, D390E, T393V, Y422F, N445D, R446G, T448A, H468Q, V482I
456	Q1L, G4C, T26I, Q28R, N29Y, E65V, A68T, A72C, Y155C, D181N, E183M, D202N, P224L, M234T, S311N, N318Y, D346E, Q349K, T393V, Y422F, N445D, R446G, T448A, R453G, H468Q, V482I
457	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A68T, A72C, Y155C, D181N, D202N, P224L, T229M, M234T, S311G, N318Y, D346E, Q349K, T393V, Y422F, N445D, R446G, R453G, H468Q, V482I
458	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, P224L, S236F, D247N, F306L, S311G, D346E, Q349K, K355Q, T393V, D404N, N417Y, Y422F, N445D, R446G, H468Q, V482I, S485T
459	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, S236F, D247N, S311G, N318I, T335I, D346E, Q349K, K355Q, T393V, Y422F, T433S, N445D, R446G, T451S, G463V, H468Q, V482I
460	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
461	G4C, Q28K, E65M, A72C, S86T, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
462	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG,

	K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468L, V482I
463	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
464	G4C, Q28K, E65M, A72C, S86T, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, T457TAAATT, H468L, V482I
465	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, T457TAAATT, H468L, V482I
466	G4C, Q28K, E65M, A72C, S86T, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, T457TAAATT, H468L, V482I
467	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, G434GAAATG, P442S, N445D, R446G, H468L, V482I, T457TAAATT,
468	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F, P442S, N445D, R446G, H468Q, V482I
469	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, S192L, D202V, S311G, D320I, D346V, Q349R, T393A, Y422F, P442S, N445D, R446G, H468Q, V482I
470	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311N, N318Y, D320I, D346A, Q349K, T393V, Y422F, N445D, R446G, H468L, V482T
471	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, D181N, E183M, D202N, T229M, S311G, A340S, D346E, Q349K, T393V, Y422F, N445D, R446G, H468Q, V482T

11. The polypeptide according to one or more of the preceding claims, which is expressed and secreted at a level of more than 100 mg/l, more preferably of more than 200 mg/l, particularly preferably of more than 500 mg/l, and most preferably of more than 1 g/l into the supernatant after introduction of a nucleic acid encoding a polypeptide having an amino acid sequence with at least 85% sequence identity to the SEQ ID NO: 2 into a yeast.

12. A nucleic acid encoding the polypeptide of one or more of claims 5 to 11, preferably having at least 95% identity to SEQ ID NO: 1.

13. A vector comprising the nucleic acid of claim 12.

14. A host cell transformed with a vector of claim 13.

15. The host cell of claim 14, wherein the host cell is derived from the group consisting of Saccharomyces, Schizosaccharomyces, Kluyveromyces, Pichia, Pichia, Hansenula, Aspergillus, Trichoderma, Penicillium, Chrysosporium, Chaetomium, Acremonium, Candida and Yarrowina.

16. The host cell of claim 14 or 15, wherein the host cell is capable of producing ethanol, preferably a yeast derived from the group of host cells comprising *Saccharomyces cerevisiae, Pichia stipitis, Pachysolen tannophilus.*

17. The host cell of any one of claims 14 to 15, wherein the host cell is a methylotrophic yeast, preferably derived from the group of host cells comprising *Pichia methanolica, Pichia pastoris, Pichia angusta, Hansenula polymorpha.*

18. The host cell of any one of claims 14 to 15, wherein the host cell is a filamentous fungi, preferably selected from the of host cells comprising *members of the genus Trichoderma, Aspergillus, Chaetomium, Chrysosporium Penicillium or Acremonium, more preferable being selected from one of the species Trichoderma sp., Trichoderma reesei, Trichoderma longibrachiatum, Aspergillus niger, Aspergillus oryzae, Chaetomium thermophilum or Chrysosporium lucknowense*

19. A method of producing a cellobiohydrolase protein according to any one of claims 1 to 11, comprising the steps:

d. obtaining a host cell, which has been transformed with a vector comprising the nucleic acid as defined in claim 12;
e. cultivation of the host cell under conditions under which the cellobiohydrolase protein is expressed; and
f. recovery of the cellobiohydrolase protein.

20. Method for identifying polypeptides having cellobiohydrolase activity according to any one of claims 1 to 11, comprising the steps of:

h. Generating a library of mutant genes encoding mutant proteins by mutagenesis of a nucleic acid having the sequence defined by SEQ ID NO: 6 (encoding SEQ ID NO: 5) or a nucleic acid according to claim 12 , preferably having the sequence defined by SEQ ID NO: 1;
i. Inserting each mutant gene into an expression vector;

j. Transforming yeast cells with each expression vector to provide a library of yeast transformants;
k. Cultivation of each yeast transformant under conditions under which the mutant protein is expressed and secreted;
l. Incubating the expressed mutant protein with a substrate;
m. Determining the catalytic activity of the mutant protein;
n. Selecting a mutant protein according to the determined catalytic activity.

21. The method of claim 19, wherein a library of mutant genes encoding mutant proteins by mutagenesis of a nucleic acid a nucleic acid according to claim 12 is generated, and wherein steps e. to g. are performed as follows:
e. Incubating the expressed mutant protein with cellulosic material;
f. Determining the amount of released sugar;
g. Selecting a mutant protein according to the amount of released sugar.

22. The method of claim 20 or 21, comprising the additional steps of:
h. Sequencing the selected mutant gene or protein;
i. Identifying the amino acid modification(s) by comparing the sequence of the selected mutant protein with the amino acid sequence of SEQ ID NO: 2.

23. Method of preparing a polypeptide having cellobiohydrolase activity, comprising the steps:
a. Providing a polypeptide having cellobiohydrolase activity comprising an amino sequence having at least 68 % sequence identity to the catalytic domain of SEQ ID NO: 2 (SEQ ID NO: 5);
b. Identifying the amino acids of this polypeptide which correspond to the amino acids which are modified with respect to the amino acid sequence of SEQ ID NO: 2, as identified in step i. of claim 22; and
c. Preparing a mutant polypeptide of the polypeptide provided in step a. by carrying out the amino acid modification(s) identified in step b. through site-directed mutagenesis.

24. The method according to claim 23, wherein the polypeptide provided in step a. is a wild type cellobiohydrolase derived from *Trichoderma reesei*.

25. Polypeptide having cellobiohydrolase activity, obtainable by the method of claim 23 or 24.

26. The polypeptide according to claim 1, wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 5 are modified as indicated in the following table:

Position	Preferred	More Preferred	Most Preferred
Q1	L	L	L
Q2	P,S	P,S	S
G4	C	C	C
A6	G,L,V	G,L,V	L
T7	Q	Q	Q
A8	S	S	S
N10	T,D	T,D	T,D
P12	Q		
T15	S		
A21	S,T,C	S,T,C	
G23	A,D,N		
S24	T,C,N	T,C,N	
T26	I,N	I,N	
T27	S,Q	S,Q	
Q28	L,K,R,N	L,K,R,N	K,R
N29	T,Y	T,Y	
G30	A	A	
A31	S		
V32	G		
N37	S		
W40	R	R	
V41	T		
G46	S		
Y47	S,F	S,F	
T48	A		
N49	S		
C50	S		
T52	D		
N54	S		
D57	S		
T59	M		
Y60	H		
D64	N	N	
E65	V,M,K	V,M,K	V,M,K
A68	T	T	
Q69	K,R	K,R	
A72	V,C	V,C	C
V84	A		
S86	T	T	T
S89	N		
S90	T,F		
K92	R	R	
S99	T		
Q109	R		
D110	G,S,N		
D111	H,E		
I116	V,K,E		
F117	Y		
K118	A,T,Q	A,T,Q	

L119	L,I		
L120	P,M		
D129	N		
V130	I		
G139	S		
A145	T		
M146	C		
G151	GCGRSG	GCGRSG	GCGRSG
V152	A,E		
K154	R		
Y155	S,C,H	S,C,H	
N157	S		
N158	D		
K159	E, KCGRNK	KCGRNK	KCGRNK
K163	C		
G167	C		
Q172	Q		
F179	I		
I180	N		
D181	N	N	N
E183	V,M,K	V,M,K	V,M,K
E187	K		
G188	C		
Q190	L,K	L,K	
S192	L,I,P,T,M	L,I,P,T,M	
S193	L,P,T		
N194	G,L,I,V,S,C,K,R,D,Q,Y	G,L,I,V,S,C,K,R,D,Q,Y	
I200	N,F		
D202	G,I,V,N,F,Y	G,I,V,N,F,Y	G,I,V,N,F, Y
H203	R	R	
D211	G		
V212	L		
A221	V		
P224	L	L	L
D228	N		
T229	A,S,M	A,S,M	
G231	D	D	
T233	S		
M234	L,I,V,T,K	L,I,V,T,K	
S236	F,Y	F,Y	
T243	G,A,L,I,V,P,S,C,M,R,D,Q,F,Y, W	G,A,L,I,V,P,S,C,M,R,D,Q,F,Y, W	
Y244	H,F		
S245	T		
N246	S,K,D		
D247	N	N	
G251	R		
F260	C		
G266	S		
K275	E		
I276	V		
I277	V		
T280	A		
L290	H		
D293	R,H		

G294	A		
T295	S		
T297	N		
T299	I,S		
S301	C		
K304	R		
F306	L,Y		
N310	D,E		
S311	G,D,N	G,D,N	G,D,N
V313	I		
I314	F		
N318	I,H,D,Y	I,H,D,Y	I,D,Y
D320	I,V,E,N	I,V,E,N	I,V,N
I321	N		
T325	A,I		
N327	Y		
T335	I	I	I
A340	G,S,T	G,S,T	
F341	C		
D343	A		
T344	M	M	
D345	E		
D346	G,A,V,E	G,A,V,E	G,A,V,E
Q349	K,R	K,R	K,R
H350	Y		
A354	T		
K355	Q	Q	
A358	E		
Q361	R		
Q362	G,R,H		
G363	P		
M364	L,S		
V367	A		
D373	E		
Y374	A,P,S,C,R,H,D	A,P,S,C,R,H,D	
A375	G,L,V,T,C,M,R,D,E,N,Q,Y	G,L,V,T,C,M,R,D,E,N,Q,Y	
A376	T		
P386	L,S		
T387	A,S	A,S	
D390	G,E	G,E	
T392	S,M,K	S,M,K	M
T393	A,I,V,S	A,I,V,S	A,I,V
P394	C		
T400	S		
P402	S		
T403	K		
D404	N		
D410	G		
N417	Y		
S418	P		
T421	I		
Y422	F	F	F

27. The polypeptide according to claim 26, wherein the polypeptide has an amino acid sequence selected from the list of the following mutations of SEQ ID NO: 5:

Consecutive Number	Mutants with respect to Seq. ID NO:5
1	G4C, A72C, Q349K
2	G4C, A72C, T344M, Q349K
3	G4C, A72C, T344M, D346G, Q349R
4	G4C, A72C, D320V, Q349K
5	G4C, A72C, P224L, F306Y, Q349R
6	G4C, A72C
7	A72V, D346A, T393A
8	G4C, A72C, Q349R
9	G4C, W40R, A72C, T344M, Q349K
10	A72V, D320V, D346A
11	G4C, A72C, N194Y, T243L, Q349R, Y374S, A375R
12	G4C, E65V, A72C, Y244H, Q349R
13	G4C, A72C, D202G, D320N, Q349R, A358E
14	G4C, A72C, D320V, Q349R
15	G4C, A72C, Q349K, S86T
16	A72V, T335I, D346A, T393A
17	G4C, A72C, E183V, K304R, Q349K
18	G4C, A72C, T243G, Q349R, Y374P, A375M
19	G4C, A72C, N194V, T243M, Q349R, Y374A, A375T
20	G4C, D64N, A72C, Q349R, A358E
21	G4C, A72C, Q349K, Q28R, S193T
22	G4C, A72C, E183K, Q349K
23	G4C, A72C, S311N, Q349K
24	G4C, A72C, N194K, Q349R, Y374P, A375Q
25	G4C, A72C, D181N, Q349K
26	W40R, D320V, Q349K, T393A
27	W40R, T335I, D346A, T393A
28	Q1L, G4C, A72C, D181N, E183K, N327Y, Q349R
29	A72C, T335I, Q349R
30	G4C, A72C, N194K, T243P, Q349R, Y374H, A375E
31	G4C, A72V, Q349R, P462del

32	G4C, A72C, S236Y, Q349R
33	G4C, A72C, S311G, Q349K
34	A72V, D320V, T335I, D346A, T393A
35	G4C, A72C, S86T, M234V, Q349K
36	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
37	G4C, A72C, G251R, Q349R
38	G4C, A72C, Q349K, D320V
39	G4C, A72C, E183K, Q349R
40	Q1L, G4C, A72C, H203R, Q349K
41	G4C, W40R, A72C, Q349K
42	G4C, A72C, Q349R, V367A
43	Q1L, G4C, A6V, C50S, A72C, I180N, D181N, E183K, Q349R
44	G4C, A72C, S311G, D320V, Q349K
45	Q1L, G4C, A72C, D181N, E183K, T243S, Q349R, P386S
46	Q1L, G4C, A72C, K154R, Q349K, T393I
47	G4C, A72C, N194G, T243F, Q349R, Y374P, A375R
48	A72V, D320V, D346A, T393A
49	A72C, Q349K
50	G4C, A72C, E183V, Q349K
51	G4C, A72C, E183K, N318Y, Q349K
52	W40R, A221V
53	G4C, A72C, K92R, Q349K
54	Q1L, G4C, A72C, S90T, D181N, E183K, Q349R
55	G4C, A72C, Q349R, Y422F
56	G4C, T48A, A72C, Q349R
57	E187K, D320V
58	G4C, S24N, E65K, A72C, Q349R
59	Q1L, G4C, A72C, S193P, Q349K
60	Q1L, G4C, A72C, delV152-K159, D181N, E183K, Q349R
61	Q1L, G4C, A72C, Q349K
62	Q1L, G4C, A72C, D181N, E183K, M234L, V313I, Q349R
63	Q1L, G4C, A72C, D181N, E183K, I200N, Q349R
64	G4C, A72C, N194K, T243Y, Q349R, A375N
65	Q1L, G4C, Q28R, A72C, Q349K

66	G4C, E65V, A72C, Q349R
67	D320V, Q349K
68	Q1L, G4C, A72C, S311G, Q349K
69	G4C, A72C, T243Q, Q349R, Y374P, A375M
70	Q1L, G4C, A72C, D320V, Q349R
71	Q1L, G4C, T15S, A72C, Y244F, Q349K
72	G4C, A72C, E183K, D346E, Q349R
73	Q1L, G4C, A72C, Q349K, T392M
74	G4C, A72C, D202N, S311N, Q349R
75	G4C, A72C, N194D, T243A, Q349R, Y374P, A375Y
76	G4C, A72C, N194Y, T243V, Q349R, Y374P
77	Q1L, G4C, A72C, Q349R
78	G4C, Q28R, E65K, A72C, S86T, D202N, H203R, S311N, D320I, A340G, D346A, Q349K, T393A, Y422F
79	G4C, A72C, D202N, Q349R
80	G4C, A72C, P224L, Q349R
81	Q1L, G4C, A72C, D181N, E183K, T229M, A340T, Q349R
82	Q1L, G4C, A72C, D181N, Q349R
83	G4C, A72C, D320V, D346V, Q349K
84	Q1L, G4C, A72C, V152A, Q349K
85	Q1L, G4C, A72C, Q349K, Y422F
86	G4C, A72C, D202V, D320V, Q349K
87	Q1L, G4C, A72C, Y155S, D181N, E183K, Q349R
88	Q1L, G4C, A72C, D181N, D247N, Q349K
89	Q1L, G4C, A68T, A72C, Q349K
90	Q1L, G4C, D64N, A72C, Q349K
91	G4C, A72C, D181N, P224L, Q349K
92	G4C, A72C, N194I, T243Y, Q349R, Y374P, A375R
93	Q1L, G4C, A72C, E183K, Q349R
94	G4C, A72C, S311G, Q349R
95	Q1L, G4C, A72C, S311N, Q349K
96	Q1L, G4C, A72C, S86T, Q349R
97	Q1L, G4C, A72C, D181N, E183K, G231D, Q349R
98	Q1L, G4C, A72C, S89N, D181N, E183K, Q349R
99	Q1L, G4C, E65K, A72C, Q349K
100	Q1L, Q2P, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K,

	T392M, Y422F
101	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
102	G4C, A72C, E183K, D202Y, N310D, Q349R
103	G4C, A72C, N194I, T243D, Q349R, Y374P, A375Y
104	Q1L, G4C, A72C, D181N, E183K, Q349R
105	G4C, Q28R, A72C, S86T, E183K, P224L, S311N, N318Y, T335I, D346G, Q349R, T393I
106	Q1L, G4C, A72C, D181N, Q349K
107	Q1L, G4C, A72C, D181N, E183K, T243I, N246D, Q349R
108	Q1L, G4C, G23N, A72C, D110G, I116V, L119I, D181N, E183K, D211G, D293R, N310D, Q349R, Q362R, G363P, M364S
109	Q1L, G4C, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
110	Q1L, G4C, A72C, S86T, D181N, E183K, Q349R, T393S
111	Q1L, G4C, G23N, A72C, V84A, D110G, D111H, I116E, F117Y, K118A, D181N, E183K, D293R, T295S, Q349R, M364L
112	Q1L, G4C, A72C, A145T, H203R, Q349K, T403K
113	Q1L, G4C, A72C, D181N, E183K, M234I, Q349R
114	Q1L, G4C, A72C, D181N, E183K, T297N, Q349R
115	G4C, Q28R, E65M, A72C, S86T, E183K, S192I, H203R, S311N, D346E, Q349K, T392M, T393A, Y422F
116	Q1L, G4C, A72C, D202N, Q349K
117	Q1L, G4C, A72C, S99T, D181N, E183K, Q349R
118	Q1L, G4C, A72C, I200F, Q349K
119	Q1L, G4C, A31S, A72C, D181N, E183K, Q349R
120	Q1L, G4C, Q28L, A72C, D181N, E183K, Q349R
121	Q1L, G4C, A72C, D181N, E183K, T233S, Q349R
122	Q1L, G4C, A21T, A72C, D181N, E183K, Q349R
123	Q1L, G4C, A72C, D346V, Q349K
124	Q1L, G4C, Y47F, A72C, D181N, E183K, Q349R
125	Q1L, G4C, A72C, D181N, E183K, M234T, Q349R
126	Q1L, G4C, A72C, N157S, D181N, E183K, Q349R
127	G4C, A72C, N194Q, T243V, Q349R, Y374P, A375Y

128	Q1L, G4C, A72C, D181N, E183K, I314F, Q349R
129	Q1L, G4C, A72C, Q349K, T392K
130	Q1L, G4C, A72C, D181N, E183K, M234V, Q349R
131	Q1L, G4C, A21S, A72C, D181N, E183K, Q349R
132	Q1L, G4C, Q28R, E65V, A72C, D181N, E183V, D228N, S311N, N318Y, D346E, Q349R, Y422F
133	G4C, A72C, N194C, Q349R, Y374C
134	Q1L, G4C, A72C, D181N, E183K, Q349R, T400S
135	Q1L, G4C, T26I, A72C, D181N, E183K, Q349R
136	Q1L, G4C, A72C, D181N, E183K, N310D, Q349R, T392S
137	Q1L, G4C, A72C, D129N, D181N, E183K, Q190L, G266S, I276V, Q349R, P386L
138	Q1L, G4C, A72C, D181N, E183K, D202N, Q349R
139	Q1L, G4C, A72C, Y155C, D181N, E183K, Q349R
140	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
141	Q1L, G4C, A72C, D181N, E183K, N246K, Q349R
142	G4C, W40R, E65V, A72C, S86T, D181N, E183K, D202I, H203R, S311D, D320N, D346V, Q349R, T392M, T393A, Y422F
143	Q1L, G4C, A72C, Y155C, Q349K
144	Q1L, G4C, A68T, A72C, D181N, E183K, Q349R
145	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, Y47F, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F
146	Q1L, G4C, W40R, E65M, A72C, S86T, S192L, D202N, H203R, S311D, D320I, T335I, D346G, Q349K, T392M, Y422F
147	Q1L, G4C, A72C, S86T, D181N, E183K, D320V, Q349R
148	G4C, Q28K, A72C, S86T, E183M, D202N, P224L, S311G, N318Y, D320N, D346A, Q349R, T392M, T393I
149	Q1L, Q2P, G4C, Q28R, W40R, E65K, A72C, D181N, S192L, D202I, H203R, P224L, S311G, D320I, D343A, D346A, Q349K
150	Q1L, G4C, Q28R, E65K, A72C, E183M, D202I, P224L, D320N, D346V, Q349K, T392M, T393V, Y422F
151	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202V,

	S311G, N318Y, D320I, D346G, Q349K, T393V, Y422F
152	Q1L, G4C, W40R, E65M, A72C, D181N, E183K, S192P, D202N, P224L, S311D, N318Y, D320V, D346G, Q349K, T392M
153	Q1L, G4C, E65V, A72C, D181N, E183K, P224L, S311G, D320N, D346G, Q349R, T392M, T393I
154	Q1L, G4C, Q28R, E65V, A72C, G151GCGRSG, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
155	Q1L, G4C, E65M, A72C, D181N, E183M, D202Y, P224L, S311D, N318Y, D320I, T335I, D346A, Q349K, T392M, T393I
156	Q1L, G4C, G23A, A72C, D110S, D111H, I116V, F117Y, K118A, L120M, D181N, E183K, D293H, G294A, N310E, Q349R, Q362G, M364S
157	Q1L, G4C, A72C, D181N, E183K, Q349R, T421I
158	G4C, Q28K, E65M, A72C, S86T, V152A, D181N, E183V, S192L, D202N, S311N, D320N, D346E, Q349R, T387A, T392M, T393I, Y422F
159	Q1L, G4C, W40R, E65V, A72C, S86T, E183V, G188C, S192T, D202Y, H203R, P224L, S311N, D320V, D346E, Q349K, T393V, Y422F
160	Q1L, G4C, E65M, A72C, S86T, E183M, D202N, P224L, T335I, D346G, Q349K, T392M, T393A
161	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F
162	G4C, W40R, A72C
163	Q1L, G4C, W40R, E65K, A72C, S86T, E183K, S192L, D202Y, P224L, D320I, D346E, Q349R
164	Q1L, G4C, A21T, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, D202N, P224L, S311G, N318Y, D320I, D346E, Q349K, T393V, Y422F
165	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F
166	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F

167	Q1L, G4C, T7Q, A8S, N10T, S24T, T27Q, Q28R, N29T, V41T, G46S, Y47S, T52D, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
168	Q1L, G4C, Q28R, E65V, A72C, K159KCGRNK, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
169	Q1L, G4C, Q28K, W40R, E65V, A72C, D181N, E183V, S192P, D202V, H203R, S311G, D320N, D346E, Q349K, T392M, T393A, Y422F
170	Q1L, G4C, Q28R, E65V, A72C, G139S, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
171	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F
172	Q1L, G4C, Q28R, E65K, A72C, D181N, S311N, N318Y, D346E, Q349K, T393V, Y422F
173	Q1L, G4C, W40R, A72C, S192L, D202N, H203R, P224L, S311N, D320I, T335I, D346V, Q349R, T393I
174	Q1L, G4C, Q28K, E65K, A72C, E183M, D202N, P224L, T229S, S311G, D320I, T335I, D346V, Q349R, T393V
175	Q1L, G4C, Q28R, G30A, E65M, A72C, D181N, D202N, P224L, S311D, N318Y, D346E, Q349K, T392M, T393V, Y422F
176	Q1L, G4C, Q28R, E65V, A72C, S68T, E183M, S311N, T335I, D346E, Q349K, T393V, Y422F
177	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F
178	T243C, A375C, N194C, Y374C
179	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, S311G, D346V, Q349R, T392M, T393V, Y422F
180	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311G, D346E, Q349K, T393V, Y422F
181	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, S311N, N318Y, D320I, T335I, D346E, Q349K, T393I, Y422F
182	Q1L, G4C, Q28R, E65K, A72C, S86T, E183K, D202N, P224L, S311G, T335I, D346A, Q349K, T393V, Y422F
183	Q1L, G4C, Q28R, E65V, A72C, L120P, D181N, E183M,

	P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
184	Q1L, G4C, Q28K, E65V, A72C, S86T, E183M, S311N, N318H, D320V, D346V, Q349K, T392M, T393A
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186	Q1L, G4C, Q28R, E65V, A72C, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F
187	Q1L, G4C, Q28R, E65K, A72C, D181N, D202N, H203R, P224L, S311D, D346G, Q349K
188	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, D390E, T393V, Y422F
189	Q1L, G4C, T27S, Q28R, E65V, Q69R, A72C, L120P, D181N, E183M, D202N, D247N, S311G, D346E, Q349K, K355Q, T387S, T393V, Y422F
190	Q1L, G4C, Q28R, E65K, A72C, E183V, S192T, D202N, S311G, D320V, D346A, Q349K
191	Q1L, G4C, W40R, E65V, A72C, S86T, E183M, D202N, P224L, S311G, D320V, D346E, Q349R, T393I
192	Q1L, G4C, Q28N, E65K, A72C, D181N, E183M, D202N, H203R, S311G, N318Y, D320N, Q349R, T393V, Y422F
193	Q1L, G4C, Q28R, V41T, G46S, Y47S, T52D, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
194	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
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196	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, T229M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F
197	Q1L, G4C, Q28K, W40R, A72C, S86T, D181N, E183M, S192I, D202Y, T299S, S311N, N318Y, D320I, D346V, Q349R, T393I
198	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, T229M, G231D, M234T, S311G, D320I, D346E, Q349K, T393V, Y422F

199	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, P224L, T229M, G231D, M234T, S311G, D320I, A340S, D346E, Q349K, D390E, T393V, Y422F
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201	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311G, N318Y, D346E, Q349K, T393V, Y422F
202	Q1L, G4C, Q28R, W40R, E65V, A72C, S86T, S192T, D202V, H203R, S311N, N318Y, D346A, Q349K, T392M, T393A, Y422F
203	Q1L, G4C, Q28K, E65K, A72C, D181N, H203R, P224L, S311G, D320V, D346G, Q349K, T392M, T393I
204	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F
205	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, S311G, N318Y, D346E, Q349K, T393V, Y422F
206	Q1L, G4C, Q28R, E65V, A72C, E183K, D202I, P224L, S311G, D320I, Q349K, T393V
207	Q1L, G4C, Q28K, A72C, S86T, D181N, E183V, S192T, D202N, P224L, S311G, N318Y, D320V, D346G, Q349R, T392M, Y422F
208	G4C, Q28R, E65K, A72C, S86T, D181N, E183M, S192L, D202N, H203R, P224L, S311D, D346E, Q349R, T392M, T393A, Y422F
209	Q1L, G4C, W40R, E65K, A72C, Q109R, D181N, E183M, S192I, D202I, H203R, S245T, D346A, Q349R, T393A, Y422F
210	Q1L, G4C, Q28K, E65M, A72C, D181N, D202N, S311N, T335I, D346E, Q349K, T393I, Y422F
211	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349R, T393V, N417Y, Y422F
212	Q1L, G4C, Q28R, W40R, E65V, A72C, D202Y, H203R, P224L, T299I, N318Y, D320V, D346A, Q349K, T392M, T393A
213	G4C, Q28R, E65V, A72C, E183M, D202N, P224L,

	S311G, N318Y, D320V, D346G, Q349K, T392M, Y422F
214	Q1L, G4C, Q28K, A72C, S86T, E183K, S311G, D320V, D346A, Q349R, T392M, T393I, Y422F
215	Q1L, G4C, Q28R, E65M, A72C, D181N, P224L, S311N, D320N, T335I, D346E, Q349K, T392M, Y422F
216	Q1L, G4C, Q28K, E65V, A72C, D181N, D202N, S311G, T335I, D346E, Q349K, T393V, Y422F
217	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F
218	Q1L, G4C, Q28R, E65K, A72C, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F
219	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, S311G, D320I, D346E, Q349K, T393V, Y422F
220	Q1L, G4C, W40R, E65V, A72C, S86T, D181N, S192T, D202N, H203R, P224L, S311G, N318Y, T335I, D346G, Q349K, T392M, T393V, Y422F
221	Q1L, G4C, Q28R, E65K, A72C, E183M, S311N, D320I, D346E, Q349K, T393I, Y422F
222	Q1L, G4C, T7Q, A8S, N10T, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
223	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202N, P224L, S311G, D346A, Q349K, T393I, Y422F
224	Q1L, G4C, N10D, Q28R, E65V, Q69R, A72C, K92R, K118Q, D181N, E183M, D202N, T280A, S311G, T335I, D346E, Q349K, K355Q, T387S, T393V, D404N, Y422F
225	Q1L, G4C, Q28R, E65M, A72C, E183M, D202N, S311G, D320I, T335I, D346E, Q349K, T393I, Y422F
226	Q1L, G4C, Q28K, E65K, A72C, D181N, E183M, D202N, S311D, D320V, T335I, D346G, Q349K, T393I, Y422F
227	Q1L, G4C, Q28K, E65K, A72C, S86T, P224L, S311N, D320I, T335I, D346E, Q349K, T393V, Y422F
228	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F
229	G4C, E65K, A72C, S86T, E183M, D202I, P224L, S311N, N318Y, D320N, T335I, D346V, Q349R, T393V, Y422F
230	Q1L, G4C, Q28R, E65K, A72C, D202N, S311N, T335I,

	D346E, Q349K, T393I, Y422F
231	Q1L, G4C, E65V, A72C, D181N, E183K, D202G, Q349R
232	Q1L, G4C, Q28R, E65K, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
233	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, F306L, S311G, D320I, D346E, Q349K, T393V, Y422F
234	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F
235	Q1L, G4C, Q28K, E65K, A72C, D181N, E183K, S192P, P224L, S311G, N318Y, D320V, D346E, Q349R, T392M, T393I, Y422F
236	Q1L, G4C, Q28K, E65M, A72C, S86T, E183M, H203R, S311D, D320V, T335I, D346E, Q349R, T393A
237	Q1L, G4C, Q28R, A72C, D181N, E183V, D202I, H203R, P224L, S311D, D320V, D346V, Q349R, T392M, T393I
238	Q1L, G4C, Q28K, W40R, E65K, A72C, S86T, D181N, E183K, S192L, D202I, H203R, S311N, D320N, D346V, Q349K, T392M, T393A, Y422F
239	G4C, E65V, A72C, S86T, Y155H, D181N, E183V, Q190K, P224L, S311N, D320V, D346V, Q349K, T392M, T393V, Y422F
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245	Q1L, G4C, Q28R, E65K, A72C, S86T, D202N, S311G, N318Y, D320I, D346A, Q349K, T393I, Y422F
246	Q1L, G4C, Q28R, A72C, D181N, S311G, N318Y, D320V, D346E, Q349K, T393I, Y422F
247	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311G,

	D320I, D346E, Q349K, T393V, Y422F
248	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, S311G, D346E, Q349K, T393V, Y422F
249	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, S311N, D320I, D346E, Q349K, T393V, Y422F
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251	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F
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254	Q1L, G4C, Q28K, E65K, A72C, S86T, D181N, E183M, H203R, P224L, S311D, D320I, D346E, Q349R, T392M, Y422F
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256	Q1L, G4C, Q28K, N29Y, E65K, A72C, D181N, S311G, T335I, D346E, Q349K, T393V, Y422F
257	Q1L, G4C, Q28K, E65M, A72C, E183M, S311G, D346E, Q349K, T393V, Y422F
258	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, D202N, S311N, N318Y, D320N, T335I, D346A, Q349K, T392M, T393V
259	Q1L, G4C, Q28K, E65K, A72C, S86T, D181N, E183M, D202N, S311G, N318Y, T335I, D346E, Q349K, T393I, Y422F
260	Q1L, G4C, Q28R, E65K, A72C, E183V, S192T, D202N, S311G, D320V, D346A, Q349K, T393V
261	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, S311N, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F
262	Q1L, G4C, S24T, Q28R, E65K, A72C, D202N, S311G, T335I, D346E, Q349K, T393I, Y422F
263	Q1L, G4C, A72C, S86T, D181N, S192L, D202N, P224L, S311G, N318Y, D320V, T335I, D346G, Q349K, T393I
264	Q1L, G4C, Q28R, E65V, A72C, D181N, P224L, S311D,

	N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
265	Q1L, G4C, Q28R, E65M, A72C, D181N, E183M, D202N, P224L, S311G, D346A, Q349K, T393I, Y422F
266	Q1L, G4C, Q28K, E65V, A72C, S86T, E183V, S192I, D202V, D320I, T335I, D346V, Q349K, T392M, T393I, Y422F
267	Q1L, G4C, Q28K, E65M, A72C, S86T, D181N, E183M, D202N, P224L, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F
268	Q1L, G4C, Q28K, A72C, D181N, D202I, S311D, N318Y, T335I, D346E, Q349K, T392M, Y422F
269	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320N, D346E, Q349K, T393V, Y422F
270	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, S311G, N318Y, D346E, Q349K, T393I, Y422F
271	Q1L, G4C, Q28K, E65K, A72C, D181N, D202N, S311G, N318Y, D346A, Q349K, T393I, Y422F
272	Q1L, G4C, Q28R, E65K, A72C, S86T, E183M, D202N, D320I, T335I, D346A, Q349K, T392M, Y422F
273	Q1L, G4C, Q28K, E65M, A72C, S86T, E183M, S311N, N318Y, D320I, T335I, D346E, Q349K, T393I, Y422F
274	Q1L, G4C, E65M, A72C, S86T, E183V, S192L, D202I, H203R, P224L, S311G, N318Y, D320V, D346A, Q349K
275	Q1L, G4C, T7Q, A8S, N10T, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
276	Q1L, G4C, E65K, A72C, S86T, D202V, S311N, D320V, T335I, D346V, Q349R, T392M, Y422F
277	Q1L, G4C, Q28R, E65K, A72C, D181N, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F
278	Q1L, G4C, Q28R, D57S, D64N, E65V, Q69K, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
279	Q1L, G4C, Q28R, A72C, S86T, E183M, S192T, D202N, H203R, P224L, S311N, T335I, D346V, Q349R, T392M, T393V
280	Q1L, G4C, Q28K, E65V, A72C, D181N, D202N, S311N, D346A, Q349K, T393I, Y422F

281	G4C, Q28K, E65M, A72C, S86T, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
282	G434GAAATG, T457TAAATT, Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
283	G4C, Q28R, E65M, A72C, S86T, D181N, E183M, D202Y, P224L, S311N, D346A, Q349K, T393I, Y422F
284	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, D202N, P224L, S311G, D320I, D346E, Q349K, T393I, Y422F
285	Q1L, G4C, T27S, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
286	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, P224L, S311G, T335I, D346A, Q349K, T393V, Y422F
287	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
288	Q1L, G4C, Q28R, E65V, A72C, S86T, D202N, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
289	Q1L, G4C, Q28K, E65V, A72C, E183M, D202N, S311G, D320I, D346E, Q349K, T393V, Y422F
290	Q1L, G4C, Q28R, E65K, A72C, D181N, P224L, S311N, N318Y, D320I, D346E, Q349K, T393V, Y422F
291	Q1L, G4C, Q28R, E65M, A72C, S90F, D181N, P224L, S311G, N318Y, D346E, Q349K, T393I, Y422F
292	G4C, Q28R, A72C, S86T, D181N, E183V, S192L, D202V, N246S, S311D, N318Y, D320V, D346A, Q349K, T393V
293	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311N, N318Y, D320I, T335I, D346A, Q349K, T393I, Y422F
294	Q1L, G4C, Q28R, A72C, S86T, E183M, S192L, H203R, S311D, D320V, T335I, D346V, Q349K
295	Q1L, G4C, Q28R, T59M, E65K, A68T, A72C, S86T, D181N, S192L, D202N, H203R, S311D, D320V, T335I, Q349R, T393A
296	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F

297	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, K355Q, T393V, Y422F
298	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, N318Y, T335I, D346A, Q349K, T393V, Y422F
299	Q1L, G4C, Q28R, E65M, A72C, S86T, D181N, E183M, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F
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301	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F
302	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, E183M, S311G, N318Y, D346A, Q349K, T393V, Y422F
303	Q1L, G4C, S24T, T27Q, Q28R, N29T, E65V, A72C, D181N, P224L, S311D, N318Y, D320N, D346A, Q349K, T392M, T393I, Y422F
304	Q1L, G4C, E65V, A72C, D181N, E183M, S192T, P224L, S311G, D320V, T335I, D346G, Q349K, T393A, Y422F
305	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202F, S311G, N318Y, T335I, Q349K, T393V, Y422F
306	Q1L, G4C, Q28K, E65K, A72C, S86T, D181N, D202N, P224L, S311D, N318Y, D320N, D346A, Q349R, T392M, T393I, Y422F
307	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, S311N, D320I, T335I, D346E, Q349K, T393V, Y422F
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310	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, S311N, T335I, D346A, Q349K, T393V, Y422F
311	Q1L, G4C, Q28K, E65K, A72C, S86T, E183M, P224L, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F
312	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, T229M, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F
313	Q1L, G4C, Q28K, E65M, A72C, D181N, E183M, S311G, T335I, D346E, Q349K, T393V, Y422F

314	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, D404N, Y422F
315	Q1L, G4C, Q28R, E65V, A72C, E183M, D202N, P224L, S311G, N318Y, T335I, D346E, Q349K, T393V, Y422F
316	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, T280A, S311G, D320I, D346E, Q349K, T393V, Y422F
317	Q1L, G4C, Q28R, E65V, Q69R, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
318	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, K275E, S311G, D320I, D346E, Q349K, T393V, Y422F
319	Q1L, G4C, Q28K, E65V, A72C, E183K, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F
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321	Q1L, G4C, S24T, T26I, Q28R, N29Y, G30A, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
322	Q1L, G4C, Q28R, E65M, A72C, E183M, S311G, D320I, D346A, Q349K, T393V, Y422F
323	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, S311G, D346E, Q349K, T393I, Y422F
324	Q1L, G4C, Q28R, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
325	Q1L, G4C, Q28K, E65K, A72C, D181N, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F
326	Q1L, G4C, Q28R, E65V, A72C, S311G, N318Y, D320I, T335I, D346E, Q349K, T393V, Y422F
327	Q1L, G4C, S24C, Q28R, G30A, E65V, A72C, Y155C, D181N, Q190K, D202N, P224L, S311G, T335I, D346E, Q349K, D390E, T393V, Y422F
328	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, P402S, Y422F
329	Q1L, G4C, Q28R, E65K, A72C, E183M, D202N, P224L, S311N, N318Y, T335I, D346E, Q349K, T393V, Y422F
330	Q1L, G4C, A21T, T26I, Q28R, N29Y, E65V, A72C, Y155C, D181N, D202N, P224L, M234T, S311G, D320I, D346E, Q349K, D390E, T393V, Y422F
331	Q1L, G4C, Q28R, E65K, A72C, S86T, D202N, P224L,

	S311D, D320N, T335I, D346V, Q349K, T392M, T393V, Y422F
332	Q1L, G4C, Q28R, E65V, A72C, S86T, E183K, D202N, S311G, N318Y, D320I, D346A, Q349K, T393V, Y422F
333	Q1L, G4C, W40R, E65M, A72C, S86T, E183V, S192L, D202I, H203R, P224L, S311G, N318Y, D320V, D346A, Q349K
334	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D346E, Q349K, T393V, Y422F
335	Q1L, G4C, Q28R, E65V, A72C, K118Q, D181N, E183M, P224L, D247N, S311G, D320I, D346E, Q349K, T393V, Y422F
336	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, D202N, P224L, S311N, D320I, D346E, Q349K, T393V, Y422F
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338	Q1L, G4C, Q28K, E65M, A72C, D181N, E183M, D202N, S311G, N318Y, D346A, Q349K, T393V, Y422F
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340	Q1L, G4C, Q28R, A72C, D181N, E183V, S192M, D202N, P224L, S311D, N318Y, D320N, D346E, Q349R, T393V, Y422F
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343	Q1L, G4C, Q28R, G30A, E65V, A68T, A72C, D181N, E183M, D202N, P224L, D346E, Q349K, T393V, Y422F
344	Q1L, G4C, Q28R, E65V, A72C, K92R, L120P, D181N, E183M, D202N, S236F, T280A, S311G, D346E, Q349K, K355Q, T387S, T393V, P402S, D404N, Y422F
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346	Q1L, G4C, Q28R, E65M, A72C, D181N, E183K, D202N,

	P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
347	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, Y155C, D181N, E183M, Q190K, D202N, S311G, D320I, D346E, Q349K, T393V, Y422F
348	Q1L, G4C, Q28R, E65V, A72C, D181N, D202N, S311G, T335I, D346A, Q349K, T393I, Y422F
349	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, D247N, S311G, D320I, D346E, Q349K, T387S, T393V, Y422F
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351	Q1L, G4C, Q28R, E65V, A72C, K92R, K118Q, D181N, E183M, D202N, S236F, S311N, N318I, D346E, Q349K, K355Q, T387S, T393V, D404N, Y422F
352	Q1L, G4C, T27S, Q28R, E65V, Q69R, A72C, K118Q, D181N, E183M, D202N, D247N, I277V, S311G, T335I, D346E, Q349K, K355Q, T393V, Y422F
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358	Q1L, G4C, Q28R, E65V, A72C, D181N, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F, T457TAAATT
359	Q1L, G4C, T26I, Q28R, E65V, A68T, A72C, Y155C, D181N, Q190K, D202N, P224L, M234T, S311G, D320I, D346E, Q349K, D390E, T393V, Y422F

360	Q1L, G4C, Q28K, E65V, A72C, S86T, E183K, S192L, D202N, D320N, T335I, D346A, Q349R, T393A, Y422F
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364	Q1L, G4C, Q28R, E65K, A72C, D202I, P224L, S311G, N318Y, D320V, T335I, D346A, Q349R, T392M, T393A
365	Q1L, G4C, E65M, A72C, S86T, E183V, D202I, P224L, S311G, N318Y, D320V, D346A, Q349K
366	Q1L, G4C, N10D, Q28R, E65V, A72C, K92R, D181N, E183M, D202N, S311G, D346E, Q349K, T387S, T393V, Y422F
367	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, E65M, A72C, S86T, E183M, D202N, P224L, S311G, D320I, T335I, D346E, Q349K, T393V, Y422F
368	Q2S, G4C, A6L, T7Q, A8S, N10T, S24T, T26I, Q28R, N29Y, G30A, E65V, A72C, E183M, P224L, S311G, D320I, D346E, Q349K, T393V, Y422F
369	Q1L, G4C, Q28R, E65V, A72C, K92R, D181N, E183M, P224L, I277V, S311G, D320I, D346E, Q349K, T393V, Y422F
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373	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28K, E65K, A72C, E183M, S311G, N318Y, D320I, T335I, D346E, Q349K,

	T393V, Y422F
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376	Q2S, G4C, A6L, T7Q, A8S, N10T, Q28R, E65M, A72C, E183M, S311G, N318Y, D346E, Q349K, T393V, Y422F
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408	G4C, Q28K, E65M, A72C, S86T, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
409	G4C, Q28K, E65M, A72C, S86T, G151GCGRSG, K159KCGRNK, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
410	Q1L, G4C, Q28K, E65V, A72C, D181N, E183M, D202N, P224L, S311G, T335I, D346E, Q349K, T393V, Y422F
411	Q1L, G4C, Q28K, E65V, A72C, S86T, D181N, E183K, S192L, D202V, S311G, D320I, D346V, Q349R, T393A, Y422F
412	Q1L, G4C, Q28R, E65V, A72C, S86T, D181N, D202N, P224L, S311N, N318Y, D320I, D346A, Q349K, T393V, Y422F

413	Q1L, G4C, A21T, T26I, Q28R, G30A, E65V, A68T, A72C, D181N, E183M, D202N, T229M, S311G, A340S, D346E, Q349K, T393V, Y422F

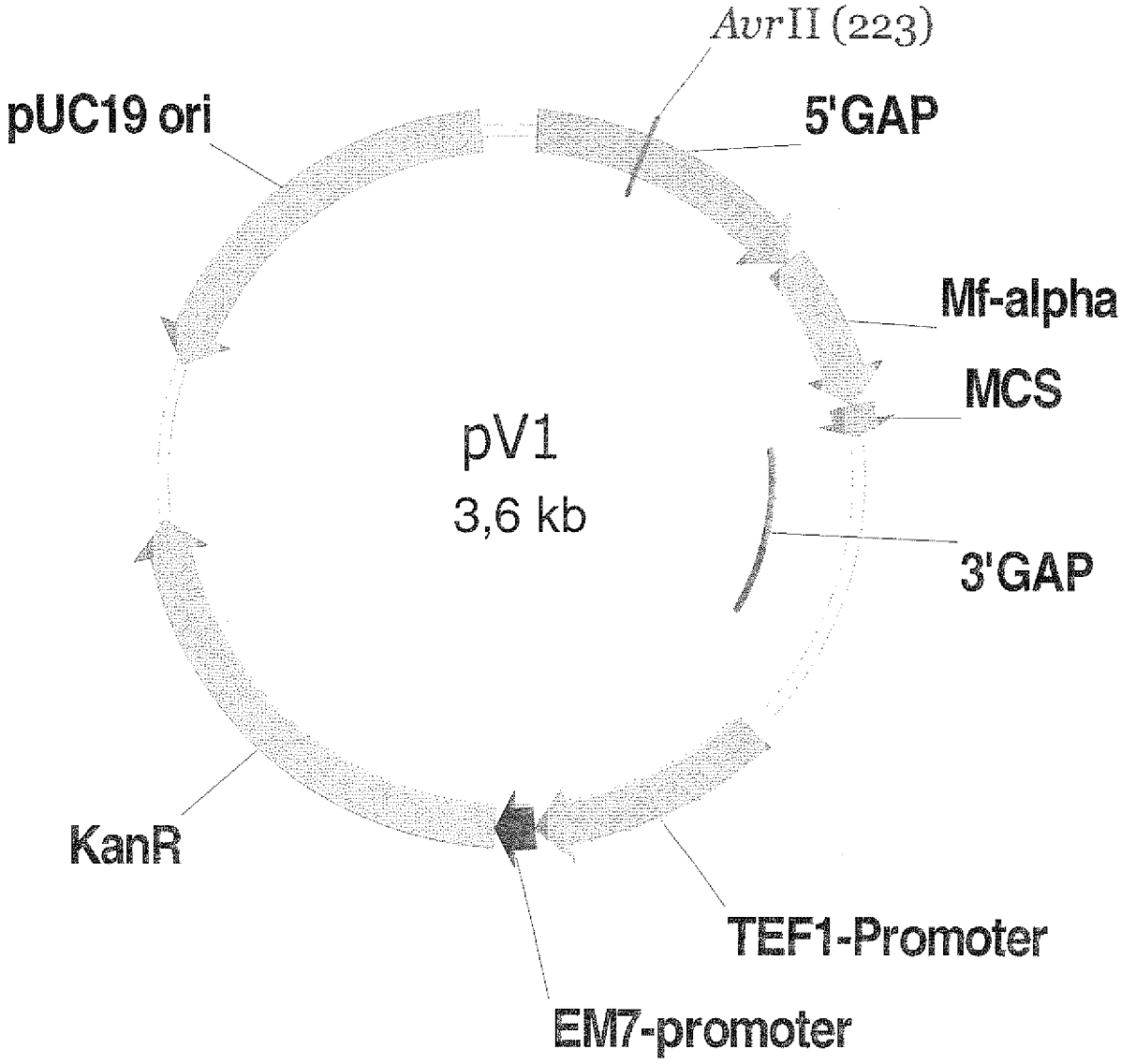
28. Polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence having at least 85 % sequence identity to SEQ ID NO: 12, wherein one or more of the following amino acid residues of the sequence defined by SEQ ID NO: 12 are modified by substitution or deletion: Q1, S2, P12, T15, S21, G23, T26, Q28, T29, G30, V32, N37, W40, T48, C50, N54, L60, E65, K69, V84, S90, D114, E119, F120, T121, L122, L123, D132, V133, G142, S148, M149, V155, Y158, N161, T162, K166, G170, Q175, F182, I183, G191, I203, D214, I215, A224, T231, G234, I237, S248, G254, W263, G269, L282, T285, G298, Y303, N307, G308, T310, E317, L318, S322, N324, G340, S341, D345, S357, M360, V363, D369, A372, P382, S388, T389, P390, T399, S400, Q406, N413, F423, P425, I426, G427, T429, P432, G435, N436, P437, G439, N441, R442, T444, T445, T446, T447, R449, P450, A451, T452, T453, S456, S457, P458, G463, P464, S467, H459, C468, G470, G472, S474, P476, V478, C479, S481, G482, T484, V487, L488, N489, Y491, Y492, Q494, C495, L496.

29. Polypeptide according to claim 28, wherein the polypeptide has the amino acid sequence of SEQ ID NO: 12 wherein one or more of the following amino acid residues are modified by substitution or deletion:Q1, S2, P12, T15, S21, G23, T26, Q28, T29, G30, V32, N37, W40, T48, C50, N54, L60, E65, K69, V84, S90, D114, E119, F120, T121, L122, L123, D132, V133, G142, S148, M149, V155, Y158, N161, T162, K166, G170, Q175, F182, I183, G191, I203, D214, I215, A224, T231, G234, I237, S248, G254, W263, G269, L282, T285, G298, Y303, N307, G308, T310, E317, L318, S322, N324, G340, S341, D345, S357, M360, V363, D369, A372, P382, S388, T389, P390, T399, S400, Q406, N413, F423, P425, I426, G427, T429, P432, G435, N436, P437, G439, N441, R442, T444, T445, T446, T447, R449, P450, A451, T452, T453, S456, S457, P458, G463, P464, S467, H459, C468, G470, G472, S474, P476, V478, C479, S481, G482, T484, V487, L488, N489, Y491, Y492, Q494, C495, L496.

30. Composition comprising the polypeptide of one or more of claims 1 to 11 or 24 to 29 and one or more endoglucanases and/or one or more beta-glucosidases and/or one or more further cellobiohydrolases and/or one or more xylanases.

31. Use of the polypeptide according to one or more of claims 1 to 11 or 24 to 29 or of the composition of claim 30 for the enzymatic degradation of lignocellulosic biomass, and/or for textiles processing and/or as ingredient in detergents and/or as ingredient in food or feed compositions.

Figure 1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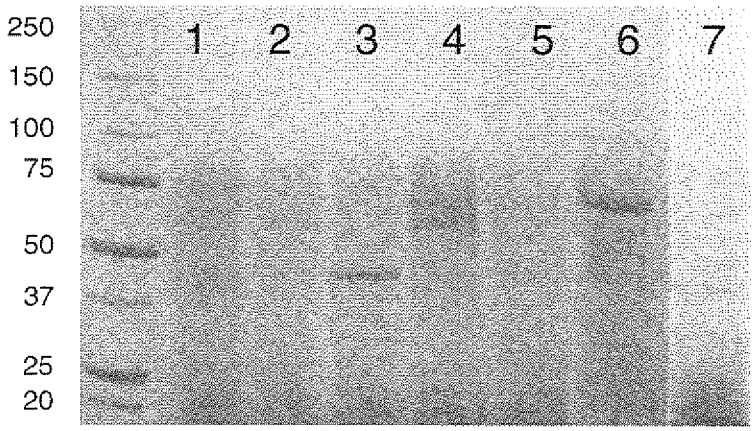
5'GAP
Mf-alpha
MCS
pV1
3,6 kb
3'GAP
KanR
TEF1-Promoter
EM7-promoter

Figure 2



1 Plain Vector
2 *Trichoderma viride* CBHI
3 *Humicola grisea* CBHI
4 *Talaromyces emersonii* CBHI
5 *Thermoascus aurantiacus* CBHI
6 *Talaromyces emersonii* CBHI fusion with *T. reesei* CBHI CBD
7 *Humicola grisea* CBHI fusion with *T. reesei* CBHI CBD

Figure 3

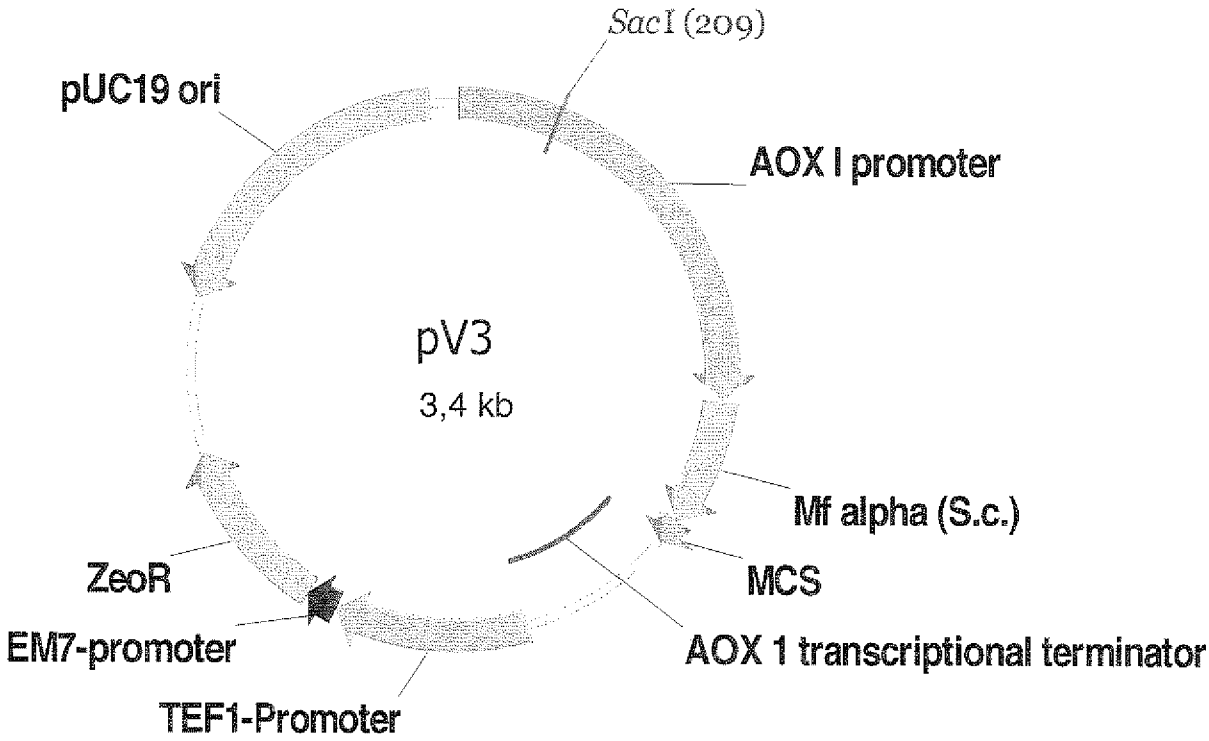


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Figure 4

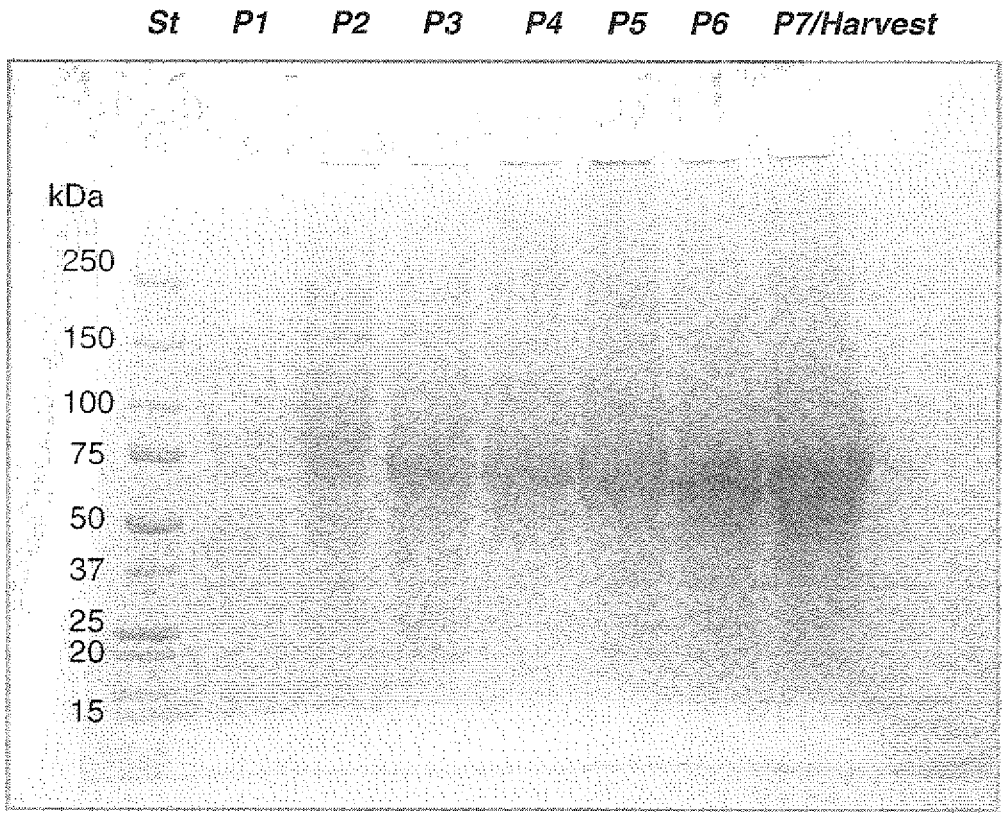
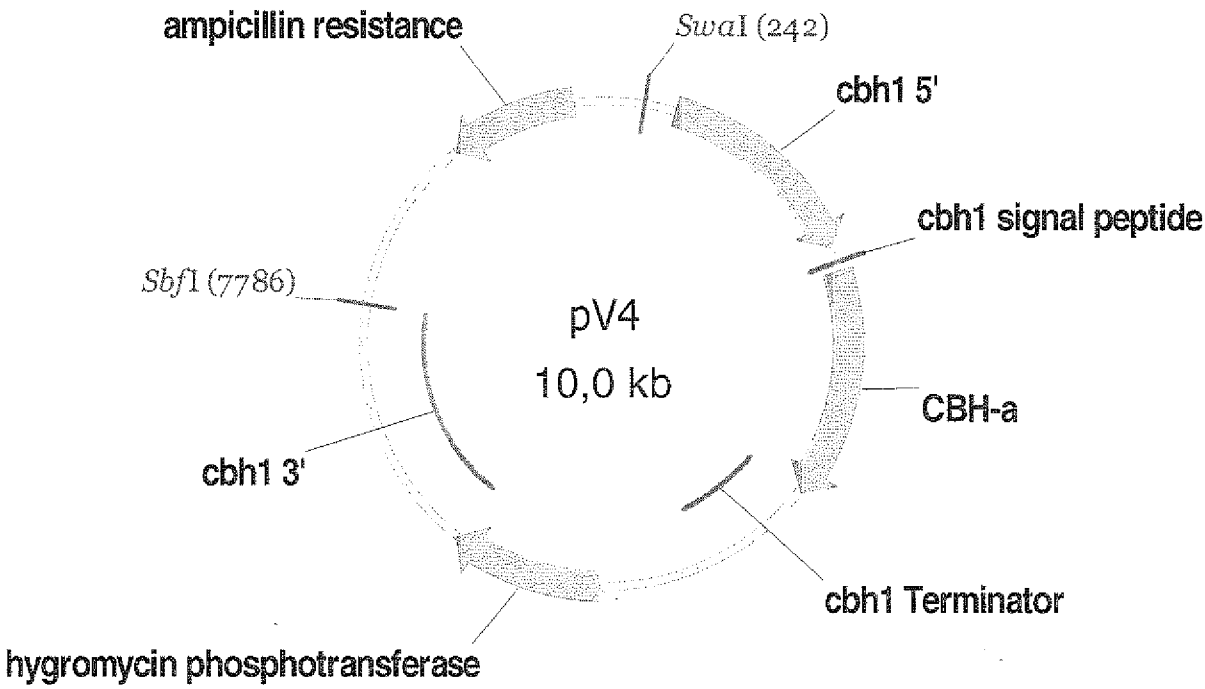


Figure 5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SwaI (242)
cbh1 5'
cbh1 signal peptide
SbfI (7786)
pV4
10,0 kb
CBH-a
cbh1 3'
cbh1 Terminator
hygromycin phosphotransferase

Figure 6

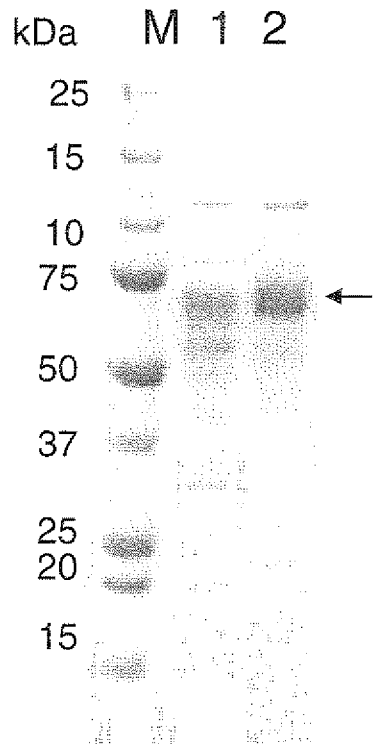
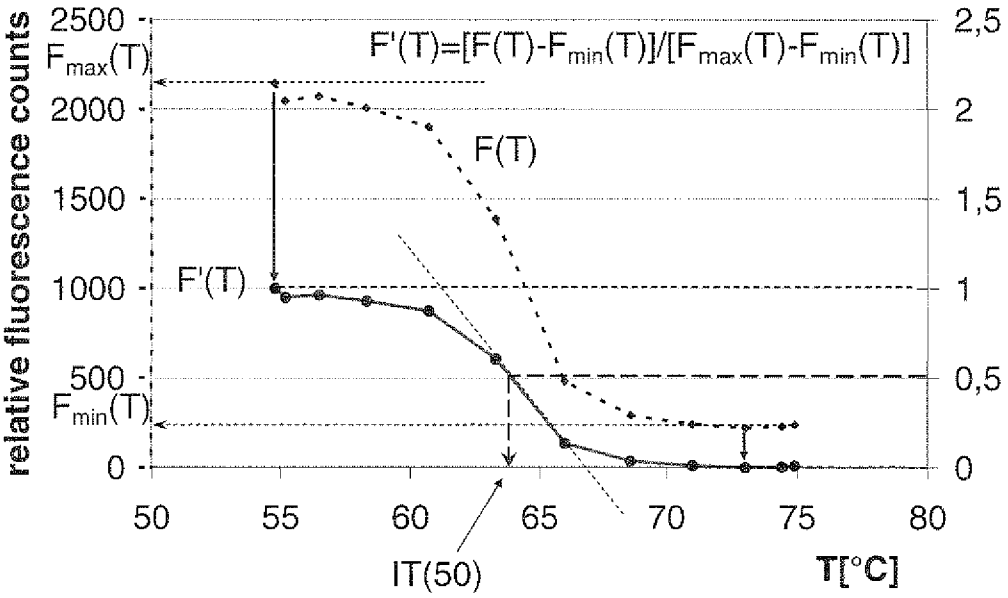


Figure 7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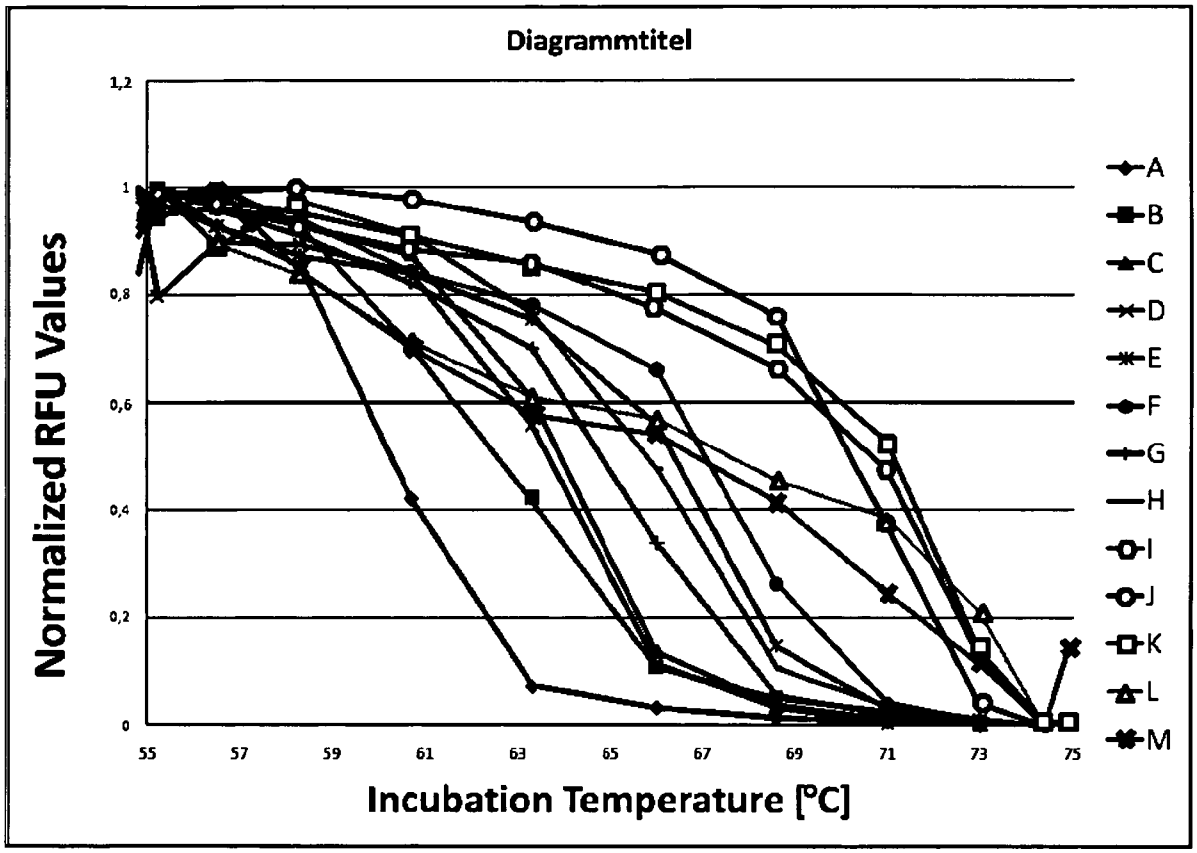
2500
2000
1500
1000
500
0
$F_{max}(T)$
$F_{min}(T)$
F'(T)=[F(T)-F_{min}(T)]/[F_{max}(T)-F_{min}(T)]
F(T)
F'(T)
2,5
2
1,5
1
0,5
0
50
55
60
65
70
75
80
IT(50)
T[°C]

Figure 8


Diagrammtitel
Normalized RFU Values
1,2
1
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0,6
0,4
0,2
0
55
57
59
61
63
65
67
69
71
73
75
Incubation Temperature [°C]
A
B
C
D
E
F
G
H
I
J
K
L
M

Figure 9

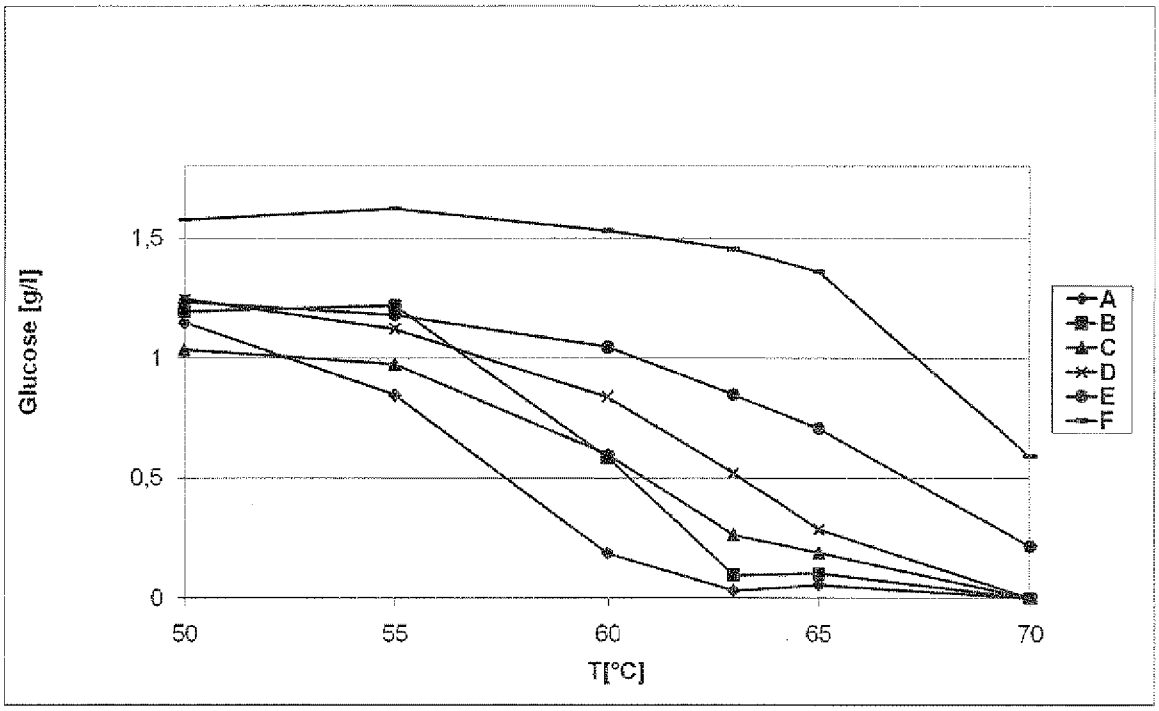

Figure 10

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              101                                                  150
T._reesei_CBHI  QKNVGARLYL MASDTTYQEF TLLGNEFSFD VDVSQLPCGL NGALYFVSMD
    SeqID_NO.2  .SNVGSRLYL LQDDSTYQIF KLLNREFSFD VDVSNLPCGL NGALYFVAMD

              151                                                  200
T._reesei_CBHI  ADGGVSKYPT NTAGAKYGTG YCDSQCPRDL KFINGQANVE GWEPSSNNAN
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              251                                                  300
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              501
T._reesei_CBHI  YSQCL
    SeqID_NO.2  YSQCL
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