# The Gene Genius

**September 2004 marks the 20th Anniversary of the discovery of DNA Genetic Fingerprinting at the University of Leicester by Professor Sir Alec Jeffreys. Here we highlight the impact of the revolutionary discovery.**

*More information on the Department of Genetics at the University of Leicester and Professor Sir Alec Jeffreys is available on www.le.ac.uk*

INSIDE



The Queen's Anniversary Prizes
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# Moment of Truth

"My life changed on Monday morning at 9.05 am, 11 September 1984," Professor Sir Alec Jeffreys said, describing the moment when he discovered the world's first genetic fingerprint.

"In science it is unusual to have such a 'eureka' moment," he added. "We were getting extraordinarily variable patterns of DNA, including from our technician and her mother and father, as well as from non human samples. My first reaction to the results was 'this is too complicated', and then the penny dropped and I realised we had genetic fingerprinting."

This momentous discovery, accidental as it was, opened up a new area of science. The research team immediately grasped its applications, including crime, paternity and identical twins, as well as work on conservation and diversity among non-human species. Later that day Sir Alec's wife added another to the list – immigration. "That was when I realised this had a political dimension and that it could change the face of immigration disputes, especially where no documentary evidence existed."

The first real immigration case came in March 1985, a decade earlier than Sir Alec had anticipated, driven by the demand from families and lawyers. "If our first case had been forensic I believe it would have been challenged and the process may well have been damaged in the courts. But our first application was to save a young boy from deportation and it captured the public's sympathy and imagination. It was science helping an individual challenge authority."

The first paternity case came hot on the heels of that dispute and then – in Sir Alec's words – "the flood gates opened". At this point, all cases were dealt with by the Leicester laboratory. Sir Alec was a research fellow for the Lister Institute who gave him funding to take on another technician to enable them to run tests on a larger scale and for two years his was the only laboratory in the world doing this work. He describes it as "exciting but exhausting", and had no regrets when ICI (now AstraZeneca) were granted a licence to set up Cellmark and make the technology commercially available.

At this time the forensic implications of genetic fingerprinting were emerging. The original process proved to be inadequate for this, and so from 1985 Sir Alec and his team developed a variation which they called "genetic profiling" for forensic use.

Again, its first application caught the public mood. Two young girls were raped and murdered in the Enderby area of Leicestershire. A man who had been arrested had confessed to one murder but not the other, and the police decided to use genetic profiling, thinking to prove him guilty of both cases. Against all expectation he was found to be innocent of both. Then the hunt was on to find a genetic profile among the entire male population of the area that matched samples taken from the two victims. No match was found, until Colin Pitchfork was overheard boasting of how he had persuaded a friend to give a sample on his behalf. Pitchfork was tested, his DNA found to match and the case was solved.

The original technology used to catch Pitchfork is now largely obsolete, though still in use in some laboratories around the world. But the techniques have been speeded up and simplified. In the UK we now have a national database of 2.5 million genetic profiles from convicted criminals, which the police say is one of the most powerful tools in their fight against crime.

# A Question of Identity

DNA genetic fingerprinting reunited a young boy with his family in the first immigration case solved by DNA evidence in 1985.

The dispute involved a family of UK citizens originally from Ghana. The youngest son had visited Ghana but on his return it was discovered that his passport had been tampered. The Immigration Authorities thought that the boy was a substitute - either unrelated to the family or the son of one the mother's sister in Ghana. He was not granted residence.

Following blood typing it was concluded that the returning boy was a member of the family, but it couldn't be determined if he was the son, or a nephew from Ghana.

Professor Alec Jeffreys was asked to use his revolutionary new technique of DNA fingerprinting to help solve the question of identity.

The father and the mother's sisters in Ghana were unavailable for testing. Added to this was that the mother wasn't sure of the boy's paternity.

However DNA evidence was conclusive. The boy was a full member of the family and had the same paternity as the rest of the children. It was 99.997% certain the boy was the son of the British mother and not a nephew.

The evidence was reviewed positively by the Home Office, and the case was dropped against the boy who was reunited with his family.

*Josef Mengele.*

# "The Angel of Death"

Josef Mengele was a Nazi war criminal notorious for grotesque human experiments that he carried out at the Auschwitz concentration camp.

After the Second World War he fled from the Allies and escaped to South America. The fugitive succeeded in living out the rest of his days without being caught.

In 1985 investigators went to the cemetery of Nossa Senhora do Rosario in the small Brazilian town of Embu to dig up the skeleton of a man who had been drowned in a swimming accident six years previously. He has been buried under the name Wolfgang Gerhard, but the investigators had information that the deceased individual was actually Mengele.

Various forensic investigations took place - indicating the body was the war criminal.

However, the Israeli authorities were sceptical and in 1988 they suggested that DNA analysis should be used to provide an alternative approach to identification.

The German government, keen to close this chapter of their history agreed and asked Professor Sir Alec Jeffreys and Dr. Erika Hagelberg, then of the Institute of Molecular Medicine at Oxford, who is an expert at extracting DNA from bones, for their help in determining whether or not the skeleton was that of Mengele.

Using DNA extracted from blood provided by Mengele's wife and son, it was concluded that it was more than 99.94% certain that the skeleton was Mengele's. Paternally inherited DNA markers were compared with those of DNA extracted from the femur of the skeleton. All were present in the bone DNA, exactly as predicted if the skeleton was that of Mengele.

The German and Israeli governments were convinced by this evidence and the case of the fugitive war criminal was closed.

# Traced through DNA

The applications and developments in DNA genetic fingerprinting are still ongoing and recently yet another crime was solved through another novel application of the scientific technique.

In 2003 Michael Little was killed by a brick thrown from a motorway bridge as he drove his lorry down the M3. The impact of the brick caused fatal damage to his heart, but not before he had steered his lorry to safety on the hard shoulder and switched off the engine before dying.

Traces of DNA were found on the brick and run through the National DNA Database – however no matches were recorded. The forensic investigators turned to the pioneering method of 'familial searching' – based on the principle that relatives will tend to have similar DNA profiles.

A similar DNA profile was found – and this traced the culprit – the brother of a man whose profile was on the database. He was convicted and sentenced to six years imprisonment – the first man to be convicted on the evidence based on the link between DNA found at the scene of the crime and that of a relative of the accused.

UK police forces have access to the world's first and largest DNA database containing more than 2.5 million samples. The size of this database and the success of the technique of 'familial searching' could lead to the solving of other crimes that have baffled police for years.

# Karen Price

In 1989 builders working in the back garden of a derelict house in Cardiff discovered the badly decomposed body of a murder victim wrapped in a piece of old carpet.

Skeletal analysis showed that it was the body of a young female.

The skull was used to make a facial reconstruction and also to compare the teeth with dental records. There was little other evidence that could be used to identify the remains.

Entomologists (insect experts) were called in and examination of the creatures living in the carpet led them to estimate that the victim had been buried some ten years previously.

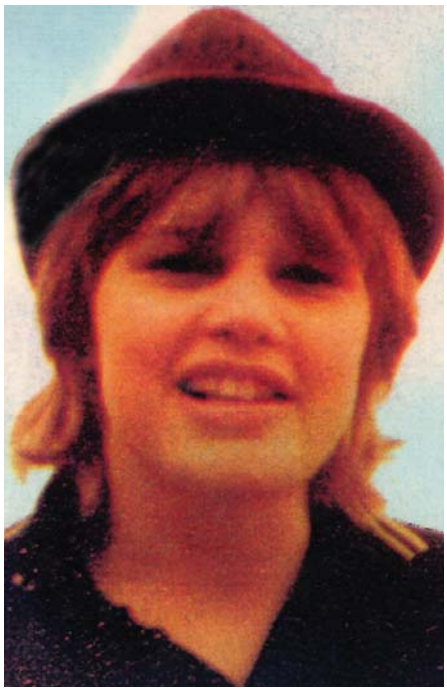
Someone recognised the facial reconstruction as Karen Price, a local 15 year old girl who had disappeared in 1981. The dental records were consistent with this identification.

Before anyone could be charged with her murder the identification had to be confirmed and the South Wales Constabulary contacted Professor Jeffreys and Dr. Hagelberg and asked them for their help with this by using DNA analysis. DNA was extracted from skeletal remains by Dr. Hagelberg and used for a parentage analysis in Professor Jeffreys' laboratory.

Alleles of variable loci from the bone DNA were compared with those from DNA extracted from the mother and father of the supposed murder victim, Karen Price.

These tests showed that it was better than 99.99% certain that the body was that of Karen Price.

This evidence, along with all the other forensic and detective work that was done, was enough to convict Karen Price's murderer ten years after her death.



*Karen Price.*

# Geneticists Prove Authenticity of Cloned Sheep

DNA fingerprinting was used by the Department of Genetics to independently authenticate the origin of the sheep Dolly, the first mammal ever to be cloned.

*Dolly the first mammal ever to be cloned.*

Professor Sir Alec Jeffreys and his team proved `beyond reasonable doubt that Dolly is indeed derived from a cell of the mammary tissue taken from the adult donor ewe', said Dr Esther Signer who carried out the analysis.

The Genetics team - Professor Jeffreys, Dr Signer and Professor Yuri Dubrova - were asked to perform DNA fingerprinting on samples from Dolly and the donor sheep, plus additional sheep as controls. This followed concerns about Dolly's origin - whether she could have been derived not from a mammary cell of the adult donor sheep, but from a contaminated sheep cell culture or from a fetal cell in the udder of the pregnant donor.

Comparisons of DNAs from Dolly and the donor ewe were indistinguishable in terms of band number, position and relative intensity. They found that each control sheep had a clearly different pattern.

The team concluded, from the estimated probabilities that an unrelated sheep or an offspring would have by chance an identical DNA fingerprint as the donor ewe, that it was extremely unlikely that Dolly could have been derived from a contaminated cell culture or from a foetal cell.

The Leicester geneticists verified that Dolly the sheep was the first living mammalian clone.

# The Discovery That Altered Destinies

Professor Sir Alec Jeffreys this year met a man whose life he helped to save.... from death row. He was the first man ever to be exonerated from death row through DNA evidence and his meeting with the University of Leicester pioneer was caught on national TV at the 2004 Pride of Britain Awards.

At the 2004 Pride of Britain Awards Professor Sir Alec Jeffreys was given a Lifetime Achievement Award for his discovery of genetic fingerprinting. A delighted Sir Alec was handed the award by TV star David Jason who said that he had 'revolutionised policing [and] helped to ensure that innocent people are not sent down.' Throughout the show every award winner was joined on stage by someone with a special connection to them. As Professor Jeffreys took the stage David Jason introduced Kirk Bloodsworth.

In March 1985 Kirk Bloodsworth was convicted of sexually assaulting and murdering a nine year old girl. The victim had been found dead after having been raped, strangled and beaten with a rock in July 1984. Bloodsworth was convicted on the basis of eye witness and circumstantial evidence. Bloodsworth was sentenced to death for these crimes and served eight years in prison, two of which were on death row. However, in 1992 the prosecution allowed for DNA testing to take place. These tests proved that Bloodsworth had not committed the crime and he was released from prison in June 1993 and pardoned in December of the same year.

Kirk Bloodsworth became the first person to be exonerated from death row by means of genetic fingerprinting.

In recognition of this historic moment the United States Federal Government has recently introduced the Innocence Protection Act that introduces the Kirk Bloodsworth Postconviction DNA Testing Program. The program will provide funding for more testing of the type that set the innocent Kirk Bloodsworth free.

At the Pride of Britain Awards he said: "In 1984 I sat in a prison cell waiting to die for a crime I didn't commit. I read about the work of Sir Alec Jeffreys and I had an epiphany: this could prove my innocence and set me free!"

The moment of this historic and monumental meeting of a man cleared of serious crimes that he didn't commit and his saviour was a truly emotional one for all involved - Professor Jeffreys had not been expecting Kirk's appearance.

Kirk Bloodsworth himself was on the brink of tears as he gave his impassioned speech, which he ended with the truly heartfelt sentiment: "I want to thank you…Sir, you truly are my white knight."

*-Rob Cane.*

# The Man Who Put The Fingerprint in Genetics

The path that led to the discovery of genetic fingerprinting began for Professor Sir Alec Jeffreys when his father gave him a chemistry set and a microscope at the age of eight.

"It might have been disastrous," he confessed. "When I was 13 or 14, I got a face full of sulphuric acid, which is why I wear a beard now. I consider it a badge of honour."

After Luton Grammar School and Luton 6th Form College, Sir Alec took a four-year biochemistry degree at Merton College, Oxford, before deciding that his real enthusiasm was genetics.

As a postdoctoral research fellow at the University of Amsterdam, under Dr Richard Flavell, he started to work with mammalian genes, developing a method for detecting specific genes in humans.

Moving to Leicester in 1977 he was in charge of a small laboratory, with one part-time technician. For the first time, the technology now existed to look at genes, and Sir Alec decided to study their inherited variation, shifting the focus from the products of genes such as blood groups, to DNA.

That year he found the first inherited DNA variation in one of his technicians and in 1978 he was able to detect additional variations in human DNA. "By 1981," he said, "we could define our goal, which was highly variable DNA.

"We stumbled on our clue, stuttered DNA, or 'minisatellites'. We had found a way of detecting lots of minisatellites variable enough to provide extremely informative genetic markers." Out of this research DNA Fingerprinting was discovered almost entirely by accident on 11 September 1984.

Since the late 1980s Sir Alec has been examining the ways DNA mutates and crosses over (reshuffles its chromosomes), looking at minisatellites and the spontaneous ways in which they add and lose stutters.

With Professor Yuri Dubrova he has studied families in the region around Chernobyl in Belarus, following the 1986 nuclear accident, to find out whether the environment we live in influences this mutation, or whether it all comes from our genes.

He is now researching alternative ways of detecting inherited rearrangements in DNA, including mutation and recombination, and their effect on human DNA diversity.

Among a long list of honours and awards are his election to the Royal Society (1986), The Albert Einstein World of Science Award (1996), the Australia Prize (1998) and the Louis Jeantet Prize for Medicine (2004). Sir Alec was made an Honorary Freeman of the City of Leicester (1993), and received a knighthood for services to genetics (1994). He was winner of the Press, Radio and TV Award for the "Midlander of the Year, 1988" and received a Lifetime Achievement Award at the Daily Mirror's Pride of Britain Awards (2004).

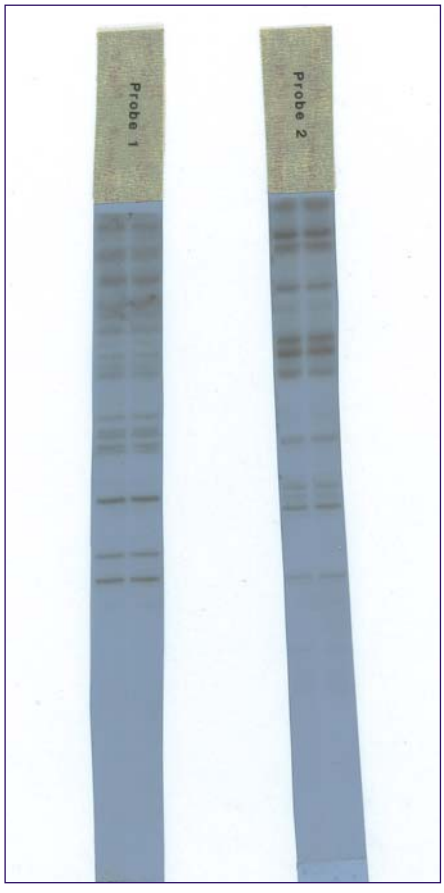
# Human Diversity

We are all genetically unique, thanks to the many sites of inherited variation within the 3,000,000,000 bases or chemical letters in our DNA that make up the human 'book of life'.

The origin of all this inherited variation in human DNA remains the focus of Professor Alec Jeffreys' research. Variation ultimately arises from two processes: mutation and crossover.

Mutation and crossover are fundamentally important processes. An analogy can be drawn with a deck of playing cards: without mutation, all the cards will be identical, and without crossover, there is no shuffling between games. Both are needed to play the game of human evolution. However, both processes are very difficult to study in humans. The traditional approach is to compare children with their parents to look for mutations or places of crossover.

Professor Jeffreys said: "Even if you have ten children, you will get at most only one or two minisatellite mutants. We needed families of millions of children, particularly to study other modes of DNA instability, so we started to use minisatellites to find an alternative way of research. Using the most sophisticated methods, we found we could type the DNA of a single molecule or cell as an alternative approach to studying inherited DNA rearrangements."




*DNA Fingerprint of Two Sets of Identical Twins.*

Once able to dispense with children in favour of cells, Sir Alec turned to the study of sperm.

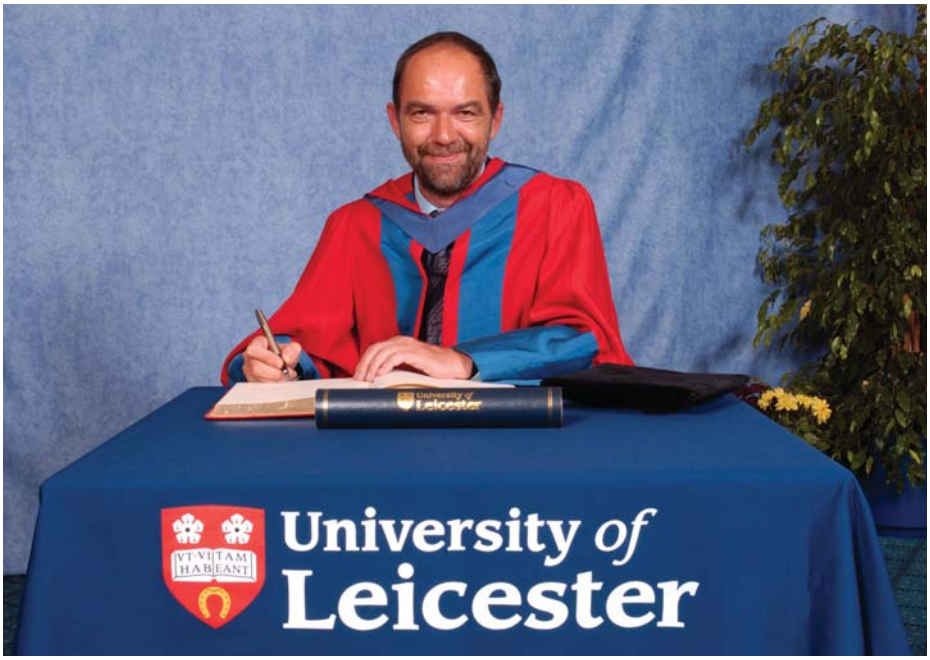
"A single ejaculation will produce one hundred million sperm, equivalent to one hundred million offspring.

"Our recombination work is important for understanding how human DNA diversity is organised, and underpins international efforts into trying to analyse common human diseases," Sir Alec said.

This is fundamental research that will illuminate the dynamics of human DNA evolution and the factors that influence the integrity of our DNA as it is transmitted from generation to generation. It will also help throw new light on the nature of human genetic diversity and of the origin of our species, of populations and of pathological changes in our DNA.

"We are not specifically looking at applications, though almost inevitably applications will arise" Professor Sir Alec Jeffreys said. "I feel I've done my bit on research application." Police officers and those fighting immigration and paternity cases must surely agree.

*-Jane Pearson.*




***Professor Sir Alec Jeffreys was awarded an honorary degree by the University of Leicester this year.***

Professor Sir Alec Jeffreys has been acclaimed across the world for his discovery of DNA profiling and for his continuing work in the field of genetics. Among his most recent awards are:

March 2004: Lifetime Achievement award at the Daily Mirror's Pride of Britain Awards. "This was fantastic because it was public recognition in the broadest sense," Sir Alec said. "It is the nearest I will ever get to an Oscar."

April 2004: Louis-Jeantet Prize for Medicine, awarded to scientists who are distinguished for the highest quality of biomedical research in Europe.

July 2004: Honorary doctorate from the University of Leicester, about which Sir Alec said: "An honorary degree from your own university is something extremely special. It is important because it is recognition from your own community, as with the award of Honorary Freeman of the City of Leicester, which I was awarded in 1993."

# Other research in the Department of Genetics has clear and important applications to modern society…

## Re-setting the Biological Clock

The major industrial accidents of the last century, Chernobyl, Three-Mile-Island and Bhopal, were all caused by human error during shift work – 25 per cent of the workforce in the industrial world works shifts.

In addition, sleep problems, particularly in older people, can lead to depression, and anyone who flies across time zones understands the misery of jet lag.

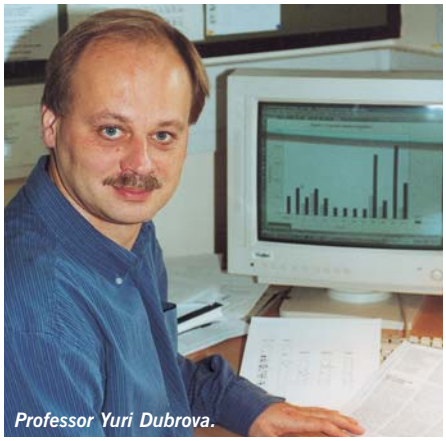
There may not appear to be a link between all this and the fruitfly but, as research by Professor C P Kyriacou at the University of Leicester Department of Genetics and Dr E Rosato in the Department of Biology shows, genetically speaking, humans and fruitflies are more alike than you might imagine.

The discovery of clock genes in the fruitfly led to the identification of these same genes in humans, and in turn to the development of therapies that attempt to alleviate some of the medical problems associated with issues such as shift work, jet lag and insomnia.

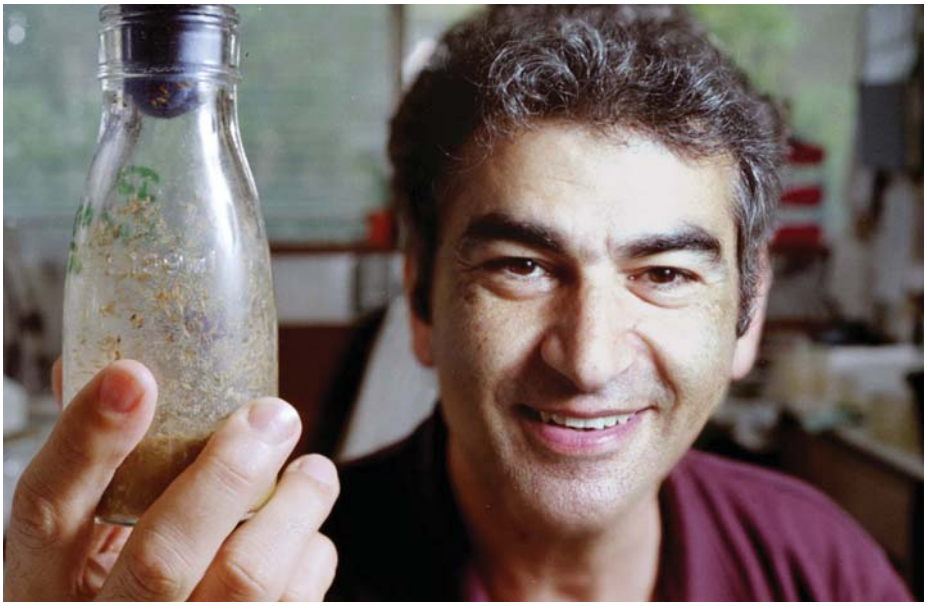
The importance of this research will increase in the future, with the growth of airline – and even space – travel and the acceptance of the 24-hour society.

## The Chernobyl Legacy

In 1986 the nuclear accident at Chernobyl in the Ukraine contaminated the surrounding regions – and beyond - with radiation. The world waited with baited breath to see what the long-term effects of this would be. Geneticists at the University of Leicester began to investigate,



*Professor Yuri Dubrova.*



***Research by Professor Kyriacou on clock genes in fruitflies has important applications in society.***

*Professor R Trembath.*

and their work continues today.

Predicting the genetic consequences for humans of exposure to ionising radiation and chemical mutagens has become one of the most important issues of human genetics. Professor Yuri E Dubrova and Professor Sir Alec Jeffreys developed a new system for monitoring radiation-induced mutation in the germline of mammals.

Tests have shown for the first time that those families from Belarus and Ukraine who were exposed to the Chernobyl radioactive contamination, and families from Kazakhstan exposed to the fallout from nuclear weapon tests, are significantly more likely to pass on mutations to their children.

Their research continues, including looking at the genetic risks of ionising radiation for humans from accidental or occupational exposure and radiotherapy. In the long term the hope is to be able to develop recommendations for establishing a mutagen-free environment.

## Hopes for Medical Breakthrough

Significant progress in identifying the genetic origins of diseases, including studies by Professor Richard Trembath at the University of Leicester, has generated new ways of identifying people who are 'at risk', as well as potential targets for therapeutic developments.

Over the past three years Professor Trembath and others in the field have identified genes responsible for example primary pulmonary hypertension. While not all of these will lead to 'miracle cures', they do promise significant opportunities for families carrying genetic disorders.

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You can find out more about pioneering work of the Department of Genetics and about Professor Sir Alec Jeffreys via **http://www.le.ac.uk**