

Cerebellar Abiotrophy and the Horse Genome Project



BACKGROUND

There are great expectations this year for the announcements of progress done on Horse Genome Mapping. Gene linkage and identification is essential for the development of testing for such Arabian horse lethals as Occipitoatlantoaxial Malformation (OAAM), Coat Color Dilute Lethal (CCDL) known as Lavender Foal Syndrome (LFS), Cerebellar Disease known as Cerebellar Abiotrophy (CA), and Severe Combined Immunodeficiency (SCID) which is the only lethal to date with a DNA test available.

The Horse Genome Mapping started in 1995 with less than 50 genetic markers on the equine map and only several genes were mapped to chromosomes. The Dorothy Russell Havemeyer Foundation convened the first Equine Gene Mapping Workshop in October 1995 in Lexington, Kentucky where scientists agreed to a collaborative effort to construct a 300-marker gene map. In 1996, the USDA-National Animal Genome Program, under the auspices of the NRSP8 program invited the new horse gene mapping community to join their program, underway since 1992. Over 200 scientists in 25 countries have been working since then on this equine map.

As of 2001, approximately 1,000 genes were mapped to chromosomes. With horses having almost twice the number of chromosomes (64) than humans (46), this horse project is an important scientific milestone. Already, families of genes are being developed to investigate equine muscle diseases, metabolic diseases, developmental bone diseases, cryptorchidism, allergic diseases and performance.

By the end of 2006, over 4,000 genes and markers were mapped using RH and linkage data, according to the announcement made 17 January 2007 at the Horse Genome Project Conference in San Diego, California. [Editor's Note: the Horse Genome Project has been completed and published as of April 2007]. Several aspects of the physiology and pathology of the horse are highly relevant to human biology and medicine. These include examples from immunology (SCID), virology (Equine Infectious Anemia retrovirus), zoonoses (viral encephalitides such as West Nile Virus and others), neurology (Cerebellar Abiotrophy and others), muscle disorders (glycogen storage diseases, periodic paralysis and others), musculoskeletal diseases, connective tissue/skin disorders (Junctional Epidermolysis Bullosa and others), reproduction, orthopedics, and respiratory biology. A full genome sequence would

support these and other equine research studies with direct application to human health. This research over the past decade has enjoyed support from the Morris Animal Foundation, Grayson-Jockey Club, AQHA Research Foundation, Dorothy Russell Havemeyer Foundation, the USDA-NRSP8, USDA-NRI and numerous additional but smaller foundations and organizations interested in different aspects of the horse genome work. [Editor's note: The new Arabian Horse Foundation was officially announced in November 2007. This new 501 (c) 3 will focus on several areas for funding, including equine research with a focus on diseases and illnesses that affect Arabian horses.] Further endorsements have come from horse industry leaders representing The Jockey Club, American Quarter Horse Association, Morris Animal Foundation, Gluck Equine Research Foundation, Les Haras Nationaux of France, The Horse Racing Levy Board and the German Equine Federation. This year, as announced by Dr. Tosso Leeb, a grant for 1.4 million EUR (1.83 million \$ US) for the development of the equine physical map (BAC fingerprinting and BAC end sequencing) was approved by the German Volkswagen Foundation.

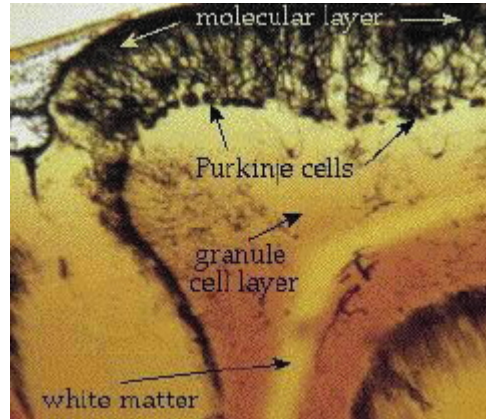
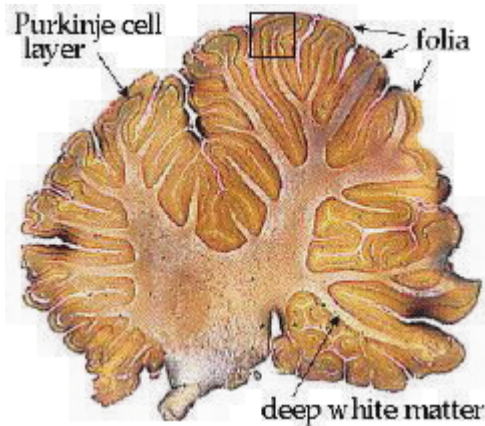
The horse is a monogastric animal that mimics human biology to a large extent. It has over 80 hereditary conditions in common with humans. At least a minimum of six inherited genetic disorders are being analyzed at present by researchers in the US (University of Kentucky, UC Davis, University of Minnesota), Japan, France and Switzerland with additional studies on the Purkinje cells being also done in Spain. With this research on the Horse Genome Mapping brought up to its present level, simultaneous studies on equine diseases will be greatly enhanced and future tests developed for diagnosis and carrier horses.

Specifically cited in the Horse Genome Project Proposal is further research into Cerebellar Abiotrophy.

PRESENT RESEARCH

The Swiss Geneticists and Clinical Researchers, Professor Dr. Vinzent Gerber, Head of Equine Internal Medicine and Professor. Dr. Tosso Leeb, from the Equine Clinic and the Institute of Genetics at the Vetsuisse-Faculty of the University of Berne are very interested in collecting blood samples from family members of any suspected Cerebellar Abiotrophy affected horse.

Cerebellar Abiotrophy is a neurological disease, most often noted in newborn Arabian foals of approximately 3 weeks to 4 months of age. It has also been found in Miniature Horses, Gotland Ponies and the Oldenburg Horse. The most notable external symptoms are a palsey-like head shaking (called intention tremors), the lack of a normal blink response although vision is correct, and an awkward exaggerated form of action with the forelimbs often similar to a military goose-step or high elevation used to cross over a very low object called hypermetric action. As these affected foals will often run into things or fall down- sometimes causing head injuries, their condition can be misdiagnosed as injuries from a blow to the head or neck, making the true neurological condition go unnoticed. This neurological condition is caused by the degeneration of the Purkinje cells post-natum due to the inheritance of a defective allele in the genetic make up. The rate and amount of Purkinje cell degeneration affects the level of this disease condition, now described as slight, moderate or severe.

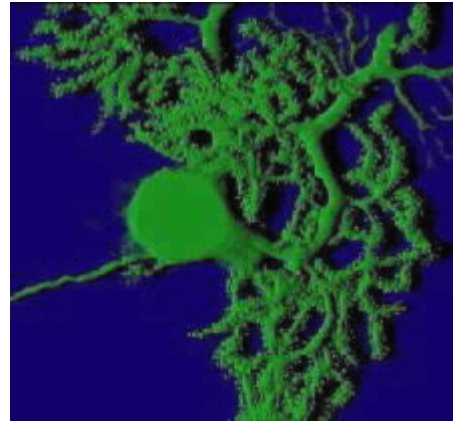
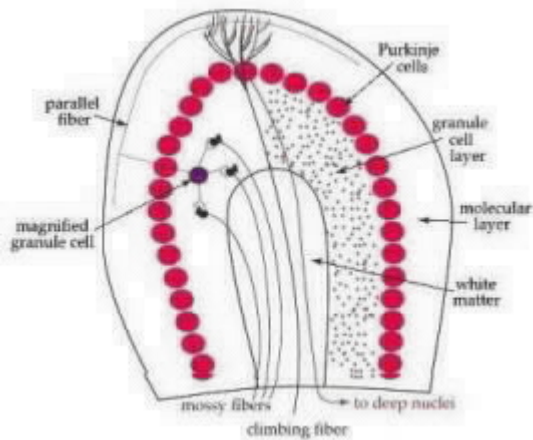


Cerebellar Abiotrophy (CA) is being recognized in all bloodlines of the Arabian horse. Indicated to be an autosomal recessive defective allele, it can be passed forward through several generations without re-appearing. This means that a horse can "carry" the disease gene, but not be affected by it. However, breeding done between two carrier horses results in a 25% probability of an affected foal being produced. If an affected horse is unrecognized for CA or otherwise used for breeding, all of its progeny will be homozygous for CA and will be 100% carriers. CA is categorized as a Lethal Genetic Disorder, although CA itself does not kill the horse. It does, however, make the horse generally unfit for riding or driving and should not be bred onwards. Most affected horses, if recognized, are euthanized before they cause severe damage to themselves or to their handlers because of their inability to control their own balance. At present, the only confirmed diagnosis which can be made is from a necropsy of the brain stem cells, called Purkinje cells, to ascertain the state of their degeneration. Once viewed, the external symptoms of Cerebellar Abiotrophy in a live foal or horse are not forgotten and are easily recognizable.

WHAT IS REQUIRED?

The Purkinje cells regulate the mobility of the horse and specifically, the fine tuned action and its movements, including balance. They send and receive electrical impulses called ions which in turn activate all fine tuned movement. To date, two specific alleles have been identified and investigated showing the locus to be recognized but proved to be incongruous themselves. Other alleles within the same location are being researched at present. With the RNA and brain samples of only four horse families and their related members on file, progress has been slow. RNA differs from the DNA (used to identify parentage for example) in that RNA uses uracil (U) as the pyrimidine for one of its four bases instead of thymine used in DNA. Also it is based on Ribose-containing nucleotides instead of Deoxyribose-containing nucleotides as found in DNA.

See diagram below and a magnified Purkinje cell on the



right:

More RNA samples are needed to identify the specific allele or combination of alleles and develop a test for “carrier” horses. All information is kept private to protect any of the horses and their owner/breeders respective breeding programs. Cases of actual affected CA have been the requirement in the past, but now they want samples from any related family members as well. It is in this realm where we could really be of help in pushing research on CA forward. If you have had a CA foal in the past, which has already been euthanized, but still have what appears to be perfectly normal siblings or otherwise related family members, these too are important for this research.

Professors Drs. Vincent Gerber and Tosso Leeb require blood samples from a minimum of 10 affected foals and at least 20 related family members. Please make direct contact with them with the contact information provided on the attached forms for sending blood samples or for further information on materials.

WHAT CAN YOU DO TO HELP?

Due to the ever diminishing genetic pool in Arabian bloodlines, the occurrence of CA appears to be on the rise. Owners interested in assisting with this research for the “over all benefit” of the Arabian Breed are an invaluable resource and all communications are welcomed. Cooperation of owners and breeders is key to helping solve this problem.

If you suspect that you have an affected foal or can supply information and samples from a related family member (sire, dam, full or half siblings) please contact Professor Dr. Tosso Leeb and/or Professor Dr. Vincent Gerber from the Equine Clinic and the Institute of Genetics at the Vetsuisse-Faculty of the University of Berne, Switzerland. (tosso.leeb@itz.unibe.ch, or vinzenz.gerber@knp.unibe.ch)

It is our hope and goal for 2008 that with this concentrated effort of your welcomed participation that the markers for CA will be identified and a test will be developed.

Please help us obtain these goals.

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QUESTIONNAIRE

Date:
Owner's Name
Horses (registered) Name:
Registration Association and number:
Horse Breed: _____ Year of Birth or Age: _____ Coat Color: _____ Horse
Gender (circle one): Male | Gelding | Female | Year of Gelding?? _____

Please either copy and paste into an email to: PD Dr. Vizenz Gerber vinzenz.gerber@knp.unibe.ch or print out and post to him at: Equine Clinic, Dept. of Veterinary Clinical Studies, Vetsuisse-Fakulty, University of Berne, Länggass-strasse 124, 3012 Berne, Switzerland.

Pedigree:

Sire:	Sire of sire:	

	Dam of sire	
Dam:	Sire of dam:	
	Dam of dam:	

Pregnancies/foals by the dam (please list known off-spring):

How long have you been the owner of the foal or how long have you known it, respectively.

Vaccination / Deworming / feeding (dam and foal)

Clinical signs (please mark as: - not observed, + mild, ++ marked, +++: severe)

- 1) Is the foal hypermetric? (exaggerated movements of the front limbs):
- 2) Is the foal ataxic? (Wobbler-like; uncoordinated movements, lack of balance, or even unable to rise)
- 3) Does the foal show tremors? (fine shaking, especially of the head)
- 4) Does the foal show a wide-based stance?
- 5) Does the foal startle easily?
- 6) Has the foal fallen or otherwise hurt itself?
- 7) Can you further describe and characterize these clinical signs?
- 8) Which were the first abnormal signs observed, and how old was the foal at this time?
- 9) Can you describe the progression (did it get worse and for how long; did signs at some point stabilize or improve?)

PERMITS:

Blood Samples: send 5 mL of blood per horse. packaged properly, by FED EX to: **Dr. Jolanta Klukowska-Rötzler, Institute of Genetics, University of Berne, Bremgartenstrasse 109a, 3012 Berne, Switzerland.** Permit required only from Non-EU countries. Priority Mail sufficient within EU. Label "Blood Product" on outside of package and be sure to attach the Swiss Import Permit to the outside of package.

Hair Samples: send 30-40 hairs with follicles intact per horse, by mail for a delivery within a 5 day limit in a clean plastic bag per individual, no permit to: **Dr. J. Klukowska-Rötzler, Institute of Genetics, University of Berne, Bremgartenstrasse 109a, P.O. Box 8466, 3001 Berne, Switzerland.**

Brain Samples: send 2 types of cerebellum samples (cut in a sagittal section through the cerebellar vermis): (i) formalin-fixed for pathological investigations and (ii) submerged in "RNAlater" for RNA analyses. Label "blood product". Permit required only from Non-EU countries. Send by FED EX to: **Dr Jolanta Klukowska-Rötzler, Institute of Genetics, University of Berne, Bremgartenstrasse 109a, 3012 Berne, Switzerland.**

Additional Contact Information:

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Questionnaire provided by Dr. Vincent Gerber and collection samples instructions by the molecular scientist Dr. Tosso Leeb. Background information compiled and written by Elizabeth Goodwin-Campiglio, pedigree researcher and Arabian horse breeder.