Preservation Without Tragedy

Managing Genetic Disorders (and Diversity): What Comes After Testing

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Due in large part to the Human Genome Project, the last 20 years has brought tremendous advancements in the study of both human and animal genetics. Using knowledge and technology garnered from this landmark project, the first map of the horse genome was completed in 2007. As a result of this major research effort, continued advancements in understanding equine genetics are expected to occur at an even more rapid pace. While the genetic components of many traits are being studied (such as complex diseases, color, and athletic performance), an ongoing area of interest is the study of genetic diseases and the development of related DNA tests.

Even though rapid advancements in DNA testing have been made in the last several years, genetic tests are not new to the horse world (the tests for SCID, HYPP and OLWS all became available during the 1990s). What is new, however, is the rate at which tests are being developed and the increased availability for access worldwide. With updates from the research community becoming regularly available to owners, at times the information can be overwhelming and confusing, not to mention controversial. This can be especially true as owners work to understand how the current “science” impacts their horses and breeding programs. When the research has implications for the selection of breeding stock, the discussion becomes even more important in regard to issues involving breed diversity. When small population closed groups are involved, where the number of individuals available may be limited to only dozens or hundreds, and not thousands of horses, the issues become crucial to discuss and understand.

In an era that allows for rapid communication across the globe, the topic of genetic disorders has taken a prominent position among key issues for owners, breeders, and horse organizations to address. Not surprisingly, with the arrival of this new information and the related technologies, there are also questions and concerns. As such, with DNA testing for genetic disorders becoming more readily available, now what?

Genetic Disorders Inevitable

The first area to address is the reality that, like other species, horses can be affected by a variety of genetic disorders, and there is no special exception for the Arabian horse. Currently, there are 10 equine genetic disorders that have DNA tests available and three of these are associated with purebred Arabian horses: Cerebellar Abiotrophy (CA), Lavender Foal Syndrome (LFS), and Severe Combined Immunodeficiency (SCID). All three of these disorders are recessive, meaning that in order to produce an affected offspring each parent must possess and pass along a copy of the disease gene. In other words, two copies of the gene mutation are required for the disorder to be expressed. Horses that are clear are just that, they possess two copies of the normal allele (gene). As such, they are physically normal and can only pass on a copy of the normal allele to their offspring. Carriers are horses that have one copy of the mutation and one copy of the normal allele. Because these are recessive disorders, carriers do not show signs of the disease. However, because carriers do possess one copy of the gene mutation, it can be passed along to their offspring (a 50% probability at each breeding).

While SCID and LFS are straightforward in that affected foals die at a very young age, CA presents a slightly more complicated situation. CA can display a wide range of expression from individual to individual, not only in degree of severity of clinical signs (ranging from very mild to extreme neurologic impairment), but also in age of onset (from months to years of age). In addition, CA also appears to display incomplete penetrance, meaning that it is possible to have exceptions with some individuals possessing the CA / CA genotype not displaying clinical signs of the disease. [See sidebar.] It is important to realize that CA / CA affected foals / horses are frequently euthanized due to the degree of neurologic impairment. However, because CA is not automatically a lethal trait, it is possible for CA / CA individuals to live to maturity, with some of these individuals
Cerebellar Abiotrophy: Update and Ongoing Research

Cerebellar Abiotrophy (CA) can be a challenging disease for researchers to study and owners to evaluate. Not only does CA display variable expression (clinical signs can range from very minor to major neurological impairment), CA also appears to display incomplete penetrance (not all horses with the CA/CA genotype appear to display clinical signs of the disease). In addition, there have been published cases of horses showing recognized onset of clinical signs beyond the typical time frame of 1–6 months of age. While most of those cases involved horses in the age range of 1–2 years, one particular case involved a 6 year old mare that did not show noticeable neurologic concerns until started under saddle as a 5 year old.

To date, a small number of horses tested as being CA/CA at the UC Davis Veterinary Genetics Laboratory have been reported by their owners as currently not having any neurologic issues. At this time, because minimal information is available regarding these cases, it is difficult to confirm how many of these horses are currently without any level of neurologic dysfunction. However, these “exception” cases are being furthered studied as part of the ongoing CA Research Project at the UC Davis VGL. [Additional information about the VGL’s CA Research Project is available at http://www.thearabianhorsefoundation.org/NewsArticles/11_CA_Research_Project_Summary.pdf]

Why CA is not as clear cut in expression as genetic disorders such as SCID and LFS is a question that researchers are seeking to answer; not only to help better understand the mechanisms behind the expression of CA, but also for the potential to downplay therapy options for horses affected with CA. In 2011, a paper by Dr. Cecilia Penedo and her group at the VGL was published in the journal, *Genomics*, describing the identification of a mutation associated with CA. This mutation is located on chromosome 2 (ECA2) and involves a single nucleic acid base change. Of the four genes located in the CA region, two of them, MUTYH and TOE1, have some brain involvement. In particular, the MUTYH gene is involved in the repair of Purkinje cells, and preliminary data indicate that in CA affected horses, there is reduced expression of MUTYH. If the MUTYH gene is not fully functioning, this could explain the variable expression of the disease. The physical differences between CA/CA horses could be due to varying levels of MUTYH function, resulting in differing amounts of Purkinje cell damage, between individual horses. Alternatively, it is also possible that a small number of horses carry a suppressor mutation that can assist in compensating for the effects of the disease.

To further study these “reportedly no-sign cases”, last fall the VGL initiated a ‘resequencing’ experiment to see if there is an additional genetic component involved in the expression of CA. Preliminary findings from this work are expected out later this year. Additional experiments to understand the effects of the mutation on either the TOE1 or MUTYH genes are also planned in order to learn how the mutation affects the activity or expression of either of these genes.

In the meantime, what can owners do to assist the research? Owners with CA/CA horses, particularly those appearing to show minimal to no neurologic signs, are encouraged to contact Dr. Penedo: mctorrespenedo@ucdavis.edu. Tel: (530) 752-7460, FAX: (530) 752-3556. Dr. Penedo is also following up with all owners of horses tested as CA/CA at the VGL. Please respond to the follow up as thoroughly and quickly as possible. In addition, to assist owners in getting a better understanding and recognition of the wide range of clinical signs and degree of expression that can be observed with CA, there are numerous videos and firsthand accounts available at: http://www.cerebellar-abiotrophy.org.

While research on CA is still ongoing, the Arabian horse community is fortunate that the production of CA/CA foals can be completely avoided with the use of testing and the selective use of carriers.
of affected foals through the use of testing and selective mating. If carriers are not bred together, there will be no affected foals. That is a very easy to understand, basic reality and it needs to be emphasized. To repeat—the production of affected foals can be completely avoided by not breeding two carriers together.* However, this does not automatically equate to not breeding carriers at all. Knowing this can be a controversial subject, it needs some further discussion and understanding.

For an individual breeder, there is no single right or wrong answer to the question of whether or not to use a carrier for breeding; it is a personal choice. Will some people choose to not use a carrier? Yes. Just as some people choose to not use an otherwise completely suitable horse due to considerations such as color, markings or pedigree elements.

However, it is important to understand that carriers can be responsibly used for breeding, and personal choice allows for a breeder to make the decision to use a carrier. And, there are many breeders willing to do this. From a breed wide perspective, carriers should not be summarily discarded from the breeding population based solely on a test result. So, if you have a breeding horse test as a carrier, it does not automatically mean there is no future in the breeding shed.

Every time a breeder makes a breeding pair selection, not only have they decided who they are going to use for breeding, but also who they are not going to use. This is a cycle that happens throughout every breeding season; some horses are selected for breeding, some horses are not. The criteria each individual breeder uses in making their breeding selections is what gives the Arabian breed such a variety of breeding programs and horses to select from. This is a variety that needs to be encouraged and maintained; especially within the preservation community, where there are numerous small bloodline groups that are completely dependent on breeders dedicated to the continued existence of these groups.

Even though a primary goal is certainly the production of zero affected foals, the breeding of Arabian horses is not just about test results. Yes, full disclosure of carrier status is an absolute must for stallions standing at stud and for breeding stock being made available for lease or purchase. This is something that needs to be emphasized and mare owners / buyers should insist on seeing test results before making purchases; so they can make informed decisions. In this day and age, the tools are readily available to avoid breeding carriers together. So, the goal of zero affected foals can be achieved.

**Genetic Diversity Key**

But, decision making also needs to take into account the best ways to also produce quality Arabian horses while maintaining as much genetic diversity as possible within the breed. Especially when dealing with small population closed groups, these additional goals cannot be met by using carrier status as the sole criterion for exclusion from breeding. Within the Arabian breed, and particularly within the Al Khamsa community, there needs to be a preservation and continuation of lines, not an exclusion or removal of them. For once these lines are gone, they are gone and cannot be replaced.

Another important consideration for a recessive disorder is that the mutated gene is not the disease; it is simply 1 of 20,000 genes in a horse’s genome. A particular recessive gene mutation only becomes a problem when it is combined with another copy of the mutation, resulting in expression of the disease. With genetic testing, these situations can be avoided. In more practical terms, the negative impact of these genetic disorders comes from the production of affected foals; not simply the existence of the mutations. The overall goal of using testing as part of the decision making process for breeding is to produce quality without tragedy; not to automatically remove horses from the breeding shed. The need for genetic diversity is too great to discard horses because of a single gene that does not express itself in the single state.

Ask yourself the following. Did you consider the horse good enough to breed before the test result came back? If yes, realize those desirable attributes for breeding have not gone away and the horse has not changed. Taking all factors into consideration, will this horse more likely than not sire / produce quality foals? That is where the focus should be. Not on whether or not a piece of paper says ‘carrier’ or ‘clear’.

Now, this does not mean there should be no effort to control the number of carriers in the breeding population. But, this needs to be done reasonably and responsibly, so there is a balance between controlling allele frequency and maintaining overall genetic diversity.

For example, if the horse was on the borderline of being desirable to use for breeding before the test result came back, then having a carrier result could reasonably tip the scales to not using the horse as breeding stock. If the horse does not have the attributes desirable for breeding before testing, they are not going to get those attributes after testing. So, what benefit is there to use the horse for breeding, especially when there is the potential to pass the mutation along to offspring that are likely to be mediocre? And, if a horse was not good enough to breed before testing, then the horse should obviously remain a non-breeding candidate after testing, regardless of the test result.

Another option available to help manage these disorders and maintain as many lines as possible is the use of suitable clear offspring of carrier horses, when available. This combines the best of both worlds, in that desirable lines can continue to be used through clear offspring, essentially providing a ‘clear route’ option within ancestral carrier lines.

**Take-Home Message**

The take home message is that a carrier or clear test result, by itself, should not be the sole factor in deciding whether or not to breed a horse. The horse should be evaluated on its own merits and that of their progeny. Being ‘clear’ does not automatically make a horse desirable for breeding; just as being a ‘carrier’ does not automatically make a horse undesirable for breeding.

In a perfect world, the gene pool for the Arabian horse would be free of potentially harmful mutations. But, we do not live in a perfect world, so we need to be realistic about our situation. And the reality is, potentially harmful alleles exist in the gene pool and will always be there in some form. But another reality is, some of these potentially harmful mutations can be tested for and the production of affected foals can be avoided. Testing is a responsibility of breeders; there is no way around this. There are practical ways to avoid the production of affected foals and control the frequency of these mutations in the gene pool, while at the same time not losing the genetic diversity so greatly valued and needed in the breed.

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* Comment based on CA affected horses that live to maturity not being considered candidates for breeding.
Breeders have the ability to boldly and responsibly face the reality of dealing with genetic conditions affecting the Arabian horse. To continue moving forward, there needs to be education, awareness and understanding. But, there also needs to be balance. Education has come a long way over the last several decades, and past experience with SCID provides a backdrop to take the knowledge gained during that experience and apply it to the handling of CA, LFS, and the other genetic disorders still to be identified. And make no mistake, genetic testing is not going to end with the three current tests.

As genomic research expands and science continues to move forward, more and more discoveries are going to be made regarding the role genetics plays in how the horse’s body functions. As caretakers of the Arabian breed, there needs to be an increased effort throughout the entire Arabian horse community for more education on how genes work in regard to the whole horse; along with understanding the necessity for genetic diversity in the breed. To take the path of trying to remove all ‘bad’ genes, without any other considerations, is not in the best interest of the breed.

While individual breeders will always have their preferences for which horses to breed, it is hoped that breeding decisions involving carriers will be informed and educated, and not based on misunderstanding or personal agendas. Testing is a tool to be used to assist in making informed breeding decisions; nothing more and nothing less. The goal of testing should be to identify carriers, not automatically eliminate them from breeding. The goal of breeding should be to avoid tragedy, while still being able to produce quality. With continued education and open discussion, this can be accomplished. The Arabian horse deserves nothing less!