Proceedings of the 11th International Congress of the World Equine Veterinary Association

24 – 27 September 2009
Guarujá, SP, Brazil

Next Meeting:
Nov. 2 -6, 2011 - Hyderabad, India

Reprinted in IVIS with the Permission of the Meeting Organizers
Equine Disease caused by known Genetic Mutations

Stephanie Valberg DVM PhD¹, Molly E McCue DVM, MS, PhD¹ and James R Mickelson PhD²

¹Department of Veterinary Population Medicine, ² Department of Veterinary Biosciences, College of Veterinary Medicine, University of Minnesota, 1365 Gortner Ave, St Paul USA 55108

The huge popularity of the Quarter horse breed at over 4 million registered horses and the depth of the American Quarter Horse Association (AQHA) support for research have led to the development of several DNA-based tests for genetic diseases affecting Quarter Horses. These include Hyperkalemic Periodic Paralysis (HYPP); glycogen branching enzyme deficiency (GBED); malignant hyperthermia (MH); equine hereditary dermal asthenia (HERDA); and polysaccharide storage myopathy (PSSM). These discoveries were greatly assisted by the recent development of equine genome maps and the complete sequencing of the horse genome performed at the Broad Institute under the auspices of the National Human Genome Research Institute (http://www.broad.mit.edu/mammals/horse/). Genetic mutations causing diseases in other breeds include Severe combined Immunodeficiency (SCID) in Arabians, Overo Lethal White Syndrome (OWLS) in American Paint horses and Junctional Epidermolysis Bullosa (JEB) in Belgian Draft Horses and a separate mutation in American Saddlebreds.

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.

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 (GBE1) 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. We are working on this.
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 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)

Overo Lethal White Foal Syndrome (OWLS)

**Breeds affected:** American Paint horses  
**Bloodlines:** Paint Horses with Overo ancestry  
**Prevalence:** >94% of OLWS 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 an 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)

**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 saddlebreds 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 α2 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)

**Conclusions**

Horses can now be screened for 8 genetic disorders that affect skeletal muscle. These genetic tests will be useful for owners wanting to make informed choices for breeding programs and for prepurchase examination as well as for veterinarians examining horses with potential muscle, skin or neonatal diseases. The development of equine genetic tools will result in a rapid expansion in the number of genetic tests available in the near future.

**Conflict of interest statement:** Dr McCue, Mickelson and Valberg hold the patent for the PSSM testing and receive patent royalties. A portion of the profits from ReLeve go to Dr. Valberg and support of research.

**References**

horses: a sodium channel mutation disseminated by selective breeding, *Nat.Genet.* 2: 144-147


