Review of Genetic Diseases of Horses
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Introduction and Definitions

Congenital Defects
Congenital defects include all undesirable traits and pathologic conditions present at birth whether they are genetic or due to intra-uterine events that results from extra-uterine influences. Congenital defects do not necessarily indicate inheritance; they simply indicate that the defect was present at birth.

Inherited Tendencies
There are characteristics in horses that are influenced by a wide variety of genes, whose pattern of inheritance is complex and whose expression has strong environmental influences. Horses have been selectively bred for centuries to promote or discourage these characteristics. The selection for or against these inherited tendencies is the basis for our current breed registries. Size, power, color, speed, conformation and many other characteristics that are genetically influenced are selected for or against by certain breed registries. Variations from ideal may be undesirable but they are not deemed to be genetic defects.

Genetic Defects
Genetic defects are pathologic conditions of proven genetic origin. These may be the result of a mutation in a gene of major effect or mutations in multiple genes (polygenic) whose effects combine to produce a deleterious or undesirable result. The degree to which some traits are expressed in horses carrying particular mutations can be influenced by environmental factors. This is called incomplete penetrance.

Undesirable traits
An undesirable trait, as designated by certain breed registries, is a condition or behavior that may or may not be present at birth, may develop over time, may or may not be a genetic defect, but precludes registration of that animal. A variation in color is an example of a characteristic that may be considered by a breed to be undesirable. Concealment of such undesirable traits by any means, including surgery, is prohibited by breed registry. It is therefore unethical for a veterinarian to perform such treatments, except when the treatment is intended to improve the health of the horse, and when the veterinarian reports the treatment to the breed registry.

Genetic Tests Available for Horses
Tests for mutations in single genes are currently (January 2014) available for 10 diseases.

Autosomal Dominant
1. Hyperkalemic Periodic Paralysis (HYPP) in the Quarter Horse
2. Type 1 Polysaccharide Storage Myopathy (PSSM) in numerous breeds
3. Malignant Hyperthermia in Quarter Horse related breeds
Autosomal Recessive

4. Overo Lethal White Syndrome in the Paint Horse
5. Combined immunodeficiency in Arabian Horses
6. Glycogen Branching Enzyme Deficiency (GBED) in Quarter Horse related breeds
7. Junctional Epidermolysis Bullosa (JEB) in Belgians
8. JEB in Saddlebred horses
9. Hereditary Equine Regional Dermal Asthenia (HERDA) in Quarter Horse-related breeds
10. Cerebellar Abiotrophy in Arabians (CA)

There are numerous other conditions strongly suspected to be due to mutations in genes of major effect, but genetic tests for these conditions are not yet available. New information in equine genetics is being generated very quickly, and any document of this type will require frequent updates, at least for the next few years.

AAEP Position Statement on Genetic Defects

Surgical Correction of undesirable traits and genetic defects

According to the American Veterinary Medical Association, Surgical correction of “genetic defects” for the purposes of concealing the defect is unethical. If surgical correction is undertaken for the purpose of improving the health of the individual, then it should be accompanied by sterilization to prevent the perpetuation of the genetic defect. The AAEP agrees with the intent of this position. Further, surgical correction of any characteristic specifically named by the breed organization as being prohibited, with the purpose of concealing the characteristic for obtaining registration, would be considered fraudulent and unethical. Such procedures offer no benefit to the horse and are intended only to deceive the breed organization. The AAEP does support surgical correction of conditions that are in the best interest of individual horses.

Identification of genetic traits

AAEP supports the use of genetic testing by veterinarians or breed associations to identify genetic mutations in animals so that owners can make informed decisions about breeding, purchase and specific treatments. Breed associations should be contacted to determine if there are any restrictions on registration of horses with genetic defects. Licensed laboratories should be used for genetic testing.

More information on equine genetic diseases is available at these websites:

http://www.vgl.ucdavis.edu/services/horse.php
http://www.cvm.umn.edu/umec/lab/home.html
http://www.ca.uky.edu/gluck/ServEPVL.asp
GENETIC TESTS AVAILABLE FOR HORSES AS OF JANUARY 2014

SEVERE COMBINED IMMUNODEFICIENCY

Breeds affected: Arabian
Bloodlines: unknown
Prevalence: 8% carriers
Age affected: 3-4 months of age when colostral immunity wanes
Clinical signs: lymphopenia (low numbers of lymphocytes in the blood), absence of the circulating immunoglobulin IgM and hypoplastic lymphoid tissue (few lymphocytes in the lymph nodes)
Mode of inheritance: Autosomal recessive.
Mutation: defect in the catalytic subunit of the DNA dependent protein kinase. A truncated unstable protein results that impairs the molecular mechanism necessary to create an almost limitless number of unique immune receptors. As a consequence SCID foals lack the ability to generated B lymphocyte and T lymphocytes.
Testing: The Arabian Horse Registry recommends that all breeding stock be tested and interbreeding of carriers avoided. Vetgen Ann Arbor Michigan tests for this mutation (www.vetgen.com)

JUNCTIONAL EPIDERMOLYSIS BULLOSA (JEB)

Breeds affected: Belgian Draft horses, Breton, Comtois, Vlaams Paard, and Belgische Koudbloed Flander draft horse breeds. A separate mutation occurs in American Saddlebreds.
Bloodlines: unknown
Prevalence: 17% of Belgian horses in North America are carriers and in European breeds 8-27% of horses are carriers. About 3% of Saddlebred are heterozygous.
Age affected: Homozygotes show signs shortly after birth
Clinical signs: Foals are typically born alive, but irregular, reddened, erosions and ulcerations develop in the skin and mouth over pressure points or after mild trauma with common secondary infections.
Mode of inheritance: Autosomal recessive.
Mutation: Drafts have a cytosine insertion (1368insC) creating a premature stop codon in the LAMC2 gene on chromosome 5, which encodes for the laminin γ2 chain. Saddlebreds have a 6589-bp deletion spanning exons 24-27 in the LAMA3 gene. These defects in LAM subunits result in an absence of laminin 5 which anchors the basement membrane zone of the dermal-epidermal junction.
Testing: University of California at Davis tests for this mutation (www.vgl.ucdavis.edu)

OVERO LETHAL WHITE FOAL SYNDROME (OWLS)

Breeds affected: American Paint horses
Bloodlines: Paint Horses with Overo ancestry
Prevalence: >94% of frame overos are heterozygotes, and present in highly white calico overo and frame blend overos as well as broodstock with no white spots
Age affected: Homozygotes show signs shortly after birth
Clinical signs: All white colored foals develop colic within 12 hours of birth, pass no fecal material and show pain that is not responsive to analgesics. There is a complete
absence of intrinsic myenteric plexus in the terminal small intestine, cecum and entire colon, with the ileum most severely affected.

**Mode of inheritance:** Autosomal recessive.

**Mutation:** Point mutation that results in a isoleucine/lysine substitution at codon 118 of the endothelin receptor B (EDNRB) gene located on chromosome 17. Endothelin B receptor is essential for normal development of the enteric ganglia and melanocytes within the neural crest.

**Testing:** University of California at Davis tests for this mutation (www.vgl.ucdavis.edu)

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**HYPERKALEMIC PERIODIC PARALYSIS (HYPP)**

**Breeds affected:** Quarter horse-related bloodlines

**Bloodlines:** Horses descendant from Impressive.

**Prevalence:** 4% of the Quarter Horse breed is affected.

**Age affected:** Signs usually begin by 2 to 3 years of age.

**Clinical signs:** Range from asymptomatic to intermittent muscle tremors and weakness. Horses homozygous for HYPP may present with difficulty swallowing or respiratory distress.

**Mode of inheritance:** Autosomal dominant.

**Mutation:** A point mutation that results in a phenylalanine/leucine substitution in a key part of the voltage-dependent skeletal muscle sodium channel alpha subunit that controls channel activity ($SCN4A$).

**Testing:** Veterinary Genetics Laboratory at the University of California, Davis on mane or tail hair roots.

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**GLYCOGEN BRANCHING ENZYME DEFICIENCY (GBED)**

**Breeds affected:** Quarter horse-related bloodlines

**Bloodlines:** Horses descendant from Zantanon and King

**Prevalence:** 8% of the Quarter Horse breed are carriers

**Age affected:** Signs usually present in utero or at birth

**Clinical signs:** Abortion or stillbirth, may be born alive and are weak at birth. With supportive care may live to up to 18 weeks of age. Death may be sudden when exercised on pasture, associated with weak respiratory muscles or the result of euthanasia due to persistent recumbency. Treatable flexural deformities of all limbs and recurrent hypoglycemia (low blood sugar) and seizures occur in some affected foals.

**Mode of inheritance:** Autosomal recessive.

**Mutation:** A point mutation in exon 1 changes a tyrosine to a premature stop codon in the glycogen branching enzyme gene ($GBEI$) that is expressed in numerous tissues.

**Testing:** Histopathological tissue samples (muscle and heart) stained for Periodic acid Schiff’s (PAS) show a variable amount of abnormal PAS positive globular and crystalline intracellular inclusions. Genetic testing is done by Veterinary Genetics Laboratory at the University of California, Davis or Vetgen in Michigan on mane or tail hair roots.
POLYSACCHARIDE STORAGE MYOPATHY (PSSM)

Two forms appear to exist. We have found the mutation for the most common form type 1 PSSM.

**For the GYS1 form of PSSM**

**Breeds affected:** Quarter horse-related bloodlines, Belgians, Percherons, Morgans, Mustangs and some Warmblood breeds

**Bloodlines:** Present in founders of QHs and therefore widespread in all QHs.

**Prevalence:** 36-50% of Belgians and Percherons, 8% of the Quarter Horse related breeds

**Age affected:** Signs usually begin by 2 to 3 years of age but may occur in Weanlings. Some horses are subclinical

**Clinical signs:** Firm painful muscles, stiffness, skin twitching, sweating, weakness and reluctance to move with light exercise. Sometimes gait abnormalities, mild colic, and muscle wasting. Serum CK and AST activity elevated except in Drafts

**Mode of inheritance:** Autosomal dominant.

**Mutation:** Point mutation that results in an arginine to histidine substitution in the GYS1 gene that codes for the skeletal muscle form of the glycogen synthase enzyme.

**Testing:** Muscle biopsy samples evaluated for presence of amylase-resistant crystalline polysaccharide

Genetic testing on mane or tail hair roots, or unclotted blood samples at the Neuromuscular Laboratory at the University of Minnesota.

**Second form of PSSM**

**Breeds affected:** Quarter Horse-related breeds, a few Arabians and possibly other light breeds

**Age affected:** Signs usually begin by 2 to 3 years of age but may occur in Weanlings. Some horses are subclinical

**Clinical signs:** Rhabdomyolysis with or without exercise.

**Mode of inheritance:** unknown.

**Mutation:** Unknown. Work in progress.

**Testing:** Muscle biopsy samples evaluated for presence of abnormal polysaccharide at the Neuromuscular Laboratory at the University of Minnesota.

MALIGNANT HYPERThERMIA (MH)

**Breeds affected:** Quarter horse-related bloodlines

**Bloodlines:** Present at a very high frequency in one QH bloodline (also in others), Often co-exists with PSSM

**Prevalence:** <1% of the Quarter Horse breed is affected

**Age affected:** Adults

**Clinical signs:** High temperature, metabolic failure and death under anesthesia. Exertional rhabdomyolysis especially if present with GYS1 PSSM mutation.

**Mode of inheritance:** Autosomal dominant.

**Mutation:** Point mutation that results in an arginine to glycine substitution in the RYR1 gene.

**Testing:** Genetic testing at UC Davis (mraleman@ucdavis.edu) or Neuromuscular Diagnostic Laboratory at the University of Minnesota.
HEREDITARY EQUINE REGIONAL DERMAL ASTHENIA (HERDA OR HC)

Breeds affected: Quarter horses
Bloodlines: Working cow and cutting horses
Prevalence: 3.5% of the Quarter Horse breed are carriers
Age affected: Signs usually begin by 1.5 years of age
Clinical signs: Wounds or sloughing skin, loose easily tented skin that does not return to its original position, scars, and white hairs at areas of hair re-growth found along the back and saddle area or areas with trauma. Healing is slow.
Mode of inheritance: Autosomal recessive.
Mutation: Point mutation that results in a glycine to arginine substitution in the equine cyclophilin B gene (PPIB) that plays a role in the processing of collagen for the anchoring of the skin to underlying tissue.
Testing: University of California at Davis tests for this mutation (www.vgl.ucdavis.edu)

CEREBELLAR ABIOTROPHY (CA)

Breeds affected: Arabians, lower frequency in other breeds that have used Arabians as foundation stock
Blood lines: Egyptian
Prevalence: Estimated 14% of the Arabians are carriers (needs further study)
Age affected: Signs usually begin by 1.5 months of age
Clinical signs: Head tremor (intention tremor) and a lack of balance equilibrium (ataxia), among other neurological deficits. Affected horses may show exaggerated action of the forelegs, a wide-based stance, and be unable to rise from a reclining position. They tend to startle easily and often fall due to ataxia.
Mode of inheritance: Autosomal recessive
Mutation: SNP found on ECA2 which down regulates MUTYH expression causing cerebellar cortical degeneration of Purkinje cells (neurons in the cerebellum)
Testing: University of California at Davis tests for this mutation (www.vgl.ucdavis.edu)

AQHA 5 Panel Test for Genetic Diseases

To help breeders make informed decisions and reduce genetic diseases, AQHA now offers a panel test for five genetic diseases: glycogen branching enzyme deficiency (GBED), hereditary equine regional dermal asthenia (HERDA), hyperkalemic periodic paralysis (HYPP), malignant hyperthermia (MH) and polysaccharide storage myopathy (PSSM1).

When the test is ordered, AQHA will send a DNA kit to the owner, who then mails it with mane and/or tail hair to the Veterinary Genetics Laboratory at the University of California-Davis for testing. Once the tests are complete, AQHA will notify the owners and put the results on the horse’s record.

The tests cost $85 for AQHA members and $125 for nonmembers. For the panel test in conjunction with the DNA test required for most breeding stock, the cost is $105 for members and $145 for nonmembers.

Genetic Implications of Cloning Horses

The subject of equine clones is fraught with controversy and has polarized members of breed organizations – for or against. Questions, scientific, ethical, and moral are numerous. Will it ultimately help or harm the equine breeds? Will it increase the incidence of genetic disease by
even more overuse of popular bloodlines, or potentially decrease disease if disease-free geldings that can then be used as breeding stallions? Should clones be registered? Are the cloned foals healthy? Is cloning morally wrong?

Some owners have used the cloning process, which was first performed on horses in 2003, to preserve their animals’ bloodlines, particularly those of high-performance equines. In response to cloning as a way to preserve bloodlines, some breed associations ruled on whether or not cloned horses can be included in their breed registries. In 2004 the AQHA board of directors approved Rule 227(a), which prohibits cloned horses or their offspring from being included in the organization's breed registry. Currently the AQHA is appealing a lawsuit challenging the membership’s decision not to register clones, claiming that the association's policy prohibiting the registry of equine clones violates U.S. antitrust laws. Federal antitrust laws prohibit monopolies or anti-competitive activities on the part of corporations and other entities. There are dozens of clones awaiting registration by the AQHA and their owners will be watching closely for the outcome of this suit.

Cloned horses and their progeny will not be barred from competition at FEI events, the world governing body for horse sports. The first foals of two cloned show-jumping geldings, “ET” and “Gem Twist,” were born last year. Multiple copies of a tremendously popular sire “Smart Little Lena” could now be accessible to breeders - theoretically indefinitely.

What is a Clone?
Simply speaking, a clone is an exact copy (like an identical twin) of an original animal. Just like identical twins, the clones do not look exactly alike and will have different face and leg markings from the original. The most famous mammalian clone was “Dolly” the sheep, born in 1996. From that date to the present day, there has been an ongoing debate regarding the legality of cloning and whether scientists should be allowed to clone humans.

The first equine clone was produced in 2003 in Italy and two years later Texas A&M University produced the first North American horse clone. A commercial equine cloning company ViaGen Inc offers gene banking and cloning services for a fee of $150,000.

All horse clones have been produced from adult donors using a method called somatic cell nuclear transfer, or SCNT. In SCNT, a veterinarian takes a sample of subcutaneous tissue from a skin sample, cultures the cells (fibroblasts), and then transfer nuclear DNA material from the donor into an oocyte (egg) that has had its nuclear DNA removed. The embryo is then cultured for a few days, cell division begins and then the embryo is transferred into a recipient mare. The viability of embryos varies but approximately one live foal is produced from every four embryos (this will vary considerably and will likely improve with time). Blake Russell, vice president of business development of ViaGen Inc, reports a remarkable 50% pregnancy rate for each transferred embryo.

The foals are healthy; however problems have been reported in the first week of life, resembling placental insufficiency according to Katrin Hinrichs, DVM, PhD of the Texas A&M group. The egg donor can come from any mare and has only a tiny strand of mitochondrial DNA that will be passed on by female clones only. Offspring of a male clone will not carry the donor mare’s mitochondrial DNA. What this means is that the offspring of the cloned colt will have the identical DNA as the original.

Little information is available at this time about the performance of the clones as they are so valuable that many are used for breeding only. The clone’s environment will, of course, also
determine the performance and personality of the clone, as well as how it is raised and trained. There are clones currently competing in reining events and their success could be traced through the NCHA.

**Why Clone Horses?**

If disease – free, exceptional individuals from underutilized pedigrees were cloned (geldings or mares), then clones could offer potential benefits by continuing these genetics. Several cattle registries are currently registering clones and advertise the animals as disease free for specific genetic diseases where tests are available.

Cloning could also potentially be used to produce embryonic stem cells to be used to repair tendon, ligament, cartilage and bone damage in horses. Embryonic cells could be taken from an embryo cloned from the adult. Since stem cells are currently harvested from other means (such as fat or bone marrow), there appears to be no benefit at present to using embryonic stem cells for therapy.

**Why Not Clone Horses?**

The reason most horse owners use for not cloning horses are ethical, frequently stating “it just doesn’t seem right to experiment with Mother Nature” or feel it is commercial exploitation of animals. The general public is fearful of potential adverse health effects from cloning, both short-term for the clone itself, and long-term for the health of future generations. Opponents believe that conventional breeding practices introduce new genetic material to continually improve the breed and health of the horse.

The biggest reason against cloning is due to the real risk of increasing the incidence of inherited diseases due to the “Popular sire effect”. Cloning, especially making several copies of one animal, amplifies one individual’s impact on the gene pool. Along with line breeding, artificial insemination, embryo transfer and other assisted reproductive techniques, cloning has the potential to increase the prevalence of disease causing mutations in the breed. Linebreeding and specialization for certain disciplines has increased the occurrence of genetic diseases, as has “genetic bottlenecking”. Examples include HERDA and HYPP in Quarter Horses, Severe Combined Immunodeficiency and Cerebellar Abiotrophy (SCID) in Arabians, and Junctional Epidermolysis bullosa (JEB) in Belgians.

Various equine diseases that have available genetic tests will be reviewed in the presentation. The use of clones in breeding programs should be considered very carefully, and breed associations should encourage genetic testing, education and research.