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A Review of Genetic Muscle Disorders in Foals of Quarter Horse-related Breeds

Stephanie Valberg, DVM, PhD; Molly E. McCue, DVM, MS, PhD; and James R. Mickelson, PhD

Authors addresses: Department of Veterinary Population Medicine, Department of Veterinary Biosciences, College of Veterinary Medicine, University of Minnesota, 1365 Gortner Avenue St Paul, MN 55108; Email: valbe001@umn.edu.

Take Home Message

Four genetic mutations that cause muscle disease in foals of Quarter Horse-related breeds have been identified. Hyperkalemic periodic paralysis can cause muscle fasciculations, dysphagia and dyspnea. Glycogen branching enzyme deficiency causes abortion or neonatal death. Polysaccharide storage myopathy type 1 and malignant hyperthermia cause severe rhabdomyolysis. Practitioners can now diagnose these disorders by DNA analysis of whole blood or hair samples.

Introduction

The American Quarter Horse Association (AQHA) promotes the health and performance of the breed through long term support of equine research. The huge popularity of the breed at over 4 million registered Quarter Horses and the depth of the AQHA support for research have led to the identification of the molecular basis for several genetic diseases affecting the breed. 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/). The purpose of this paper is to review genetic diseases that affect muscle structure and function in foals of Quarter Horse related breeds.

Hyperkalemic Periodic Paralysis (HYPP)

Hyperkalemic Periodic Paralysis (HYPP) is an autosomal dominant trait affecting Quarter Horses, American Paint Horses, Appaloosas, and Quarter Horse crossbred animals worldwide. A missense mutation in the alpha subunit of the voltage-dependent skeletal muscle sodium channel (SCN4A) located on equine chromosome 11 results in an amino acid substitution. All horses affected with HYPP have been descendants of the stallion Impressive (born 1968- died 1995). Current estimates indicate that 4% of the Quarter Horse breed is affected with higher prevalence in halter and pleasure horses.
Clinical signs: Foals heterozygous for the dominant mutation generally do not exhibit signs until over 2 years of age. In adults clinical signs include facial muscle hypertonicity, prolapse of the third eyelid, sweating and muscle fasciculations. During mild attacks, horses remain standing. In more severe attacks, clinical signs may progress to swaying, staggering, dog-sitting, or recumbency within a few minutes.

Foals that are homozygous for the HYPP mutation often show clinical signs by a few weeks of age and they are usually more severely affected than heterozygotes. Signs include fasciculations, difficulty nursing due to facial hypertonicity and dysphagia, respiratory stridor and periodic obstruction of the upper respiratory tract. Endoscopic findings include pharyngeal collapse and edema, laryngopalatal dislocation and laryngeal paralysis. Homozygous affected horses also often exhibit consistent dysphonia (high pitched whinny).

Pathogenesis: The substitution of phenylalanine for leucine in the sodium channel results in a failure of a subpopulation of sodium channels to inactivate during depolarization when serum potassium concentrations are increased. This results in persistent depolarization of muscle cells followed by temporary weakness. Whereas a proportion of sodium channels in skeletal muscle of heterozygotes function normally, all sodium channels in foals homozygous for HYPP will have the defective amino acid substitution. This likely explains the increased severity of disease in homozygous affected foals.

Diagnosis: The definitive test for identifying HYPP is the demonstration of the base-pair sequence substitution in SCN4A. Submission of mane or tail hair with roots should be made to a licensed laboratory such as the Veterinary Genetics Laboratory at the University of California at Davis (www.vgl.ucdavis.edu). Foals born in 2007 or later that test homozygous affected for HYPP (H/H) are not eligible for registration by the AQHA.

Treatment: Membrane hyperexcitability can often be attenuated in acute episodes by administration of calcium gluconate (0.2-0.4 mL/kg of a 23% solution diluted in 1 L of 5% dextrose). Dyspnea due to laryngeal or pharyngeal obstruction may require a tracheostomy. Clinical signs in heterozygous HYPP horses can often be managed by feeding a balanced diet containing between 0.6 and 1.1% total potassium concentration and meals containing <33 g of potassium. Homozygous affected horses are more difficult to manage and may in addition require acetazolamide (2-3 mg/kg every 8-12 hours, orally) or hydrochlorothiazide (0.5-1 mg/kg every 12 hours, orally).

Glycogen Branching Enzyme Deficiency (GBED)

GBED is an autosomal recessive glycogen storage disorder in Quarter Horse related breeds. A nonsense mutation in the GBE1, located on equine chromosome 26, introduces a premature stop codon of the GBE1 gene. GBED has likely been in the Quarter Horse breed at least since its inception in 1940 and it is not possible to determine if any given horse has GBED based on pedigree analysis. Approximately 8% of both Quarter and Paint Horses are carriers of GBED and thus can produce affected foals when bred to another carrier.
Clinical Signs: Fetal abortion is a common presentation of GBED. \(^{14,15}\) GBED was detected in 2 - 4% of 2\(^{nd}\) and 3\(^{rd}\) trimester abortions submitted to two diagnostic laboratories. \(^{14}\) Foals that survive to parturition are often hypothermic and weak but gain strength when given milk and assisted to stand and nurse. Correctable flexural deformities of all 4 limbs are common. Progression of signs can be highly variable. Some foals have early onset of ventilatory failure while other foals show muscle weakness or intermittent collapse due to hypoglycemia. Sudden death is reported in some foals whereas others are euthanized due to muscle weakness and inability to rise. \(^{14,16}\) Most GBED affected foals die or are euthanized by 8 weeks of age, however, one foal survived with nursing care to 18 weeks of age. Common hematological findings in foals with GBED include a low white blood cell count, often about 4,000 cells/ul, as well as moderate elevations in serum creatine kinase (CK), aspartate transaminase (AST) and gamma glutamyl transferase (GGT). \(^{13}\)

Pathogenesis: The developing fetus and foal are highly reliant on a continual supply of glucose from mare’s milk, liver glycogen, or storage depots in tissues. GBED affected foals lack of the enzyme necessary to create a compact, highly-branched, energy-dense, bioavailable glycogen molecule. Thus, in GBED foals the supply of glucose to the brain, heart and skeletal muscles is highly limited resulting in death in utero or signs of seizures, weakness or collapse in neonates.

Diagnosis: Muscle biopsy specimens from foals with GBED often, but do not always, contain basophilic globules and eosinophilic crystalline material in hematoxylin and eosin stains. \(^{13}\) To clearly identify affected feti or foals a Periodic acid Schiff’s stains (PAS) should be performed on heart and skeletal muscle. This stain shows decreased normal background staining for glycogen and PAS positive globular inclusions with, in some cases, additional smaller crystalline inclusions. Abnormal polysaccharide can be identified in neural tissue and is inconsistently found in the liver. \(^{15}\) The most accurate diagnosis of GBED can be obtained through genetic testing of the foal for homozygous status or the dam/sire for heterozygous status. Many stallion owners offer a free repeat breeding to owners that lose foals and if a diagnosis is not established the owner will have a 25% chance of having another GBED affected offspring on repeat breeding. The Veterinary Genetics Laboratory at the University of California, Davis (\textit{www.vgl.ucdavis.edu}) and Vet Gen in Michigan (\textit{www.vetgen.com}) are licensed by the University of Minnesota to test for GBED. Mane or tail hairs with roots intact or fetal liver tissue can be submitted. Diagnostic laboratories should be encouraged to screen aborted feti for GBED either through PAS staining of cardiac samples or via genetic testing. Testing also should be strongly advised for prepurchase evaluation of broodmares or stallions.

Treatment: There is no treatment for GBED. Early recognition and euthanasia can save owners of foals in neonatal intensive care units considerable expense.

Polysaccharide Storage Myopathy (PSSM)

Polysaccharide storage myopathy (PSSM) is a glycogen storage disorder that affects numerous breeds. \(^{17-19}\) A dominant mutation in the glycogen synthase gene (\textit{GYSI}) located on equine chromosome 10 was recently identified in Quarter Horses that were selected based on the presence of abnormal amylase-resistant polysaccharide inclusions in the skeletal muscle fibers. \(^{5}\)
The mutation was likely introduced at the inception of the breed and cannot be suspected in any given horse based on simple pedigree analysis. Because some Quarter Horses with elevated muscle glycogen content do not possess the GYS1 mutation, PSSM is being subdivided into type 1 and type 2. The form of PSSM that is due to the GYS1 mutation is termed type 1 PSSM. The smaller percentage of Quarter Horses with a glycogenosis that do not have the GYS1 mutation are classified as having type 2 PSSM. The acronyms EPSM and EPSSM have also been used for polysaccharide storage myopathy, but this should be re-evaluated. The prevalence of PSSM in Quarter Horses is 10% based on a diagnosis by muscle biopsy and the prevalence of the GYS1 mutation is approximately 8% in Quarter Horses and Paints.

Clinical signs: In adult Quarter Horses, the average age of onset of clinical signs of exertional rhabdomyolysis is 5 years and <20 minutes of exercise at a walk and trot is the most common triggering factor. Clinical signs range from stiffness, sweating, exercise intolerance, gait abnormalities and reluctance to move to colic-like pain, recumbency and inability to rise.

Clinical signs of PSSM have been documented in a small number of Quarter Horse foals. Reported clinical signs include stiffness, weakness, firm painful muscles, difficulty rising, dogsitting and recumbency. Serum CK activity is usually moderately to severely elevated in foals with clinical signs. Triggering factors for rhabdomyolysis in foals diagnosed with PSSM include exercise, high grain diets and diseases such as pneumonia or diarrhea. The number of foals affected by PSSM may have been underestimated. This is because accumulation of abnormal polysaccharide in muscle of PSSM affected horses can take up to 2 yrs to develop and clinical signs precede abnormal polysaccharide accumulation. Genetic testing for PSSM will greatly assist in determining how frequently type 1 PSSM contributes to rhabdomyolysis in foals.

Pathophysiology: The dominant GYS1 mutation appears to be a “gain of function mutation” that may cause unregulated basal activity of glycogen synthase. Glycogen synthase activity is also increased by insulin and by high intramuscular glucose 6 phosphate. In horses with the GYS1 mutation, clinical signs of muscle pain may be exacerbated by enhanced individual insulin sensitivity as well as by meals that produce elevated blood glucose and insulin levels. One possible explanation for rhabdomyolysis is that when the glycogen synthase enzyme is constantly active, the reciprocally controlled phosphorylase enzyme is constantly inactive impairing the cells ability to derive energy from glycogen. Rhabdomyolysis in PSSM horses has been associated with a cellular energy deficit. The characteristic amylase-resistant abnormal polysaccharide in type 1 PSSM is likely due to the addition of more straight chains of glucose molecules relative to branched chains in a muscle cell with unregulated elevated glycogen synthase activity. Over time this likely creates a glycogen molecule that is less highly branched than normal and resistant to amylase digestion.

Diagnosis: PSSM should be suspected in foals with appropriate clinical signs and persistent elevations of serum CK activity. A diagnosis of both type 1 and type 2 PSSM can be made by histologic evaluation of a muscle biopsy from horses older than 2 years of age. A definitive diagnosis of type 1 PSSM can be made by genetic testing for the GYS1 mutation. Genetic testing is performed at the Veterinary Diagnostic Laboratory at the University of Minnesota on hair roots or whole blood samples. If foals test positive for the GYS1 mutation, we recommend that the dam and sire also be screened for the
genetic mutation so owners can make informed decisions about further breeding. Genetic testing of Quarter Horse related breeds for the \textit{GYS1} mutation may be advisable for prepurchase examination. Owners should be aware that testing for \textit{GYS1} mutation will not exclude other possible causes of exertional rhabdomyolysis. A second form of PSSM (type 2) may have a genetic basis in Quarter Horses but this has yet to be identified. Muscle biopsy is necessary to identify type 2 PSSM.

\textit{Treatment:} For an acute episode, a few days of stall confinement may be indicated in foals showing pronounced stiffness or weakness. Nutritional support in the form of mare’s milk or foal pellets should be supplied. The mare should either be switched to a low starch high fat supplement that the foal can share or the mare’s grain should be kept inaccessible to the foal. The foal’s hydration status should be assessed and either oral or intravenous fluids administered if necessary as myoglobin is toxic to the kidneys and persistent dehydration, in addition to myoglobinuric, can result in development of acute renal failure. Sedatives and anti-inflammatories may be administered to the well-hydrated foal to relieve anxiety and pain. Wherever possible stall confinement should be limited to <48 h after the episode of rhabdomyolysis as prolonged stall confinement may result in an increased incidence of rhabdomyolysis episodes due to PSSM. Small paddock turn out with limited ability to move around is recommended once stiffness subsides.

In recumbent foals, in addition to IV fluids and nutritional support, a constant rate infusion of either detomidine, lidocaine, butorphanol or ketamine may be useful to control severe pain and struggling. Dantrolene sodium (4mg/kg, Q4-6 h, orally) may decrease muscle cell necrosis. Assistance to stand every few hours either manually or using a sling is necessary to improve muscle function and circulation. Cautious handwalking for no more than a few minutes at a time is recommended once the foal is stable and strong enough to ambulate.

\textit{Control:} Owners of foals positive for PSSM need to be aware that their foal/horse will always need to be managed for this condition as it cannot be cured. Furthermore, this horse will also have at least a 50% chance of producing an affected foal. With adherence to diet and exercise recommendations, at least 80% of horses show notable improvement in clinical signs; many return to acceptable levels of performance. Dietary management is directed at providing adequate, but not excessive, calories by decreasing the glucose load, providing adequate dietary protein for a growing foal and using fat as an alternate energy source.\textsuperscript{25} Decreasing the dietary starch to <10% of daily digestible energy and increasing dietary fat up to 13% of daily digestible energy is recommended.\textsuperscript{25} Growing foals have a higher protein requirement than adults especially with regard to lysine. Feeding alfalfa hay rather than grass hay combined with a commercial low starch high fat ration such as Re-Leve concentrate is recommended for weanlings to meet their nutritional needs.\textsuperscript{a} As much turn out as possible with other horses to encourage daily exercise is recommended for long term management of foals with PSSM. The objective is to increase aerobic capacity and augment the capacity of the muscle to oxidize fat and glycogen as energy substrates.

\textsuperscript{a} Re-Leve, Kentucky Equine Research, Lexington KY 40383
Type 1 PSSM due to the GYS1 mutation has also been identified in several non-Quarter Horse related breeds. Practitioners are encouraged to see our website for information about type 1 PSSM in these breeds. (http://www.cvm.umn.edu/umec/lab/home.html)

**Malignant Hyperthermia**

An autosomal dominant mutation in the skeletal muscle ryanodine receptor (RYR1) on equine chromosome 10 has been identified in 2 Quarter Horses that developed marked hyperthermia and metabolic acidosis during inhalation anesthesia. Many additional cases have been identified in our Neuromuscular Diagnostic Laboratory. The prevalence of the RYR1 mutation in the general Quarter Horse population is quite low; however, when present, particularly with PSSM, it may cause signs of muscle pain stiffness and cramping or anesthetic myopathy.

*Treatment:* The most successful outcome for a horse with suspected malignant hyperthermia would be pretreatment with oral dantrolene (4 mg/kg, orally) 30-60 minutes prior to anesthesia. There is no cost effective means to deliver dantrolene to horses intravenously once an episode has begun. Unfortunately once a fulminant episode is underway it is difficult to prevent cardiac arrest.

*Diagnosis:* The MH mutation may exacerbate signs of other myopathies and therefore we recommend testing in horses with difficult to manage forms of PSSM or in Quarter Horses and Paints with a family history of post-anesthetic complications. Testing is available through the Veterinary Diagnostic Laboratory at the University of Minnesota. http://www.vdl.umn.edu/vdl/ourservices/neuromuscular.html

**Conclusions**

Quarter Horses and related breeds can now be screened for 4 genetic disorders that affect skeletal muscle. These genetic tests will be useful for owners wanting to make informed choices for breeding programs and for pre-purchase examination as well as for veterinarians examining horses with potential muscle diseases. If genetic testing is normal in horses with a suspected muscle disorder, a muscle biopsy may be necessary to identify the cause of the myopathy.

**Conflict of Interest Statement;** Drs. McCue, Mickelson, and Valberg hold the patent for the PSSM testing and receive patent royalties. A portion of the profits for Re-Leve go to Dr. Valberg and continuing research.

**References**


