An introduction to the genetic diseases and disorders that affect the Arabian horse (Part two of the genetics series)

Caution & Knowledge

BY AHA'S EQUINE STRESS, RESEARCH AND EDUCATION COMMITTEE

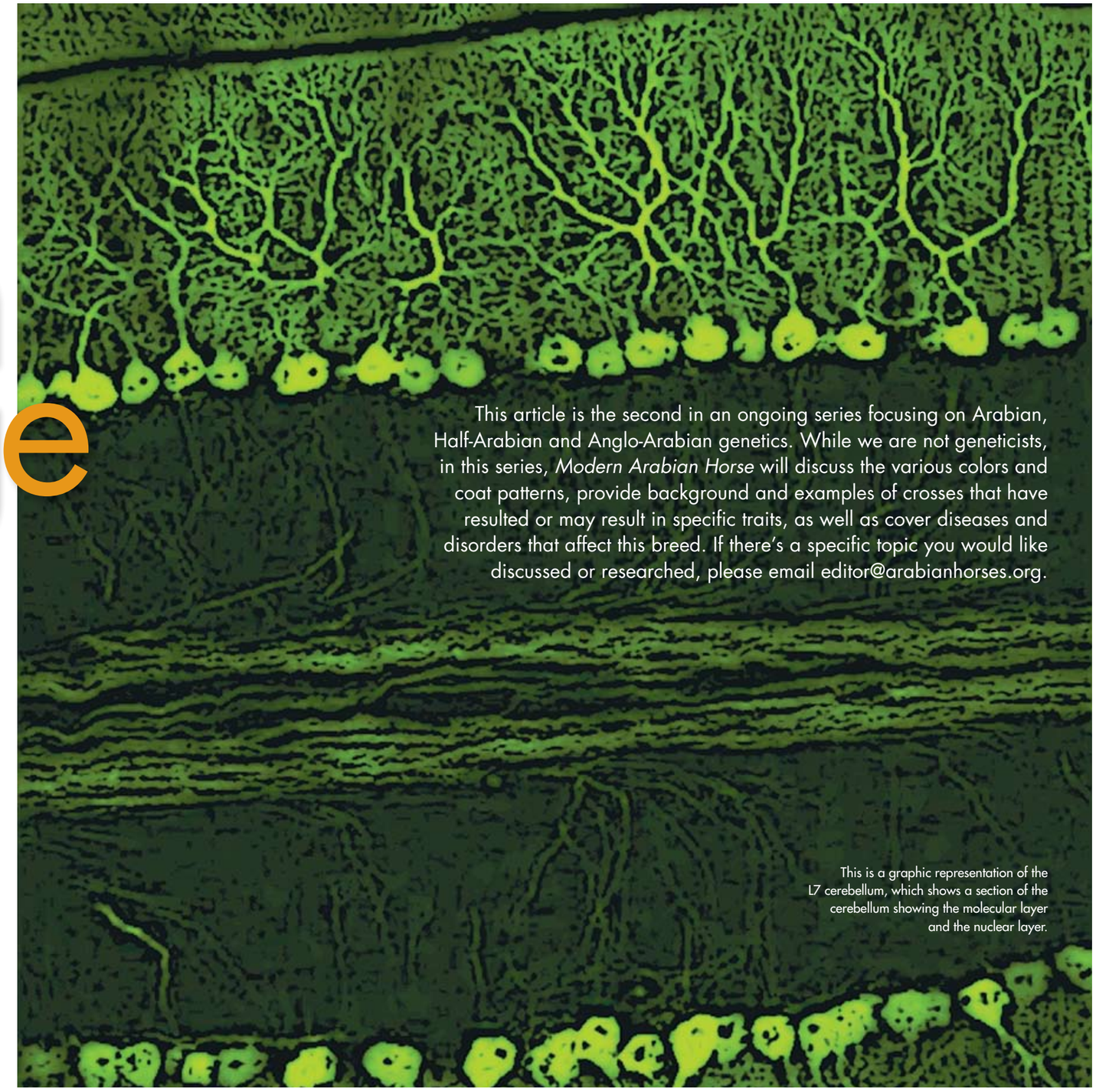
The DNA blueprint a breeder relies on for producing the "just right" foal is the same DNA blueprint that determines how that foal's body will work. Sometimes the instructions given by the genes can result in a malfunction of important body functions, such as the immune or nervous systems.

Because these diseases and disorders are inherited, they are known as being genetic in nature. Sometimes they are lethal, either by natural death or humane euthanization to end the visible suffering of the foal. Other times, the foal is able to live an extended time, but may face varying levels of disability during its life.

Genetic conditions exist among a variety of horse breeds and even among different species, including humans. So, these are not something unique to the Arabian breed. However, there are some conditions that are of special interest to the Arabian horse owner. Inheritance of most of these is not known, but only hypothesized.

Which genetic diseases and disorders are found in the Arabian breed and what are their clinical signs?

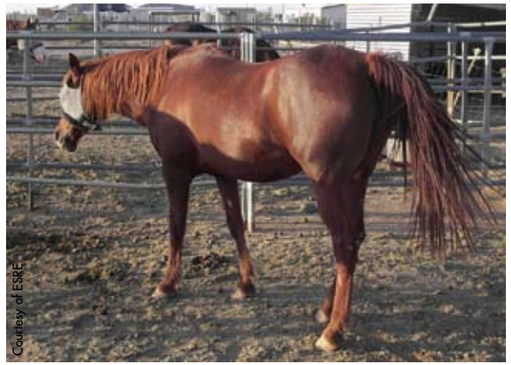
Cerebellar Abiotrophy (CA): The Purkinje cells in the brain's cerebellum begin to die, resulting in a severe lack of coordination. The degree of severity can vary, but most affected individuals are euthanized before adulthood, due to the hazard they present to themselves and others.



This article is the second in an ongoing series focusing on Arabian, Half-Arabian and Anglo-Arabian genetics. While we are not geneticists, in this series, *Modern Arabian Horse* will discuss the various colors and coat patterns, provide background and examples of crosses that have resulted or may result in specific traits, as well as cover diseases and disorders that affect this breed. If there's a specific topic you would like discussed or researched, please email editor@arabianhorses.org.

This is a graphic representation of the L7 cerebellum, which shows a section of the cerebellum showing the molecular layer and the nuclear layer.


Brenda Wahler


Courtesy of ESRE


Brenda Wahler

The following are examples of horses showing or possessing signs of cerebellar abiotrophy (CA). TOP: This photo illustrates the head bob and hypermetric gait. Basically, this filly's head is out of sync with her feet. This can be seen in the leading foreleg, especially. In person, you'd see the head is jerking up with each stride, which is extremely awkward-looking. MIDDLE: The wide-legged stance, which is indicative of CA, can be seen with this mare. ABOVE: The horse on the left is also somewhat showing the wide-legged stance in front. She also has a tendency to stand with her hocks touching, as if she were a 3-legged stool.

An affected foal is usually born without clinical signs. However, as they begin to grow, the degeneration of the Purkinje cells begins. Clinical signs include a head tremor and severe incoordination, combined with an inability to accurately gauge distance. Additional signs include an exaggerated gait and when at rest, a wide-legged stance. Young horses with CA are also hyper-reactive and somewhat more prone to rearing than ordinary horses, with the frequent result that they lose their balance and fall. Clinical signs may not appear immediately, but are often first noticed at times when the foal is under close scrutiny, such as weaning.

CA is often mistakenly diagnosed as Wobbler's Syndrome or as head trauma from an injury. Wobbler's Syndrome is caused by compression of the spinal cord, due to malformation of the cervical vertebrae during growth, and can be diagnosed with the assistance of radiographs. Clinical signs can also be misdiagnosed as head trauma from an accident, because foals often injure themselves by falling over backwards or colliding with a fence. However, both conditions are quite different from CA and care should be taken to differentiate them.

Although clinical signs and case history can lead to a diagnosis of CA, at this point in time, the only way to confirm such a diagnosis is to examine the brain tissue after euthanasia.

Juvenile Epilepsy: Although not generally fatal, it can be disabling and there has been a suggested genetic link to Lavender Foal Syndrome. Affected foals are born normal, but will have periodic epileptic seizures, beginning anywhere from 2 days to 6 months after birth. Between seizures, they appear normal. Treatment can include the use of traditional anti-seizure medications, which may reduce the severity of the clinical signs. Affected individuals usually outgrow the condition between 12 and 18 months.

Lavender Foal Syndrome (LFS) [also known as Coat Color Dilution Lethal (CCDL) or Dilute Lethal]: This is a neurological disorder thought to be caused by a brain lesion. An affected foal cannot stand at birth and usually has seizures. LFS foals are frequently born with a telltale diluted coat color that can make the hairs appear to be a dull lavender, a pinkish-brown or somewhat silvery. In many cases, the foal was also a product of a difficult delivery. If the coat color is overlooked or not present, foals may be misdiagnosed as having neonatal maladjustment syndrome (known as "dummy" foals), due to a lack of oxygen from the dystocia. Foals are usually euthanized within a few days after birth.

Occipito-Atlanto-Axial Malformation (OAAM): This is a condition where the cervical vertebrae fuse together in the neck and at the base of the skull, causing compression and injury to the spinal cord. Affected foals are often unable to stand and nurse, but in other cases, the clinical signs may not become noticeable for several weeks. Clinical signs range from mild incoordination to the paralysis of both front and rear legs. This is the only cervical spinal cord disorder seen in horses less than one month of age, and a radiograph can assist in diagnosing the condition.

Severe Combined Immunodeficiency Disorder (SCID): An affected foal is born with a severely weakened immune system. Because their natural defense system against infection is not functioning properly, by the time they are five months or so of age, they generally die of an opportunistic infection (such as pneumonia) or they are euthanized.

How are they inherited?

SCID is known to be an autosomal recessive trait and CA is also thought to be an autosomal recessive trait. While the genetic nature of LFS and OAAM are not yet fully understood, some researchers have suggested that these are also autosomal recessive traits. "Autosomal" means the trait is not sex linked, and "recessive" means that in order for a foal to be affected, it must have two copies of the mutated allele, receiving one copy from each parent.

The mode of inheritance for Juvenile Epilepsy has not yet been determined. However, there are different theories at present; one suggests that, like epilepsy in humans, multiple genes may be involved. Another theory suggests that it could be an incomplete form of LFS, and a third concern is that it possibly is an autosomal dominant trait. A "dominant" trait means that an affected foal only needs to inherit one copy of the mutated allele to show clinical signs. An example of a dominant trait is Hyperkalemic Periodic Paralysis in American Quarter Horses.


Courtesy of ESRE

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How frequently do they occur?

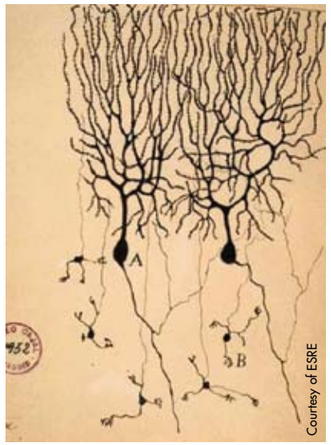
Although affected foals are definitely in the minority of foals born, these genetic diseases and disorders occur often enough that all breeders need to be aware of them. Because it is not possible to test every Arabian horse for every genetic condition, estimates have to be made based on what testing is available and the number of affected foals reported.

Table 1: Probability of Gene Combinations Resulting in Affected, Carrier & Clear Offspring

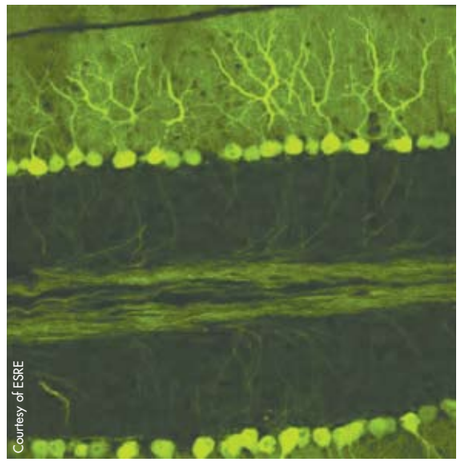
GENETIC STATUS		
X = no recessive allele x = recessive allele	Carrier parent (Xx)	Affected Parent (xx)
Carrier parent (Xx)	25% affected (xx) 50% carrier (Xx) 25% non-carrier (XX)	50% affected (xx) 50% carrier (Xx) 0% non-carrier (XX)
Non-carrier (clear) Parent (XX)	0% affected (xx) 50% carrier (Xx) 50% non-carrier (XX)	0% affected (xx) 100% carrier (Xx) 0% non-carrier (XX)

(Two non-carriers bred together will never produce a carrier or affected foal. Although it is unlikely two affected horses would be bred together, it is possible, and would produce 100 percent affected foals)

These photos are of a healthy L7 Cerebellum. They are a section of the cerebellum showing the molecular layer (upper realm) and the nuclear layer (lower realm). In the upper realm the fanned out branching of Purkinge cells can be clearly seen. The bulb at the base of each is the axon of the Purkinje cell. (The forms that look like trees etched in green.) An activity-induced green fluorescence signal can be observed when cerebellar slices are illuminated with blue light and parallel fibre-Purkinje cell synapses are thus activated, allowing micro-photography. These photos are actually of a mouse cerebellum but the reaction is similar to the Purkinje cells in any mammalian horse brain, including horses. These are healthy cells.



Courtesy of ESRE


Courtesy of ESRE

Prior to SCID testing becoming available in 1997, SCID carrier estimates ranged from 8 percent to 25 percent. From the start of testing in 1997 through May 2, 2007, VetGen, Inc. has tested about 7,700 horses with 17% testing as SCID carriers and 0.3 percent testing as affected. Although this is not a truly random sampling, it does provide a snapshot of the prevalence of SCID in the Arabian gene pool. It is important to note that the number of affected foals in these figures is based only on those foals tested by VetGen (it does not include SCID affected foals who did not have samples submitted to VetGen for testing).

Based on probability statistics for the behavior of an autosomal recessive gene, estimates of CA carriers range from 17 percent to 35 percent, with 25 percent often being used as an average. Because the condition is underreported, researchers can only state "this disease affects a significant number of horses every year."

The number of affected foals born with recessive genetic conditions is directly tied to the frequency of two carriers being bred together (***see table 1***). An affected foal cannot be produced unless two carriers are bred to one another. However, a carrier bred to a non-carrier results in a 50/50 chance the ensuing foal will also be a carrier. For every two carriers bred together, there is a 25% chance an affected foal will result from that mating. Because some horses with CA can be bred, it is important to remember that all foals from a CA affected parent will be carriers, even if bred to a CA clear Arabian or a horse of another breed.

Does linebreeding or inbreeding "cause" these diseases?

No. However, the more the gene pool is reduced by closely breeding related horses, and if carriers are present, the frequency of the mutated allele(s) has the potential to in-crease in the population.

Is there any bloodline of Arabian horse more or less likely to have genetic conditions?

No, all lines in the Arabian breed have the potential to carry genetic conditions. For example, SCID and CA have appeared in virtually all modern bloodline groups and appear to be distributed throughout the breeding population. In addition, while LFS is often associated with horses of Straight Egyptian or heavy Egyptian breeding, it has been identified in other breeding groups.

Doesn't the SCID test find all genetic problems?

No, although it was a wonderful breakthrough, SCID testing cannot determine carrier status of other conditions (just as parentage testing with DNA cannot be used for genetic disease testing). Each condition requires its own special test.

Did one horse or bloodline "cause" these diseases? Aren't these diseases a sign of "impure" breeding?

No and No. Cellular mutations are caused every time a cell divides; usually they have little to no effect. However, sometimes these mutations do end up altering a cell's function.

In addition, while some historical animals are very likely to have been carriers (based on pedigree analysis of get or grandget who produced affected foals), there is anecdotal evidence that at least some of these conditions appeared even in desert bred Arabians. To quote the late Dr. Ann Bowling: "Deleterious mutations that occur in purebred breeds are usually chance "hitch-hikers" in highly successful breeding lines, otherwise, the homozygous genotypes that produce the problem conditions would be so rarely encountered as to be overlooked or written-off as problems with unknown causes."

Can't we eliminate genetic diseases by not breeding known carriers?

Without a test, it is impossible to identify all carriers. Just because a horse has "so far" never produced an affected foal does not mean it is "clear." Because stallions can sire many offspring, they are more likely to eventually be revealed as a carrier. Mares, however, may be unrecognized carriers. Even if bred to a carrier stallion, statistical probability may mean that they never produce an affected foal. Thus, a recessive gene can be passed on for generations without an affected foal being born.

Further, by removing all known carriers from the breeding population, the already limited Arabian gene pool would become even more limited and the breed could lose some highly valued bloodlines. In addition, a less-diverse breeding population may actually allow other genetic conditions to become more widely distributed. The success of SCID testing indicates that if known carriers are bred, with careful, selective breeding and testing of offspring, even carrier lines can be "cleared" of the gene.

The SCID test allows people to avoid ever breeding an affected animal, and allows breeders to make an informed choice to breed or not breed a carrier, as they may choose. However, for the remaining conditions, until there is a DNA test, there is no way to know which horses carry the gene, short of producing an affected foal. Likewise, even when two carriers are bred, there is an equal statistical probability that their offspring will be clear or affected; thus guilt by association may unnecessarily taint the reputation of horses that actually do not carry the gene at all.

This is why it is so critical for breeders to support the ability of modern science to locate the genes that cause these conditions. Developing genetic tests is a must!

The role of the Equine Stress, Research and Education Committee is to discuss the types of stress-related horse abuse that occur today and make recommendations on how to eliminate or reduce stress; to foster and encourage educational programs, specifically breed improvement and animal husbandry; and to study and make recommendations on related topics of drugs and medication, stress, research contributions and other subjects. Special thanks to Lisa Goodwin-Campiglio, Beth Minnich and Brenda Wahler for helping to put together this article.

ARE TESTS AVAILABLE TO DETERMINE CARRIERS?

Currently, SCID is the only condition that has a test available. It can be ordered through FOAL for $99/test:

Arabian F.O.A.L. Association
Marguerite Illing, Treasurer, 853 Cooley Road, Parksville, NY 12768-5336
http://www.foal.org/user/orderkit.pdf

UC Davis in California is doing research on CA and LFS. Interested persons in the United States and Canada should contact Dr. Cecelia Penedo at:

Veterinary Genetics Laboratory
One Shields Avenue, Davis, CA 95616-8744
Phone (530) 752-2211, Fax (530) 752-3556
http://www.vgl.ucdavis.edu/research/equine/CA.html

In addition, Dr. Monica Aleman at UC Davis is researching juvenile epilepsy. For more information, contact: mraleman@ucdavis.edu, (530) 752-1170 or (530) 752-7267, Neuromuscular Disease Laboratory, UC Davis

Researchers at the **University of Berne** in Switzerland are also investigating CA and breeders in Europe, the Middle East and Australia who can provide DNA samples are urgently needed. They will be working in a loose collaboration with Dr. Penedo at UC Davis.
http://www.vetsuisse.unibe.ch/genetic/content/e2353/e2734/index_eng.html

For additional information, contact the molecular geneticist; Prof. Dr. Tosso Leeb, Institute of Genetics, University of Berne, Bremgartemstr. 109a, P.O. Box 8466, 3001 Berne, Switzerland, e-mail: tosso.leeb@itz.unibe.ch

And/or: Vincent Gerber, PhD. DACVIM, DECEIM, FVH. Head of Equine Internal Medicine, Vetsuisse-Fakulty, University of Berne, Langgass-strasse 124, 3012 Berne, Switzerland, e-mail: vinzenz.gerber@knp.unibe,ch

It is vitally important for breeders and owners to understand that without samples, it is virtually impossible for researchers to advance their work. For example, the Swiss need 10 brain specimens from CA affected horses and a minimum of 20 blood samples from related family members in order to give their research a solid base to work from.

Even though the idea of submitting blood and brain samples can be uncomfortable, and certainly a very personal decision for a breeder or owner; it is a necessity, so that a test can be developed. Once a test is developed, breeders have the ability to never produce an affected foal again. That is the ultimate goal.