Science and the Al Khamsa Horse: Genetics

Genetic Disorders and the Arabian Horse: How Far Have We Come and Where Are We Headed?

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Introduction and the Bigger Picture

Like other species, horses can be affected by a variety of genetic disorders. Currently, 10 of these disorders have DNA tests available: Severe Combined Immunodeficiency (SCID), Cerebellar Atrophy (CA), Leukodystrophy (LFS), Hyperkalemic Periodic Paralysis (HYP), Hereditary Equine Regional Dermal Atrophy (HERDA), Glycogen Branching Enzyme Deficiency (GBED), Ovarian Lethal Syndrome (OLWS), Type I Polysaccharide Storage Myopathy (PSSM), Malnourished Hyperthermia (MH) and Junctional Epidermolysis Bullosa (JEB)—two different types, one for Belgians and one for Saddlebreds.

Although HYP, SCID and OLWS tests have been available since the 1990s, the remainder of these tests have become available within the past decade. For these more recent tests, most are new within the past five years and in some cases, only since 2008–9. Much of the progress in recent years, however, can be attributed to the work that has been done through the Genome Horse Project. With the mapping of the equine genome completed in February 2007, a rapid increase in developing more genetic tests is expected, as additional tools that scan for genetic mutations become available. Not only will this new technology save years of work and hundreds of thousands of dollars in research funding, the real benefit for having the equine genome sequenced will be to get a better understanding of complex diseases such as laminitis, insulin resistance and arthritis (just to name a few) and be able to develop new therapies and treatments to help improve the health and well being of all horses.

In short, “successful use of genomic tools will help horse breeders, veterinarians and horse owners do what they already do even better... anticipate problems, predict outcomes and enjoy the unique interaction between horses and people,” as quoted from Dr. Ernest Bailey in the Equine Research Coordination Group White Paper, “The Equine Genome: What It Means for the Future of Horse Health.” In addition, Dr. Bailey comments “the point is to understand the interplay of genes and management, then allow breeders and horse owners to continue doing what they have always done, while making informed choices.” In a nutshell, this is the true value of genetic tests to provide tools for breeders and owners to use, to make informed decisions. These tests should not be used against breeders nor should breeders feel the need to hide from using this new technology. The information provided by these tests should be used to make decisions that are in the best interest of the horses and the breed, not to advance private agendas or wage personal battles.

For breeders and owners of purebred Arabian horses, three of these testable disorders are of particular interest: SCID, CA and LFS. (While PSSM has been reported in Arabians, the incidence appears to be exceptionally low.) In addition, there are three more conditions of interest that appear to have a genetic basis, but do not yet have tests available, that can also affect purebred Arabian horses: Juvenile Idiopathic Epilepsy (JIE), Guttural Pouch Tympany (GPT) and Osteo-Atlantoaxial Malformation (OAM). It is important for Al Khamsa breeders and owners to be aware that, at a minimum, cases involving SCID, CA, LFS, JIE and GPT have been reported in horses of Al Khamsa breeding.

Most of the genetic disorders overviewed in this article are autosomal recessive traits. "Autosomal" means the trait is not sex linked, so both sexes can be equally affected. "Recessive" means that in order for the trait to be expressed, the foal must receive two copies of the mutated allele (gene); receiving one copy from each parent. As such, both parents of an affected foal are by definition carriers. For recessive traits, a horse that has inherited one copy of the mutated allele, along with one copy of the normal allele, is classified as a carrier. Even though a carrier does not physically express the trait, they have a 50/50 chance every time they are bred of passing the mutated allele onto their offspring. Each time two carriers are bred together there is a 25% probability of producing an affected foal, a 50% probability of producing a carrier offspring and a 25% probability of producing a clear offspring. A horse that has inherited two copies of the normal allele is considered clear and will not pass the mutation along to their offspring.

An important consideration to remember for recessive traits is that a carrier horse will not always produce affected offspring; therefore it is possible for a recessive trait to remain hidden and skip generations. With the availability of tests for SCID, CA and LFS, there is no longer a need for guessing whether or not a horse is a carrier and more importantly, production of affected foals can be completely avoided.

Summary Overview
Severe Combined Immunodeficiency (SCID)

SCID is the only disorder in this group that involves the immune system. Found also in humans, mice and dogs, SCID is a lethal autosomal recessive disorder that results in a foal being born with an improperly functioning immune system. SCID in Arabians was first reported in the veterinary literature in 1973, and in 1980 an autosomal recessive mode of inheritance was determined based on breeding experiments conducted at Washington State University. However, it wasn’t until 1997 that researchers at the University of Texas developed a direct DNA test for SCID. SCID is caused by a mutation involving the enzyme DNA-PKcs (DNA-protein kinase catalytic subunit), a key component of the immune defense system. Because the foal’s immune system is not functioning properly, as the antibodies the foal receives from its dam’s colostrum wear off, the foal is unable to fight off infection from bacteria and viruses found in the normal living environment. As such, the foal will eventually die from an opportunistic infection, such as pneumonia, usually by about 5 months of age. Short of attempting a bone marrow transplant, there is no treatment for SCID-affected foals.

Those who are newer to the breed may not fully appreciate how significant the SCID research effort was. However, those who have been involved with Arabians since the 1970s and 80s will remember well how much of a concern SCID was and how devastating the disorder was to some breeding programs. Through efforts of IAHA’s FOAL Program Commission, working in conjunction with the Morris Animal Foundation, Arabian horse owners and breeders helped raise over $200,000 in funding, along with providing valuable samples for advancing SCID research. In addition, SCID information provided by FOAL and various Arabian horse magazines was invaluable for helping to raise awareness of SCID and educating owners and breeders. Development of a test for SCID was such a significant accomplishment that “SCID Testing” was listed as #10 in the Arabian Horse Association’s Centennial 100 voting. The Arabian horse community played a vital role in SCID research and this is a part of history that should never be forgotten.

In 1998, a carrier frequency of 8.4% was estimated from a random sample of 250 foals at the time of registration, correcting a much higher number from a less well designed earlier study. This carrier frequency, 8.4% under random mating, predicts an affected foal incidence of 0.18%. Since 1997, VeGen has tested almost 9,500 horses with the tested SCID carrier frequency averaging 16.5% (this is biased upward compared to the random sample because relatives of known carriers have been tested).
Additionally, since testing began in 1997, VetGen has tested ~30 SCID affected foals. How far have we come in managing SCID since the 1970s? A very long way, and it is an example to use as we deal with other genetic disorders.

SCID test results can be voluntarily reported to FOAL for inclusion in their public SCID test result list. Links to report forms and the public reporting list can be found at http://www.foal.org.

SCID test kits can be ordered from FOAL for $99/test at http://foal.org/KitsOrder.pdf or by contacting:
Arabian FOAL Association
Marguerite Illing, Treasurer
PO Box 198
Parkville, NY 12768-5336

e-mail: willis@Hughes.net

Cerebellar Abiotrophy (CA)

CA is one of several disorders affecting Arabsians that involves the nervous system. Found also in dogs, cats and several species of livestock, CA is an autosomal recessive disorder that results in degeneration of the Purkinje cells located in the cerebellum region of the brain. The Purkinje cells are large neurons that transmit electrical signals between the inner and outer layers of the cerebellum, at which point the signal is then carried to the body. Because the Purkinje cells control coordination and the refinement of movement, the degeneration of these cells results in varying levels of ataxia (problems with balance).

Foals affected with CA appear normal at birth. However, generally around six weeks of age (although it can occur later), the degeneration of the Purkinje cells results in physical indicators that can be wide ranging in expression and degree of severity. These clinical signs include: lack of balance, head tremor, a wide-based stance when standing still, exaggerated action when moving and the inability to get up if they have been lying on their side. In addition, CA-affected foals often fall from their lack of balance and can also stumble more easily, sometimes causing them to rear and fall. As a result, CA affected horses are more prone to injury, so they can be misdiagnosed as having some type of head or neck trauma. In some instances, CA cases can also be misdiagnosed as Wobbler’s syndrome or another neurologic disorder, such as EPM (see p.14). CA-affected horses are often euthanized because of the danger they can pose to themselves and those around them, due to their problems with balance and coordination. CA-affected horses that are not euthanized are generally limited to life as a pasture pet.

CA is thought to have been present in the Arabian breed for centuries, if not longer. Previously referred to as Cerebellar Hypoplasia, several papers were published during the 1970s and 80s discussing clinical signs, pathology and a proposed genetic link for CA. In the mid- to late 1980s, additional research findings and some newly published work confirmed an autosomal recessive mode of inheritance for this disorder. In the early 1980s, the late Dr. Ann Bowling began a small CA breeding herd at the UC Davis Veterinary Genetics Laboratory (VGL). The herd was composed of CA-affected horses and CA carriers that were donated to the UC Davis veterinary hospital. In addition to these breeding experiments helping to establish the mode of inheritance for CA, samples from these horses provided the foundation for the CA DNA research that has been conducted at the UC Davis VGL. This DNA study has led to the development of a marker based genetic test for CA which became commercially available in 2008. Dr. Cecilia Penedo and her group have currently narrowed the region of interest down to a small area on chromosome 2 and are continuing work to identify the exact mutation for CA, so a direct DNA test can be developed. The UC Davis CA Project is another example of how support from the Arabian horse community has provided valuable contributions for helping to move research forward and this continued support will be vital for the CA work still to come.

Through March 18, 2010, the UC Davis VGL has tested 2,828 samples, with 19.7% being tested as CA carriers and 1.4% testing as CA-affected (note 2 of the affected foals are Danish Sport Horses with Arabian ancestry on both sides of their pedigree). CA test results can be voluntarily reported to cerebellar-abiotrophy.org for inclusion in their public CA test result list. The cerebellar-abiotrophy.org website is also a valuable source of additional information on CA. Links to report forms and the public reporting list can be found at: http://www.cerebellar-abiotrophy.org.

More information on CA and CA test kits are available from the UC Davis VGL:
http://www.vgl.ucdavis.edu/genomic/cerebellar/
http://www.vgl.ucdavis.edu/services/horse.php or by contacting:
Dr. Cecilia Penedo
Veterinary Genetics Laboratory
University of California, Davis
One Shields Avenue
Davis, CA 95616-8744
Phone (530) 752-2211
Fax (530) 752-3556

Lavender Foal Syndrome (LFS)

LFS, also known as Coat Color Dilution Lethal (CCDL), is another of the disorders affecting Arabsians that involves the nervous system. LFS is a lethal autosomal recessive disorder caused by a mutation in the MYOSA gene located on chromosome 1. Affected foals are born with episodes of tetany: the foal will lay on its side, rigidly extending its limbs, neck and back and often make paddling motions. In addition, LFS affected foals are unable to stand and often cannot roll from their side to sit upright. Frequently born with the characteristic dilute coat color (which has been described as lavender, pale pink or silver), LFS affected foals often have a difficult delivery and while they possess a strong sucking reflex and can be bottle fed, they generally die or are euthanized within a few days of birth. Because of the dystocia that frequently occurs during the birth of an LFS affected foal, some cases are misdiagnosed as a "dummy foal" (oxygen deprivation during delivery). While LFS is commonly associated with horses of Straight Egyptian or heavy Egyptian breeding, it is important to note that LFS has been reported in other bloodline groups.

Although LFS has been recognized for over 50 years, there has been very little published literature on this disorder. The first documented description of LFS appeared in the book Horse Genetics by the late Dr. Ann Bowling, published in 1996. In the latter part of the 1990s, Cornell University initiated some work on LFS, and in 2004 several researchers in the US and abroad, affiliated with the Horse Genome Project, also began work on LFS. Due to retirement of some key researchers, a very limited availability of samples from LFS affected foals and lack of the necessary funding to pursue genetic research (especially in the time prior to the equine genome being mapped in 2007), neither project progressed very far. However, some of the samples banked during this time would be used for research efforts several years later. In 2005 and 2006, publications from the US and South Africa provided information on several LFS-affected foal case studies, providing significant information on clinical signs and pathology of the disorder. And in 2008, researchers at Cornell University, in collaboration with the newly restructured Arabian Horse Foundation, reactivated their LFS Project, which resulted in rapid advancement for developing a test. In spring 2009, Cornell published preliminary results on mapping LFS using the SNP50 chip, a technology that became available with the mapping of the equine genome. Later in 2009, Cornell announced the development of a direct DNA test for LFS. Additionally, in a separate project, researchers in South Africa also announced the development of a direct DNA test for LFS in the latter part of 2009. Results from the Cornell LFS Project have been published in the April 2010 issue of PLoS Genetics. [This paper can be found on the AHA website.]

The Cornell LFS Project is a wonderful example of how research can be moved forward when breed organizations collaborate with researchers and owners respond to requests for samples from researchers. In addition to funding and general support provided by the Arabian Horse Foundation, the Arabian horse community also responded by sending literally hundreds of samples, representing a variety of Arabian breedlines, to Cornell to assist in developing the LFS DNA test. This type of engagement with the research community is key for continuing to advance research efforts in equine health.

Information on the commercial availability of the Cornell LFS test will be made available as soon as the details are finalized. Owners in need of
Juvenile Idiopathic Epilepsy (JIE)/Juvenile Epilepsy Syndrome (JES)

JIE is another neurologic disorder that can affect some Arabian horses. JIE is caused by a disruption in the brain's electrical activity which results in seizures. Research suggests that JIE is an autosomal dominant trait, which means that only one copy of the mutated allele is required for a foal to be affected; therefore, only one carrier parent is needed to produce an affected foal. Affected foals are born normal and appear normal between seizures, but will begin to have periodic seizures starting anywhere from about two days to six months after birth. Although JIE is not generally fatal and is self-limiting, in that the seizures generally disappear by one to two years of age, the disorder can be temporarily disabling and injury can occur during an episode. Treatment can include the use of traditional anti-seizure medications, such as diazepam and phenobarbital, which may reduce the severity of the seizures.

In 2006, a publication covering 22 cases of JIE in Egyptian foals was published by researchers at UC Davis, where JIE has been researched since the 1980s. In addition to the proposed dominant mode of inheritance, there has also been a suggested genetic link to Lavender Foal Syndrome; further research into this proposed link is being pursued. In order to continue moving research on JIE forward, owners of JIE-affected foals or horses who suffered from JIE as foals are encouraged to submit samples to help support research efforts.

For further information on JIE or to submit samples, please contact:
Dr. Monica Alman
Neuromuscular Disease Laboratory
University of California
One Shields Avenue
Davis, CA 95616-8746
Phone (530) 752-1170 or (530) 752-7267
Email: maralman@ucdavis.edu

Guttural Pouch Tympany (GPT)

GPT is a condition affecting the guttural pouches, which are large spaces extending from the Eustachian tubes (more commonly known as the ear tubes). Current research indicates that GPT is a polygenic trait, meaning that multiple genes are involved in expression of the trait. In addition, genetic studies have also shown there is some sex limitation involved, which is consistent with data indicating that fillies are two to four times more likely to be affected than colts. A malfunction of the Eustachian tubes causes the guttural pouches to become distended with air as a result of air being able to enter but not escape. GPT is seen in younger horses, ranging anywhere from birth to a year or so in age. The classic sign of GPT is the non-painful swelling in the parotid region, which is the area just behind the jaw. This clinical sign combined with radiographs of the skull generally provides enough information for a diagnosis of GPT. Correction of the physical defect causing this condition requires surgery. Because GPT can be associated with respiratory infections, affected horses may need to be treated with NSAIDs and antimicrobial therapy.

During the past decade, researchers in Germany have published several papers studying GPT in Arabian horse owners, breeders and enthusiasts. It is the hope of this author that in the coming years the Arabian Horse Foundation will become a valuable tool for the Arabian horse community to become active again with important research projects, including but not limited to those directed at genetic disease research relevant to the Arabian breed. In its first year of providing funding for research, in 2008 the Foundation awarded funds to Dr. Cecilia Penedo and the CA Research Project being conducted at the UC Davis VGL and also to Dr. Samantha Brooks and the LFS Project being conducted at Cornell University. In 2009, additional funds were provided to the CA Research Project and awards for 2010 will be announced later this year.

The ability of the Foundation to support research is directly tied to the amount of financial support the Foundation receives from Arabian horse owners, breeders and enthusiasts. It is the hope of this author that in the coming years the Arabian Horse Foundation will be named alongside the AQHA Foundation and the Grayson Jockey Club Research Foundation for being leaders in equine health research. But this achievement will only happen with strong grassroots support from the Arabian horse community. For some perspective, the 2008–10 approved project funding for the AQHA Foundation equine research program is over $400,000. For 2009 and 2010 awards, the Arabian Horse Foundation research award will likely have about 2% of that to work with. While AQHA is certainly a larger organization and has been heavily involved in research for many years, there is no reason why the Arabian horse community cannot be as engaged in supporting the Arabian Horse Foundation. With $33,000 AHA members, plus Arabian horse owners and enthusiasts who are not AHA members, at just $10–20/year the donations add up quickly. And of course, larger donations are even better.

The Arabian Horse Foundation is a 501(c)(3) organization and contributions are tax deductible. Donors can also specify their donation for the general fund or to a specific area (research, rescue/rehoming, and/or scholarships). Donations can be made online at http://www.arabianghorsesfoundation.org/donate.html or by sending a check to: Arabian Horse Foundation, Treasurer Jim Cada, 1024 K. Street, Lincoln, NE 68508.
AHA Task Force on Genetic Diseases

In early 2009, AHA President Lance Walters appointed the AHA Task Force on Genetic Diseases to assist in guiding the association in developing policies and educational programs. For the 2009 AHA Convention, the Task Force submitted resolutions requiring the disclosure of CA and LFS carrier status to interested parties; both of these resolutions were unanimously passed by the delegates. The Task Force also sponsored a Convention Forum on genetic diseases and the Arabian horse. Additional information about the forum and Task Force activity can be found at: http://www.arabianhorses.org/education/general/docs/10Generic_forum_slides.pdf.

AHA Equine Stress, Research and Education Subcommittee on Genetic Disorders

As a recommendation of the Task Force, the AHA Equine Stress, Research and Education Committee initiated a Genetic Disorder Subcommittee in January 2010. This subcommittee has been charged with developing educational materials and (in collaboration with the Arabian Horse Foundation and FOAL) to act as a 'think' tank for additional projects. The Genetic Disorders Subcommittee has updated and expanded the AHA Genetic Disorders Information page on the AHA website at http://www.arabianhorses.org/education/general/default.asp. One of the new features of the page will be a monthly question and answer forum on genetic disorders. Anyone interested in submitting a question for consideration should send their question to considernell@comcast.net.

What is the next step?

Science is allowing us the opportunity to continue learning and improving the care we can offer our horses. While some findings may initially pose challenges to breeders and owners, it is important that we keep an open mind and be willing to learn, and not react out of fear or misunderstandings wanting to adopt the “see no evil, hear no evil, speak no evil” mantra. This is not in the best interest of our horses. The Arabian horse community has come a long way in the last few decades and has several success stories to be proud of. We need to continue moving forward with this effort and support research activities.

Gait Irregularities: Lameness or Illness?

Not every gait irregularity signifies a need to worry about a neurological disorder, but any gait irregularity can be difficult to diagnose. Obviously, the first step is to see if lameness is involved. The database of articles at http://www.TheHorse.com can be of help to both owner and veterinarian.

Ohio State has published an evaluation of Kinetic Gait Analysis to help with diagnosis. An article about this research can be found at The Horse website, Article #13769.

If lameness is ruled out, then a more complete exam can identify possible locations and causes of problems. Dr. Stephen Reed of Rood & Riddle Equine Hospital in Lexington, Kentucky, described selected equine neurologic diseases in his presentation at the 2008 American Association of Equine Practitioners Convention. This lecture can be found at The Horse website, Article #13629.

A complete history and neurological exam, as described by Dr. Reed, involves looking at the type of irregularity: deficiency (lack of movement), discharge (a seizure or spasm or repetitive non-functional behavior), or release (exaggerated, weak or incoordinated response).

Disorders that can cause neurologic signs include CVM (cerebral vertebal sionotic myopathy) or wobbler syndrome, EPM (equine protozoal myelonephritis), EHV-1 (equine herpesvirus-1), toxicosis from moldy hay or grain, and botulism.

CVM is not normally found in Arabian horses, and genetic influence is still under investigation. Neurological pressure is created by narrowing of the vertebral canal holding the spinal cord. Narrowing can be caused by arthritic processes in an older horse, developmental issues in a younger horse, or malalignment in horses associated with extreme flexion and raised neck as in Saddlebred-style showing. Developmental and orthopedic disease in growing horses can result from nutritional causes, either too much rich food in aiming for early growth, or an imbalance of essential nutrients.

EPM is caused by a protozoal infection of the spinal cord by the parasite Sarcocystis neurona, resulting from a horse consuming contaminated pasture, feed or water containing the encysted stage of the parasite. Postural facial muscle is the source of contamination. Blood tests are possible, but not definitive. A tap of the cerebral spinal fluid can indicate an immune response, but blood contamination of the tap can confuse the issue. If other causes of ataxia are ruled out, response to treatment is often the best indicator of the disease. Prevention is aided by keeping this from away from horses and feed and water, and reducing stress whenever possible.

EHV-1 (and EHV-4 upon occasion) are viruses that can cause respiratory illness, abortion, or in rare cases, serious neurological illness. Older horses and those under stress are more likely to have bad outcomes. Neurological outbreaks of EHV-1 require major effort to avoid spreading the disease from horse to horse, with human intermediaries.

Untreated, all neurological disease can end in disability or death, so prompt identification of the cause and treatment are essential.