Cerebellar Abiotrophy Research Project at the UC Davis Veterinary Genetics Laboratory (VGL)

- Historical background, progress to date and future plans -

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with special thanks to Dr. Cecilia Penedo/UC Davis VGL for reviewing this material

Since the 2007 re-structuring of the Arabian Horse Foundation to include funding support for equine health research, the Foundation has proudly supported the Cerebellar Abiotrophy Project being conducted in the lab of Dr. Cecilia Penedo at the Veterinary Genetics Laboratory, University of California/Davis. To help provide additional information about this study, the Foundation has prepared this project summary.

The Foundation thanks our donors, along with owners who have submitted samples, in their ongoing support of this important research effort.

Overview

Equine Cerebellar Abiotrophy (CA) is a genetic neurological disorder found predominantly in Arabian horses. Identified in a wide range of bloodlines within the breed, the mutation responsible for causing CA is thought to be present in the Arabian breed for centuries, if not longer. Previously referred to as Cerebellar Hypoplasia, several papers were published during the 1970's and 1980's discussing clinical signs, pathology and a proposed genetic link for CA. In the mid-late 1980's, additional research findings and some newly published work confirmed an autosomal recessive mode of inheritance for this disorder.

In the early 1980's, 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 led to the development of a marker based genetic test for CA, by the lab of Dr. Cecilia Penedo at the VGL, which became commercially available in 2008. In February 2011, the Penedo group published a paper in the journal, Genomics, describing the identification of a mutation associated with CA. Currently, Dr. Penedo's group is continuing to further study this mutation.

Inheritance of CA and the Frequency of the CA Mutation in Other Breeds

In addition to the February 2011 Genomics paper, Dr. Penedo's group has also had two other CA related publications this year:

1) The July 2011 issue of the American Journal of Veterinary Research published a paper on the inheritance of CA, based on work done by the Penedo group. This publication overviews a statistical analysis that involved a total of 804 Arabians, including 29 CA affected horses (15 males and 14 females). The results confirm previous research that CA is consistent with a single gene Mendelian autosomal recessive mode of inheritance. In more simple terms, the inheritance of CA involves one gene, with both sexes having an equal potential to be affected, and two copies of the mutation (one from each parent) are required in order for a foal to be affected.

In addition, inbreeding coefficients were calculated for 16 of the CA affected horses and compared with a group of 16 horses from the general Arabian horse population. The average inbreeding coefficient was 8.71% for both groups, which suggests that CA affected horses are not more inbred than unaffected horses. And finally, the frequency of the CA associated mutation was determined to be 16%. However, the researchers make an important note that this frequency calculation is specific to the families used in the study and is not necessarily reflective of the entire breed. Of particular note, is the "substructuring" within the breed that has led to the selective breeding of horses within specific bloodline groups, such as Egyptian, Polish, Spanish, etc. As such, the frequency of the CA associated mutation may vary among these subgroups.

2) Another paper by the Penedo group, which appeared in the March 2011 issue of the Equine Veterinary Journal, is especially illuminating in that the mutation associated with CA was found in several breeds with an Arabian ancestral element. More specifically, the study looked at 1,845 non-Arabians representing 31 breeds and among that group at least once CA carrier was identified in each of the following three breeds: Bashkir Curly Horse, Trakehner and Welsh Pony. Based on pedigree analysis and additional DNA study, researchers concluded that the CA mutation was introduced into these breeds by an Arabian ancestor(s). In the case of the Bashkir Curly Horse, it appears the CA mutation was introduced by a single Arabian stallion that was used in the 1960's for developing the breed, while the Trakehner and Welsh Pony carriers were at least half-Arabian. See the below tables for additional information on the frequency of the mutation identified in other breeds and the breeds used in the study. The results from this study reinforce the importance of CA awareness and testing for breeds that have Arabian ancestry.

Table 1: Incidence of CA in three breeds of horses

Breed	# horses tested	# carriers	Carrier frequency	Allele frequency
Bashkir Curly horse	143	8	5.6%	2.80%
Trakehner	147	2	1.40%	0.68%
Welsh pony	150	1	0.70%	0.33%

Source: Brault, et al. The frequency of the equine cerebellar abiotrophy mutation in non-Arabian horse breeds. Equine Veterinary Journal. doi: 10.1111/j.2042-3306.2010.00349.x

Table 2: Survey of 31 horse breeds genotyped for the potential causative mutation of CA

Breed	# Tested		Breed	# Tested
Akhal-Teke	46		Paso Fino	86
Andalusian	47		Percheron	86
Bashkir Curly	55		Performance horse	24
Belgian	59		Peruvian Paso	58
Clydesdale	51		Quarter Horse	102
Connemara	63		Shetland pony	69
Friesian	44		Shire	57
Hackney	54		Standardbred	82
Hanoverian	29		Tennessee Walking horse	82
Holsteiner	42		Thoroughbred	172
Kentucky Mountain horse	45		Trakehner	55
Lippizaner	70		Warmblood*	40
Miniature horse	106		Welsh pony	64
Morgan horse	70			
Norwegian Fjord	70		**TOTAL HORSES TESTED**	**1845**

**Warmblood group: representatives from American WB, Dutch WB, Sport horses, and Swedish WB*

Source of data: Brault, et al. The frequency of the equine cerebellar abiotrophy mutation in non-Arabian horse breeds. Equine Veterinary Journal. doi: 10.1111/j.2042-3306.2010.00349.x

"Reportedly Asymptomatic" Affected Horses

Through the past several years of testing, an interesting aspect of CA has been brought to the attention of the researchers at the VGL; a small group of horses (currently 12 known at the VGL) which have been tested as CA/CA (affected), whose owners report show no clinical signs of being affected. To further study these "reportedly asymptomatic" CA affected horses and to see if there is an additional genetic component involved in the expression of CA, the VGL has incorporated another round of whole genome scanning, this time utilizing a new tool called the Equine SNP chip. Information gained form this part of the research project may assist in determining why some horses that are CA/CA are reportedly not showing signs. While data from this work is currently being analyzed and should be available later this year, here are some initial findings:

- The study design involved 24 controls (not affected) and 34 affected cases (26 with clinical signs and 8 that tested as CA/CA but were reported by their owners to not show any clinical signs).

- Results from analyzing the 24 controls (not affected) and 26 affected cases (showing signs) showed highly significant associations with SNPs on ECA2 around the area where CA has already been mapped. Additional analysis to include 8 cases showing no signs did not change the results. Based on these analyses, the genome location of CA from the earlier research has been confirmed.

- Additional statistical methods to refine the analyses are being done to determine if other regions of the horse genome could have an effect on CA.

Ongoing Research Efforts

Because the potential causative mutation for CA is tied to more than one gene, the VGL is conducting further study of the two candidate genes, MUTYH and TOE1. Part of this ongoing work includes “expression studies” to help evaluate the functional aspects of these two genes and determine what effect this mutation has on them. Obtaining this information will help researchers gain a better understanding of what initiates the degeneration of the Purkinje cells and allow for final confirmation of the causative mutation for CA**.**

As such, continued support is needed for this project.

The Arabian Horse Foundation is looking forward to continued partnership with Dr. Penedo and the UC Davis VGL in further investigation of this disease and finding the answers to the questions Arabian horse owners still have about Cerebellar Abiotrophy. With a mutation based DNA test for CA now available, the Arabian horse community can have complete confidence in a genetic test that can provide accurate information and guide in making wise breeding choices. With the use of testing, the production of affected foals can be completely prevented. The Arabian horse community is fortunate to have this valuable tool available for use as part of their breeding herd management program.