GENETIC DISORDERS IN ARABIAN HORSES:

Current Research Projects

Article provided by World Arabian Horse Organization

Researchers have already identified over 13,000 genetically inherited traits in humans, more than 5,000 of them are disorders or other abnormalities which may be fatal or disabling genetic conditions. Many of these conditions also occur in animals including horses of all breeds, so Arabians are not the only breed of horse to have problems with inherited disorders. However, some genetic disorders are breed specific and in this article we will be looking only at the most serious genetic disorders which are known to affect Arabian horses.

It is important to understand that inherited genetic disorders in Arabian horses know no boundaries. They have been reported in all blood lines of the Arabian breed and reported cases have come from almost all countries where Arabians are being bred today. It is also important to understand that there is nothing to be gained from "pedigree witch-hunts". Through science, we can all learn to deal with facts as they are today, and not to 'point fingers' at individual horses from the past which may or may not have been the original sources of these genetic disorders. It also has to be said that it may not be possible or wise to eliminate a genetic disorder altogether, because by doing so an unwanted side effect might be to also eliminate other beneficial traits and diminish, rather than enhance, the gene pool. Carrier horses may be safely bred to clear horses, thus retaining desirable traits and preferred pedigree crosses without producing affected foals.

It is to everyone's benefit to become more informed about the genetic disorders in our Arabian horses, to support the researchers in their work and whenever possible to take the necessary steps to selectively avoid the production of affected foals. By identifying the genes responsible and having gene tests available, these can be used as tools by responsible owners when planning breedings, so that carriers are not bred to carriers. In this way affected foals, with all the attendant heart-break that this causes to their breeders, would not be produced.

Fortunately, a few Universities around the world have for many years been continuing their research in order to create gene tests to identify carriers of the various inherited equine genetic disorders, not only those found in Arabians. The Equine Genome Project is now complete, and a full 'map' of the horse's genes available to researchers. Universities also hold vast databanks of DNA, much of it from registered and parent-verified horses of many breeds, with known pedigrees going back generations. These databanks hold the key to the future of equine gene test research, as it is only through the collection of large numbers of samples that the location of the mutant alleles can be established and genetic carrier tests developed.

The research to identify the specific genes which cause these disorders is extremely time consuming and expensive, especially when it is into the relatively rare conditions such as Lavender Foal Syndrome. Many individuals and institutions involved with Arabian horses have supported this research in many countries over the years, both by submitting samples from their horses and with financial donations - their generosity is outstanding and is to be applauded. As a direct result, a test for Severe Combined Immunodeficiency Disorder (SCID) has been available since 1999, a new test for Lavender Foal Syndrome (LFS) has become available within the last year, and an indirect marker test became available for Cerebellar Abiotrophy (CA) last year.

It is important to understand that SCID, CA and LFS, the three conditions for which testing is now available, are all autosomal recessives, which means that carriers of these genes are completely free of clinical signs and do not have any negative consequences to their health or performance. Autosomal recessive traits are found in many mammal species. "Autosomal" means the trait is not sex linked, and "recessive" means that in order for a foal to be affected, it must have 2 copies of the mutated allele, receiving one copy from each parent. It is only when two carriers are bred together than an affected foal can be produced. Following the diligent work of many researchers in many countries over the past decades, these tests can now be used as tools by responsible owners when planning breedings, along with all the many other considerations that go into making such decisions. Tests do not yet exist for other known disorders in the breed such as JES (Juvenile Epilepsy Syndrome), GPT (Guttural Pouch Tympany), or OAAM (Occipital Atlanto-Axial Malformation)

Genetic Disorders in the Arabian Breed

There are four known genetic conditions in Arabian horses, which usually result in death or euthanasia of the affected animal. These are:

1. Severe Combined Immunodeficiency Disorder (SCID) (test available)
2. Cerebellar Abiotrophy (CA) (indirect marker test available)
3. Lavender Foal Syndrome (LFS) (test available)
4. Occipital Atlanto-Axial Malformation (OAAM) (test not yet available)

Two other conditions for which tests are not yet available are Juvenile Epilepsy Syndrome (JES) and Guttural Pouch Tympany (GPT), the latter also occurs in other breeds. These are not usually fatal, but can be disabling if not treated. Further research is needed to determine whether GPT is also a genetic condition.

Here is some further information on the above conditions:

Severe Combined Immunodeficiency Disorder (SCID)

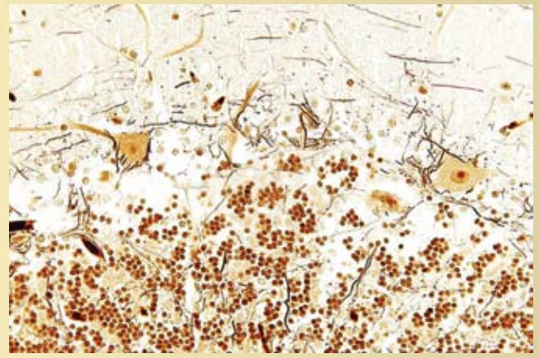
Several forms of SCID occur in mammals, including humans ("bubble baby syndrome"). They are not all the same, different genes and different modes of inheritance have been found in different species. SCID was first reported in Arabian foals in 1973 by McGuire and Poppie, Australia. In 1980, Perryman and Torbeck in the USA showed that SCID in Arabian horses was inherited as an autosomal recessive condition. After many decades of expensive and time-consuming research, the good news is that for over 10 years there has been a DNA test available for the SCID found in Arabian horses, which was developed and patented by VetGen in America, that can detect whether a horse is clear of the SCID gene, is a carrier of SCID gene, or is an affected foal which has inherited the gene from both parents.

A foal affected by SCID is born with no immune system, and generally dies of an opportunistic infection such as pneumonia, usually before the age of five or six months. Breeders who suspect SCID can have the foal or both parents gene tested, and if positive may opt for early euthanasia of an affected foal to prevent further suffering.

Since SCID is an autosomal recessive disease, matings between two clear animals as well as matings between a clear and a carrier animal will never produce an affected animal.

For more information, please visit the VetGen website: **http://vetgen.com**

Cerebellar Abiotrophy (CA) also referred to as cerebellar cortical abiotrophy (CCA), is a neurological disease found in Arabians and some other breeds, which affects the neurons known as Purkinje cells in the cerebellum of the brain, causing them to die off. Put simply, without Purkinje cells, an animal loses its sense of space and distance, making balance and coordination difficult. In most cases, the neurons begin to die off shortly after the animal is born and the condition is noticeable when the animal is less than six months old, though sometimes the onset of symptoms is gradual and the animal is much older before the owner notices a problem. Cerebellar Abiotrophy is different from Cerebellar Hyperplasia.



High magnification picture of Purkinje cells which are located in the cerebellum of the brain.


Photo Brenda Wohler.


Photo by Susan Lipton courtesy of Brenda Wohler.

These photo's are of a CA affected purebred Arabian filly. She is pictured left at two years of age showing the typical abnormal gait of a CA affected horse. She is shown below at age seven and for the first time in her life her owners have been able to get her in good bodily condition.

An affected foal is usually born without any clinical signs, but after six weeks and even as late as 18 months the following notable symptoms may be observed: A palsy-like head shaking called 'intention tremors' affecting only the head and not the neck or body, particularly noticeable when the foal is trying to focus on something; the lack of a normal blink response although vision is correct; and an awkward exaggerated form of action with the forelimbs called 'hyper-metric action' similar to a military goose-step or high elevation used to cross over a very low object. Sometimes in a badly affected individual it appears that the hind legs are also affected, but not usually. This hyper-metric action involves a shooting out and up of the foreleg directly from the elbow at both the walk and the trot. The hoof is brought down to the ground with a thump, often heel first. When cantering on level ground the horse looks as if it is cantering uphill, like a butterfly stroke in swimming. It is a highly exaggerated gait. The more stressed the horse, the more exaggerated the gait. Their spinal column is not involved; they do not lose weight; they are not in pain; they are neither lethargic nor show signs of increasing weakness, or loss of muscle tone.

As affected foals will often run into things or fall down, sometimes causing head injuries, their condition can be misdiagnosed as trauma from a blow to the head or neck, making the true neurological condition go unnoticed. A CA affected horse has little to no control over its balance and has difficulty judging distances between itself and an object. Hence, they startle easily and appear panicky and hyper-active. When maintained in a constant environment, the older the horse or foal becomes the more it adapts to the surroundings and its own disabilities, thus appearing as if it is improving. Change the environment and the affected horse will have to undergo a serious of hopefully minor 'accidents' before it has adapted to the new distances and objects. Often an older affected horse will have a 'horse buddy', which will be their guide. Horses with CA will often be referred to mistakenly as 'Wobblers', which is a condition of the spinal cord, not of the brain, or are misdiagnosed as a head injury caused by an accident. The degree of severity varies, with some foals having fast onset of severe coordination problems, others showing milder symptoms. In theory, mildly affected horses could live a full lifespan, but in practice, most are euthanized before adulthood because they are so accident-prone as to be a danger to themselves and others. They are not safe to ride.

Although the clinical signs are distinctive, until recently the only way to confirm a diagnosis of CA was to examine the brain after euthanasia. Research on Cerebellar Abiotrophy has been ongoing since the mid 1960s, carrying on the research started by the late Dr. Ann Bowling, well-known author and geneticist, whose studies in 1984 were unable to be published prior to her untimely death. This research has been a 'team effort' by geneticists at the Universities of Cornell, Michigan, Iowa and UC Davis in the USA and the Universities of Bern and Zurich in Switzerland, of Ghent in Belgium, of Cordoba in Spain, and in Australia by Professors Dr. J D Baird and Dr. C D Mackensie.

In August 2007 it was announced that locus of the mutant allele had been located, which was a major breakthrough. In September 2008 it was announced that Dr. Cecilia Penedo and her assistant Leah Brault from the Veterinary Genetics Laboratory at the University of California (UC Davis) had identified the chromosomal region which harbours the causative mutation and found sufficient "markers" to develop an indirect marker scanning test (early version of a diagnostic test) which indicates the presence or not of CA. This test can determine whether the horse is clear, a carrier, or affected. This indirect test has been available at a number of laboratories world-wide since 2009, most of which are co-operating with UC Davis to corroborate their test results. Dr. Penedo and her team are continuing to analyze the genes within this region in order to develop a direct test. The accuracy of the indirect test is estimated at 1:1000, meaning that in every 1000 tested horses the result of one might be different from the eventual direct test, for which accuracy is estimated to be 1:10,000.

STOP PRESS: CA Test – updated information as of January 2011

We have been informed by the Arabian Horse Foundation of America that further research conducted at the UC Davis Veterinary Genetics Laboratory (VGL) by Drs Leah Brault and Cecilia Penedo has identified a mutation that is associated with CA. This potential causative mutation involves two overlapping candidate genes that are undergoing further study. This is an important finding as it moves the currently available CA test from a marker based screening test to a more fully developed DNA test.

The Arabian Horse Foundation in America has provided additional funding to the VGL to incorporate whole genome scanning into the project, to further validate the location of the CA gene. Further details on the research and development of the CA test will be published in an upcoming issue of the journal Genomics. Another planned publication is to be in the Equine Veterinary Journal, on a survey of 31 breeds and finding the CA mutation that is being studied in Arabians also in the Trakehner, Bashkir Curly and Welsh Pony breeds. We thank them and all of their donors who have helped support this important research project, along with the owners who have submitted samples and provided information to the UC Davis team. The Arabian Horse Foundation has also announced that plans are currently being made for additional research this year to look at the functional aspects of the two candidate genes being studied. As such, continued support is important and needed. There is a wealth of information on their website: **http://www.arabianhorsefoundation.org** which also has a donations page.

Since CA is an autosomal recessive disease, matings between two clear animals as well as matings between a clear and a carrier animal will never produce an affected animal.

Lavender Foal Syndrome (LFS), also called Coat Colour Dilution Lethal (CCDL). Lavender foals are characterized by an unique coat colour and neurological dysfunction which leaves them unable to stand. Because LFS is relatively rare, there is little in the veterinary literature about it. The Animal Health Diagnostic Centre at Cornell University College of Veterinary Medicine in America has recently announced that a genetic test for Lavender Foal Syndrome is now available. For further information please visit this link:

http://ahdc.vet.cornell.edu/news/lfs.cfm

The most striking feature of LFS affected foals is that they are born with a coat colour dilution that lightens the tips of the coat hairs, or even the entire hair shaft. Coat colour is a dull pinkish-grey, the hairs may be somewhat silvery and the skin tends to be an unhealthy pink colour. In a few cases, the coat colour is a very unusual iridescent silver to pale lavender blue. Some affected foals do not exhibit this particular colour, but are unusually pale compared to normal foals. Hence the description 'lavender' refers to this unique colour

Foals born with Lavender Foal Syndrome usually die within a few days of birth or are euthanized on humane grounds as they are not able to survive.

at birth, but Coat Colour Dilution is probably a more accurate description.

In many cases, foals have had a difficult delivery (dystocia) which can also be harmful to the mare. All LFS foals are never able to stand and nurse. Foals may therefore be misdiagnosed as having neonatal maladjustment syndrome, also known as “dummy” foals, due to a lack of oxygen from the dystocia, or the symptoms may appear similar to spinal cord injury, but the LFS affected foal is generally distinguished from these by the peculiar coat colour.

The neurological dysfunction is characterized by opisthotonus, a position where the head and neck are drawn back, with the body and legs rigid, and is accompanied by convulsions or spasms. This condition is due to a disturbance of the central nervous system. Although unable to right itself, an LFS foal may have a strong suckle reflex and may be bottle fed, however this is usually to no avail. Nystagmus or involuntary, rapid eye movements are a secondary sign of opisthotonus and is present in some LFS foals. Foals with LFS often have seizures, and if they do not die they are usually euthanized within a few days of birth on humane grounds as they are incapable of survival. LFS should be considered a possibility in the differential diagnosis of any newborn Arabian foal with a markedly dilute coat colour exhibiting a seizure-like disorder at birth.

The Arabian Horse Society of Australia also actively promoted LFS research at the University of Queensland and a gene test is now also available at the State Veterinary Diagnostic Laboratory in Menangle, NSW, please contact the The Arabian Horse Society of Australia for more information. A gene test for LFS has also been developed by the Onderstepoort Veterinary Genetics Laboratory in Pretoria, South Africa, please contact the The Arab Horse Society of South Africa for more information.

Since LFS is an autosomal recessive disease, matings between two clear animals as well as matings between a clear and a carrier animal will never produce an affected animal.

Occipital Atlanto-Axial Malformation (OAAM). This is a condition where the cervical vertebrae fuse together in the neck and at the base of the skull, compressing the spinal cord. Although rare, it has been recorded in Arabian horses as well as other horse breeds and a variety of other domesticated animals. Symptoms range from mild in-coordination to the paralysis of both front and rear legs. Some affected foals cannot stand to nurse, in others the symptoms may not be seen for several weeks. This is the only cervical spinal cord disorder seen in horses less than 1 month of age. X-rays or necropsy can diagnose the condition. There is no genetic test for OAAM, and the condition is not well researched at present. There are some researchers who feel that it is a congenital defect caused during foetal development, others believe it may have a hereditary component and also be an autosomal recessive.

Any breeder with an affected foal and a definite veterinary diagnosis of OAAM should contact their own Registering Authority or Breed Society or nearest Veterinary College in the first instance, to find out if there are any research projects known of in their region.

Juvenile Epilepsy Syndrome (JES)/Juvenile Idiopathic Epilepsy (JIE), sometimes referred to as “benign” epilepsy. Epilepsy is relatively uncommon in horses compared with other species and as yet little information is available. This condition is not usually fatal and appears to be self-limiting Affected foals are born normal and appear normal between epileptic seizures, usually outgrowing the condition between 12 and 18 months. They may show signs of epilepsy anywhere from two days to six months from birth. Most foals will have what is called ‘cluster seizures’. Usually occurring before the third month birthday these are multiple seizures over a three day period with signs of confusion, blindness, head rubbing, depression, inability to eat, nurse or even drink. Affected foals may suffer serious injury as a result of falling to the ground, against hard objects or into fences. The more severe seizures may cause the horse to lose consciousness and the eyes roll back into the head.

After a seizure, the foal experiences a phase (the postictal phase) that may include depression, blindness, confusion, head pressing and/or loss of suckling reflex. Because pneumonia has been found to be the most common concurrent disease for foals with JES/JIE, it is recommended that foals not nurse or eat until the postictal phase is over, to help prevent any aspiration of milk or food into the lungs from a weakened swallowing reflex, which can potentially lead to pneumonia.

Dr. Monica Aleman at UC Davis in California, who is currently undertaking research into this disorder, has pointed out that a foal cannot be considered to have epilepsy unless it has had more than two seizures. Close observation is essential as some seizures may be slight. Because some forms of epilepsy can be caused by injury or infection, it is important to rule out other potential causes of seizures. The mode of inheritance for Juvenile Epilepsy Syndrome has not yet been determined and 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 HYPP in American Quarter Horses.

CONTACT FOR RESEARCH INTO JES:

Dr. Monica Aleman, MVZ, PhD, Dipl. ACVIM.
Email: mraleman@ucdavis.edu
Neuromuscular Disease Laboratory, University of California One Shields Avenue, Davis, CA 95616-8744, USA. Tel: +1 (530) 752-1170 or +1 (530) 752-7267

Guttural Pouch Tympany (GPT) This rare condition occurs in horses of several breeds, appearing from birth to 1 year of age and is more common in fillies than in colts. It is thought to have a genetic, possibly polygenic, inheritance but more study is needed. Latest research indicates a sex-specific quantitative trait locus which would explain the two to fourfold higher incidence of GPT in females.

Foals are born with a defect that causes the pharyngeal orifice of the eustachian tube to act like a one-way valve. Air can get in, but it cannot get out. The affected guttural pouch is distended with air and forms a characteristic large non-painful swelling. Breathing is noisy in severely affected animals, which may also be more susceptible to upper respiratory infections. Swallowing can also be difficult, with milk or fodder discharged from the nostrils or even inhaled into the lungs, leading to pneumonia. Diagnosis is based on clinical signs and X-rays. Veterinary treatment can control upper respiratory infections, but they often recur so surgical intervention is generally needed to correct the malformation of the guttural pouch opening to provide a route for air in the abnormal guttural pouch to pass to the normal side and be expelled into the pharynx. Foals that are successfully treated should grow up to have fully useful lives. Research is ongoing at the University of Veterinary Medicine in Hanover, Germany.

Summary

From the information available to date on horses tested for SCID and CA the percentage of carriers appears

at first glance to be high. Available information puts the carrier percentage from tested horses for SCID at around 16%. As the LFS test is so new, the numbers tested are too low as yet to determine the figures. For CA, from a total of 6650 tested horses at UC Davis up to 31 December 2010, the percentge of carriers is currently 19.25% and thhe percentge of CA-affected horses is currently 1.07%. However, it is worth bearing in mind that rates of carriers in the first few thousand tested horses are likely to be higher than in the total population due to owners initially testing potential carriers, firstly horses who have produced a suspicious foal, and secondly the horses who are by or out of a known carrier.

Just to make sense of the percentage of carriers in the breed it is worth calculating how many affected foals are likely to be bred for a given percentage when breeding without access to tests. A 20% carrier ratio sounds terrible, it means one in five horses is a carrier. However if you bred together a herd of horses in which 1/5 stallions is a carrier and 1/5 mares is a carrier your chances of breeding two carriers together are 1/5 x 1/5 = 1/25. So in 25 matings you only have one chance of breeding a carrier to a carrier. Your other 24 breedings will be clear to clear or clear to carrier, none of which can produce an affected foal. Of your carrier to carrier matings only 1/4 is likely to produce an affected foal so the overall likelihood of breeding an affected foal from a herd with 20% carriers is 1/4 x 1/25 = 1/ 100. Given the fact that few Arabian breeders produce 100 foals in a year or even over a period of several years, and taking into account all the other potential causes of foal fatalities, a 1/100 chance does not make breeding from a SCID, CA or LFS carrier as 'dangerous' to the breed as a whole as one might first assume.

Having said that, with the tests now available none of these figures particularly matter, as breeders can avoid ever breeding another carrier to carrier. Voluntary disclosure of horses' tested status, whether they are used for breeding or being offered for sale, should become the norm, rather than the exception. Responsible owners of stallions who stand at public stud are testing and declaring the results. Mare owners can then decide whether to look elsewhere or test their mare and continue. There is no reason that carriers should not be used for breeding provided care is taken not to breed carrier to carrier. Through responsible testing and carefully planned breedings, owners can now eliminate the possibility of an affected foal ever being born.

WAHO does not at this time support any proposition that SCID, CA and/or LFS carriers should be formally excluded from breeding by any Member Registry. Nor does WAHO currently support any proposition for mandatory testing and disclosure. However, WAHO very strongly supports the concept of voluntary testing and disclosure, and encourages all Member Registries to do their utmost to educate, encourage and support their owners and breeders do do so. The Registry Office at Windsor House can advise members and owners of their nearest recognized laboratory offering gene testing for SCID and LFS and the indirect marker test for CA. Details of the known laboratories currently offering the various gene tests may also be found at the Cerebellar Abiotrophy website: **http://www.cerebellar-abiotrophy.org**
and click on the link "Where to Test for CA and other Genetic Disorders"

Perhaps one day in the future the 'brave new world' of gene therapy and epigenetics will lead to a way to cure both humans and animals affected by the various genetic disorders that exist in all mammals, either by replacing the mutated 'damaged' gene with a healthy copy of the same gene, or by "turning off" the mutated gene. Until that day dawns, the mantra for all Arabian horse owners should be:

"TO PREVENT AFFECTED FOALS, TEST BEFORE YOU BREED"

For further in-depth information, we recommend visiting the following two websites which have extensive information and many interesting articles or links to articles:

VetGen:
http://vetgen.com/equine.html

The Cerebellar Abiotrophy website:
http://www.cerebellar-abiotrophy.org

WAHO would like to thank Lisa Goodwin-Campiglio, Life Member WAHO, SZED Spanish Arabians, Mallorca, Spain, who contributed the original basis article and who has been campaigning tirelessly to raise awareness of the research into genetic disorders in Arabians, especially CA.
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