Genetics of Muscle Disease

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KEYWORDS

• Biopsy • DNA • Equine • Horse • Inherited • Myopathy

KEY POINTS

- Genetic testing should be included in any workup of recurring muscle disease.
- Validated genetic tests exist for the inherited muscle diseases hyperkalemic periodic paralysis, malignant hyperthermia, glycogen branching enzyme disease, type 1 polysaccharide storage myopathy, and myosin heavy chain myopathy.
- For diseases without validated genetic tests, diagnosis via clinical presentation, serum creatine kinase and aspartate aminotransferase activities, and muscle biopsy are warranted.

INTRODUCTION

In the field of equine muscle disorders, many conditions have a genetic basis. Thus, genetic testing is an important part of the diagnostic evaluation in these cases. Genetic testing is the only way to determine a specific genetic cause in horses with clinical signs of these conditions, which can lead to specific treatments and improved outcomes with some conditions. For others, genetic testing can guide breeding management practices and guard against creating foals with lethal conditions.

An important consideration with genetic testing is that it is testing for a specific mutation in a specific gene. Genetic heterogeneity can exist with some conditions and the DNA test is only testing for one of those conditions. For example, polysaccharide storage myopathy (PSSM) in horses is defined as the accumulation of abnormal glycogen in the skeletal muscle.[1] However, with the identification of the genetic mutation for Type 1 PSSM, it became evident that additional types of PSSM exist across horse breeds that may be due to another genetic cause.[2] This constitutes genetic heterogeneity, where different mutations can cause what appears to be the same disease.

Another important consideration is phenotypic heterogeneity. This is where the underlying DNA change, or genetic variation, is the same but affected animals present with different clinical signs. Other genetic, epigenetic, and environmental factors

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account for part of this heterogeneity. An example of phenotypic heterogeneity in the horse is myosin heavy chain myopathy (MYHM), where a horse can present with either nonexertional rhabdomyolysis or immune-mediated myositis.[2]

The genotype–phenotype relationship can be described by 3 terms: penetrance, expressivity, and pleiotropy (**Fig. 1**). Penetrance is the percentage of individuals carrying a particular mutation that exhibit certain detectable phenotypic traits (ie, clinical signs). For example, glycogen branching enzyme deficiency (GBED) is 100% penetrant, with all homozygous foals clinically affected by this lethal disease.[3] Expressivity is the degree of phenotype severity in an individual that exhibits detectable mutant phenotype. In horses, type 1 PSSM demonstrates variable expressivity, with some horses demonstrating severe signs of rhabdomyolysis and others may be subclinical.[2] Pleiotropy is defined by a gene that, when mutated, leads to multiple phenotypes, often in multiple tissues or organs.

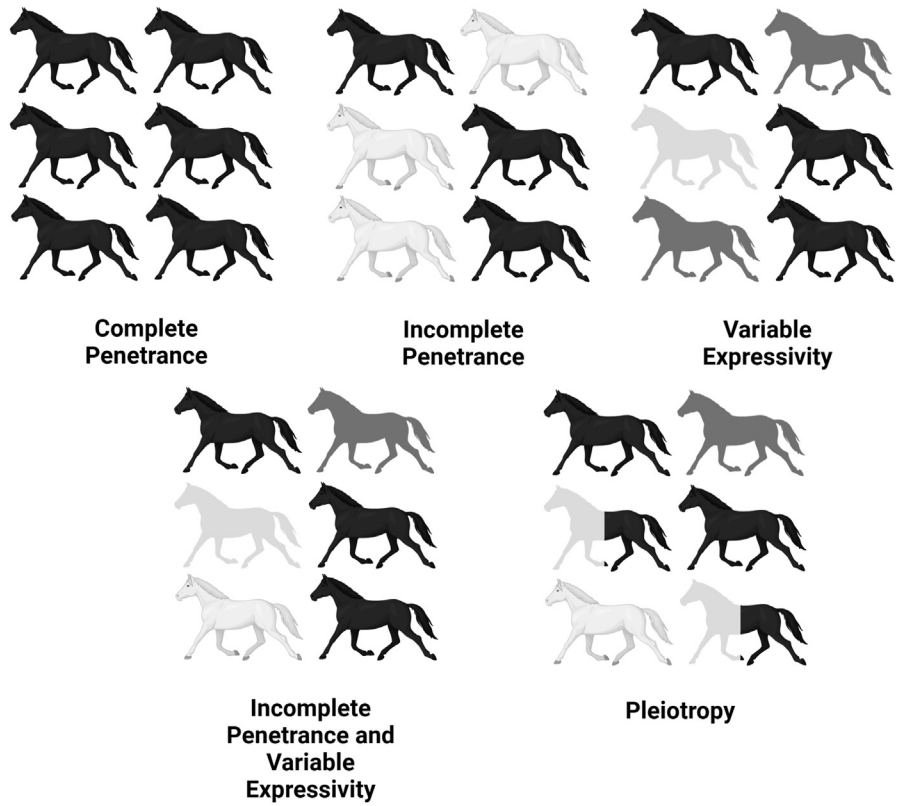

Fig. 1. Visual representation of the terms: (1) Complete penetrance, where all individuals with the DNA variant demonstrate the full phenotype; (2) incomplete penetrance, where a subset of individuals with the DNA variant demonstrate the full phenotype and a subset are subclinical (50% in this example); (3) variable expressivity, where all individuals with the DNA variant demonstrate a phenotype but the phenotype varies from mild to moderate to severe; (4) incomplete penetrance with variable expressivity, where a subset of individuals demonstrate a spectrum of the phenotype (mild to severe) and another subset are subclinical; and (5) pleiotropy, where the DNA variant has different effects in different tissues or organs.

Heritable muscle diseases in horses disrupt energy metabolism pathways, muscle contractility, and muscle structure. In the horse, many of the first genetic tests identified were for muscle disorders. From a breed registry perspective, the American Quarter Horse Association (AQHA) has mandated that all breeding stallions have a 5 panel genetic test on file prior to registration of foals resulting from breedings after January 1, 2015 (https://www.aqha.com/genetic-testing). This panel includes genetic tests for hyperkalemic period paralysis (HYPP), GBED, PSSM1, malignant hyperthermia (MH), and the nonskeletal muscle disease hereditary equine regional dermal asthenia. Since 2018, the American Paint Horse Association also required breeding stallions to have the 5 panel genetic disease test results on file, plus lethal white foal syndrome prior to the registration of their foals. In January of 2023, the AQHA added MYHM to the required testing panel for breeding stallions. However, any stallion that was registered before January 2023 is not required to add MYHM retroactively. This article focuses on the available genetic tests for inherited equine muscle disorders and discusses ongoing efforts for other myopathies.

EQUINE MUSCLE DISORDERS WITH DNA TESTS

Hyperkalemic Periodic Paralysis

Clinical signs

HYPP results in episodic weakness and paralysis. Episodes typically last between 15 and 60 minutes and horses may appear completely normal between episodes.[4,5] Muscle fasciculations and sweating in flanks, necks, and shoulders may be observed. During severe attacks, horses may dog sit or become recumbent.[4,5] Potassium concentrations are often elevated (5–9 mEq/L) during HYPP attacks but can return to normal shortly thereafter.[4] Serum creatine kinase (CK) activity may be normal or mildly increased during episodes.[4,5] Homozygous foals may demonstrate respiratory stridor, dysphagia, or respiratory distress.[6] Factors that can precipitate HYPP episodes include feeding diets high in potassium, anesthesia and stress, including transport.[4] When undergoing anesthesia, clinicians should inquire about the HYPP status of any Quarter Horse or related breed, especially if the horse displays the heavy muscling that is often observed with the HYPP phenotype.[7]

Genetic etiology

HYPP is inherited as an autosomal codominant trait.[8] HYPP was the first hereditary disease in horses for which the molecular defect was determined. The disease has only been reported in Quarter Horse and Quarter Horse-related breeds. The genetic etiology is a missense mutation (F1416 L) in the voltage-dependent skeletal muscle *sodium channel alpha-subunit* (*SCN4A*).[8] The mutation results in failure of a subpopulation of sodium channels to inactivate when serum potassium concentrations are increased. The excessive influx of sodium and efflux of potassium results in persistent depolarization of muscle cells followed by temporary weakness.[8] The designation for genotypes is heterozygous affected, N/H; homozygous affected, H/H; and normal unaffected, N/N.

HYPP affects Quarter Horses, American Paint Horses, and Quarter Horse-related breeds. The mutation was linked to the popular Quarter Horse sire, Impressive, whose offspring dominate the halter horse industry.[7] Since the disease is inherited as a codominant trait, homozygotes demonstrate more severe episodes.

Prevalence

Prevalence estimates demonstrate that approximately 1.5% of Quarter Horse breeds and 4.5% of the American Paint Horse breed are affected, when evaluated across all performance disciplines.[9] Within a discipline, however, HYPP affects 56% of the halter

horse population as of 2009.[9] The disease appears to be rare in cutting, reining, and racing Quarter Horses.[9] In a sampling of 296 horses that had muscle biopsies submitted to the University of California Davis (UC Davis), only one was identified to have HYPP and also had concurrent MYHM.[10] In Brazil, allele frequencies were evaluated in the bull-catching (vaquejada) Quarter Horse and found in 1 out of 126 horses tested (H/N; 0.8%).[11] The allele frequency of HYPP has not decreased over the years, despite available testing, due to the preferential selection of affected well-muscled horses by halter horse show judges.[7]

Treatment and Management of HYPP is covered in Dr Monica Aleman's article, "Disorders of Muscle Mass and Tone," in this issue.

Malignant Hyperthermia

Clinical signs

Rhabdomyolysis due to MH can follow exercise or anesthesia but can be very intermittent.[12–14] The unusual feature to distinguish MH as an underlying cause of exertional rhabdomyolysis is an increased body temperature during episodes.[13] Clinical signs during anesthesia include hyperthermia, lactic acidosis, and muscle rigidity.[14] Halothane anesthesia was first noted to induce episodes[14] but there is a risk with any type of anesthesia. Episodes are often fatal when triggered.[10]

Genetic etiology

MH is inherited as an autosomal dominant trait and only the heterozygous state has been described.[13] The disease has only been identified in Quarter Horse and Quarter Horse-related breeds. The genetic etiology is a missense mutation (R2455G, based on the most recent EquCab3.0 assembly) in the *ryanodine receptor type 1* gene (*RYR1*).[12] The mutation results in excessive release of calcium into the myoplasm and a hypermetabolic state. The designation for genotypes is heterozygous affected, M/N, and normal unaffected, N/N.

Prevalence

MH is rare, with the highest prevalence in halter and pleasure horse lines.[13] In the sampling of horses with muscle biopsies submitted to UC Davis, 6 horses were identified as M/N.[10] Of these, 2 had concurrent MYHM, 2 had concurrent PSSM1, and these 4 horses had presented for rhabdomyolysis and acute death. The one horse that only had MH on genetic testing was presented for anesthesia-associated myopathy. All 6 of these MH cases were fatal.[10] In Brazilian vaquejada Quarter Horses, there were no MH cases identified out of 126 horses.[11]

Treatment and management

To prevent an episode, pretreatment with dantrolene (4 mg/kg) 30 to 60 minutes prior to anesthesia is advised.[15] Repeated doses of dantrolene should be avoided since muscle weakness can occur with higher doses.[15] During an episode, hyperthermia and acidemia should be treated with alcohol, chilled intravenous fluids with sodium bicarbonate and mechanical ventilation. However, most cases are fatal once an episode is underway.[10]

Glycogen Branching Enzyme Deficiency

Clinical signs

Clinical signs of GBED include stillbirth, transient flexural limb deformities in neonatal foals, hypoglycemic seizures, and respiratory or cardiac failure (**Fig. 2**).[16,17] Genotyping of 190 Quarter Horse foals that were aborted, stillborn, or died near term of unknown causes identified that 4% were homozygous for GBED.[16–18]

Fig. 2. A Quarter Horse foal affected with glycogen branching enzyme deficiency (GBED).

Genetic etiology

GBED is inherited as an autosomal recessive trait that affects Quarter Horse and Quarter Horse-related breeds.[3] GBED is caused by a nonsense mutation (Y34*) in the *glycogen branching enzyme* gene (*GBE1*).[3] The mutation results in the inability to create the branched structure of glycogen. As a result, cardiac and skeletal muscle, liver, and brain cannot store or mobilize glycogen to maintain normal glucose homeostasis. The designation for genotypes is heterozygous carrier, Gb/N, homozygous affected, Gb/Gb, and normal unaffected, N/N.

Carrier frequencies range from 8% to 11% in the Quarter Horse and 4% to 7% in Paint Horse breeds.[9,18] Within Quarter Horse disciplines, Western pleasure horses had the highest prevalence of carriers (26%), followed by cutting (14%) and working cow horses (10%).[9] In the sampling of horses with muscle biopsies submitted to UC Davis, 14 out of 296 horses were identified as Gb/N.[10] Nine of the 14 horses had other disease variants (MYHM, PSSM1, MH) that likely explained the disease findings, with the carrier status for GBED identified as an incidental finding.[10]

Treatment and management

There is no effective treatment. Despite the level of care, all affected foals died or were euthanized by 18 weeks of age.[16,17]

Type 1 Polysaccharide Storage Myopathy

Clinical signs

Clinical signs of PSSM are affected by environmental factors, such as diet and turnout, and by breed. Horses with PSSM may be asymptomatic or demonstrate signs of exertional rhabdomyolysis.[1] In Quarter Horses, clinical signs of PSSM develop at around the age of 5 years, with less than 20 minutes of slow exercise (walk and trot), especially if the horse has been rested for several days.[19] Acute episodes are associated with markedly increased serum CK activity and myoglobinuria.[19] In Draft breeds, muscle fasciculations and gait abnormalities can be evident,[20] with an average age diagnosis at 8 years.[21] Many Draft horses may be asymptomatic.[22] Despite a high incidence of both diseases in Belgian Draft horses, there is no association between the gait abnormality “shivers” and PSSM1.[21] In Warmbloods, clinical signs include reluctance to collect and engage the hindquarters, lumbosacral pain, gait abnormalities, and muscle atrophy, with an average of onset between the age of 8 and 11 years.[23,24] Serum CK activity is often increased from normal values by 2 fold or greater after 15 minutes of light exercise.[25] Older horses homozygous for the PSSM1 mutation can develop gradual pronounced topline atrophy.

Genetic etiology

PSSM1 is inherited as an autosomal dominant disease in Quarter Horses and Quarter Horse-related breeds, Draft horses, and Warmbloods, among other breeds.[26] The genetic mutation is a missense mutation (R309H) in the *glycogen synthase 1* gene (*GYS1*).[26] The mutation results in unregulated glycogen synthesis and potentially impaired aerobic glycogen metabolism. The designation for genotypes is heterozygous affected, P/N, homozygous affected, P/P, and normal unaffected, N/N.

In Quarter Horses and American Paint Horses, the prevalence of PSSM1 ranges between 6% and 10%.[9,27] The highest frequency was found in halter horses (28%) and the lowest in barrel racing Quarter Horses (1.4%).[9] The prevalence of PSSM1 in draft breeds ranges from 36% to 92% between North American and continental European draft breeds, respectively.[27,28] The mutation has been identified in over 20 breeds, including Irish drafts, Gypsy Vanner breeds, and Warmbloods.[2] It is not commonly found in lighter horse breeds, including Arabians, Standardbreds, and Thoroughbreds.[27,29] In the sampling of horses with muscle biopsies submitted to UC Davis, 33 out of 296 horses were identified as P/N.[10] Of these, 24 had histologic diagnosis of PSSM1, 6 had myonecrosis with no evidence of abnormal glycogen accumulation and variants at multiple loci (MYHM, GBED, MH), and 3 had normal histology.[10] In Brazilian vaquejada Quarter Horses, there were 3/129 PSSM1 horses identified.[11]

Treatment and Management of PSSM1 can be found in the article by Drs Anna M. Firshman and Stephanie J. Valberg, "Polysaccharide Storage Myopathy," in this issue and "The Role of Nutrition in Managing Muscle Disorders" by Dr Joe Pagan in this issue.

Myosin Heavy Chain Myopathy

Clinical signs

Myosin heavy chain myopathies include 2 distinct phenotypes that are due to the same underlying genetic mutation (ie, phenotypic heterogeneity).[30] The first is nonexternal rhabdomyolysis, which is not induced by exercise and presents as stiffness, muscle pain, weakness, and recumbency.[31] Serum CK and aspartate aminotransferase (AST) activities are often very high (>100,000 U/L) and myoglobinuria is common.[31] Muscle atrophy is a frequent sequala to these episodes (**Fig. 3**).[31] The second disease is immune-mediated myositis. Clinical signs are biphasic in the population, affecting young horses ($\leq$8 years) or older horses ($\geq$17 years).[32] Clinical signs, consisting of rapid muscle atrophy of the topline muscles, can occur following respiratory disease exposure, particularly with *Streptococcus equi equi, Streptococcus zooepidemicus*, or a respiratory virus.[32,33] Clinical signs can often develop after vaccination against influenza, equine herpes virus 4, or *S. equi equi*.[32,33] Serum CK and AST may be moderately elevated during the acute phase of the disease but can be normal in later phases.[2] In some horses with immune-mediated myositis, systemic calcinosis or calciphylaxis can occur.[34] This is a rare, but fatal syndrome of calcium accumulation in soft tissues and organs. Ventral edema is an early indicator of systemic calcinosis and additional signs include mild fever, stiffness, muscle atrophy, and multiple organ failure.[34] Hyperphosphatemia is evident with these cases, with a product of total calcium concentration (mg/dL) multiplied by phosphorus concentration greater than 65 g/dL (1 mg/dL of calcium = 0.25 mmol/L; 1 mg/dL of phosphorus = 3.1 mmol/L).[2]

Genetic etiology

MYHM is inherited as an autosomal codominant disease of Quarter Horses and Quarter Horse-related breeds with variable penetrance.[30] The genetic mutation is a missense mutation (E320G, based on the most recent EquCab3.0 assembly) in the

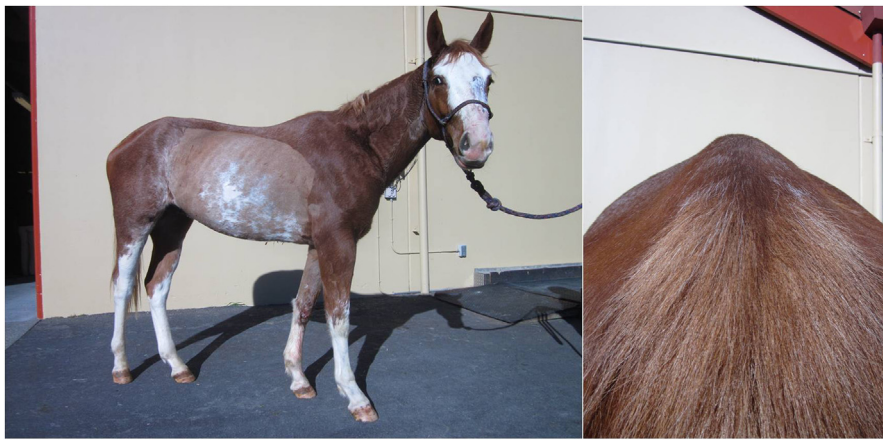

Fig. 3. A Paint Horse yearling that recovered from a pectoral abscess due to *Corynebacterium pseudotuberculosis* and subsequently developed immune-mediated myositis, due to the genetic mutation in myosin heavy chain 1 (MYH1, myosin heavy chain myopathy). Note the severe and widespread muscle atrophy.

myosin heavy chain 1 gene.[30] This genetic variant appears to result in a hypercontractile phenotype that could lead to the observed myopathy.[35] The mutation was initially discovered in horses with immune-mediated myositis[30] but later confirmed to also cause nonexertional rhabdomyolysis, as described earlier.[31] The designation for genotypes is heterozygous affected, N/My, homozygous affected, My/My, and normal unaffected, N/N. Homozygotes (My/My) typically demonstrate more severe clinical signs and recurrence of disease as compared with heterozygotes.[30,31]

In a recent retrospective study aimed at identifying potential triggers of atrophy and stiffness in horses with MYHM, atrophy occurred more frequently in My/My horses.[36] Additionally, fewer My/My horses fully recovered.[36] Three months before observed clinical signs, 47% of MYHM Quarter Horses had been vaccinated or had respiratory or gastrointestinal disease.[36] Inciting causes were not identified in over half the cases. While there did not appear to be a difference in performance success among My/My, My/N, and N/N horses, only 2 out of 10 My/My horses were still actively competing at the time of the study.[36]

Allele frequencies were estimated to be approximately 7% in the general Quarter Horse population and highest among reining (24%), working cow (17%), and halter horses (16%) and the allele was not detected in the barrel racing and racing Quarter Horse subpopulations studied.[37] In the sampling of horses with muscle biopsies submitted to UC Davis, 60 out of 296 horses were identified as having MYHM.[10] Of these 60 horses, 47 (78%) had histologic diagnosis of immune-mediated myositis. Within the 27 out of 60 homozygous (My/My horses), 16 had clinical signs and muscle enzyme activities consistent with severe rhabdomyolysis with myonecrosis on biopsy. Heterozygous horses (33 out of 60; My/N) were less likely to have this severe rhabdomyolysis, with only 6 out of 33 affected.[10] In Brazilian vaquejada Quarter Horses, 10 out of 122 (8%) MYHM horses were identified.[11]

Treatment and Management of MHYM can be found in the article by Drs Sian A. Durward-Akhurst and Stephanie J. Valberg, "Myosin Heavy Chain Myopathy and Immune-Mediated Muscle Disorders," in this issue.

INHERITED EQUINE MUSCLE DISORDERS WITH ONGOING RESEARCH EFFORTS

Type 2 Polysaccharide Storage Myopathy and Myofibrillar Myopathy

Following the discovery of the DNA mutation causative for PSSM1, the term PSSM2 was assigned to cases where clinical signs of exercise intolerance were identified, in addition to abnormal aggregates of polysaccharide in muscle fibers of horses that did not possess the *GYS1* mutation.[38] PSSM2 was identified as the most common form of PSSM in the Warmblood and Arabian horses.[39]

Subsequent histologic analyses of muscle biopsies from Warmbloods and Arabians with PSSM2 identified abnormal aggregates of desmin, a cytoskeletal protein, in a small percentage of type 2A muscle fibers.[40,41] Glycogen appeared to pool between these disorganized myofibrils.[40,41] Thus, the subset of PSSM2 horses with these findings were reclassified as having a myofibrillar myopathy (MFM), with PSSM2 likely being an earlier manifestation of MFM in these horses.[29,40,41]

Commercial genetic testing is currently offered for PSSM2 and MFM using single nucleotide polymorphisms (SNPs) in the genes *myotilin* (*MYOT:* P2, corresponds to the SNP rs1138656462), *filamin C* (*FLNC*: P3a, rs1139799323 and P3b rs1142918816), and *myozenin* (*MYOZ3*: P4, rs1142544043; https://www.equiseq.com/). These variants were proposed as DNA tests for PSSM2 and MFM, based on the knowledge that various mutations in *MYOT* and *FLNC* have been associated with MFM-like disorders in humans.[42] However, careful assessment in well-phenotyped cases of PSSM2 and MFM in horses has completely refuted these commercial tests.[43]

In the Quarter Horse breed, PSSM2 does not appear to be associated with MFM.[44] Additionally, the P2, P3, and P4 variants offered commercially were not associated with PSSM2 in Quarter Horses.[44] In fact, 57% of healthy Quarter Horses, as diagnosed on muscle biopsy, would be misdiagnosed with PSSM2/MFM using this commercial test.[44] Thus, there are currently no validated genetic tests for PSSM2 or MFM and muscle biopsies are still required for diagnosis.

In Quarter Horses with PSSM2, amylase-resistant polysaccharide is apparent and muscle glycogen concentrations are higher than control horses, but lower than PSSM1 horses.[45] PSSM2 in Quarter Horses can be managed like PSSM1 and is detailed in Anna M. Firshman and Stephanie J. Valberg's article, "Polysaccharide Storage Myopathy," in this issue. PSSM2 does appear to be inherited in the Quarter Horse breed, and variants in 12 candidate genes impacting glycogen metabolism were recently excluded as being associated with the phenotype.[45] Thus, genetic investigations continue for PSSM2 in the Quarter Horse breed, but muscle biopsies are still required for diagnosis.

Recurrent Exertional Rhabdomyolysis

Recurrent exertional rhabdomyolysis (RER) occurs in approximately 7% of Thoroughbred racehorses, especially young nervous fillies, and in 6% of Standardbred racehorses.[46–48] RER may also occur in racing Quarter Horses, Arabian, and Warmblood horses.[49] Episodes of rhabdomyolysis occur intermittently and are associated with sudden increases in serum CK activity.[50] RER appears to be inherited,[51,52] with modifying environmental factors that affect the frequency and severity of these episodes. Using equine SNP genotyping arrays, heritability estimates ranged from 0.41 to 0.46 (Thoroughbreds) and 0.39 to 0.49 (Standardbreds), further supporting that RER is moderately heritable.[53]

With RER, increased sensitivity to potassium-induced, caffeine-induced, and halothane-induced muscle contracture in vitro suggested that altered myoplasmic calcium regulation may underlie this disease during exercise.[54] Genes that regulate

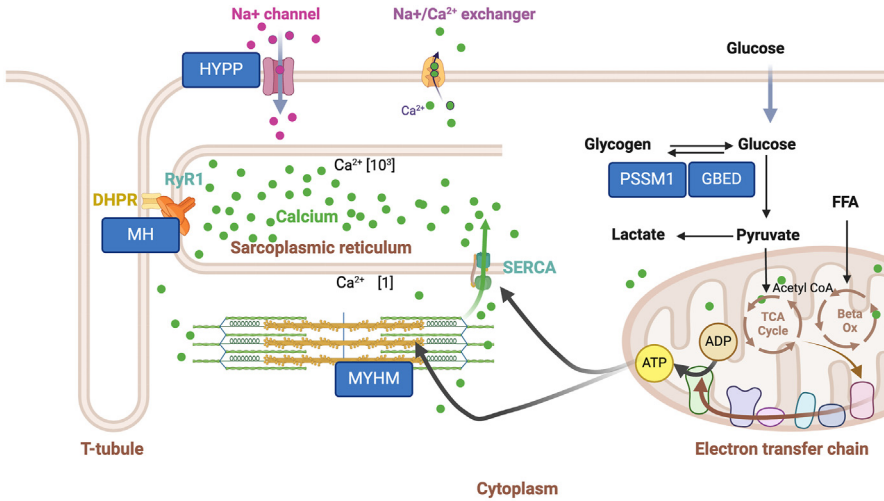

Fig. 4. Diagram outlining where each genetic mutation in the horse affects the resulting protein in skeletal muscle. Genetic disease abbreviations for equine specific diseases can be found in the text. DHPR, dihydropyridine receptor; FFA, free fatty acids; RyR1, ryanodine receptor 1; SERCA, sarcoendoplasmic reticulum calcium ATPase; TCA, tricarboxylic acid cycle. (*Created in* BioRender. Valberg, S. (2025) https://BioRender.com/l03e998.)

myoplasmic calcium, including *RYR1, ATP2A1*, and *CACNA1S,* were initially excluded as candidate genes using microsatellite markers.[55] The genes *sarcolipin* (*SLN*), *myoregulin*, and *dwarf open reading frame*, which are transmembrane regulators of the sarcoplasmic reticulum calcium transporting ATPase, were subsequently excluded as candidate genes.[56] However, it was uncovered that equine *SLN* encodes a uniquely truncated peptide that is specific to the horse and of evolutionary interest.[56] Subsequent studies revealed that horse skeletal muscle contractility and susceptibility to exertional rhabdomyolysis are promoted by enhanced sarcoplasmic reticulum calcium uptake and luminal calcium storage.[57] Thus, horses have evolved to have a delicate balance between optimal skeletal muscle performance and disease.

Attempts to identify a genetic cause for RER have continued.[58] However, to date, no causative single gene has been identified. Gene expression pathway analyses repeatedly support perturbation of pathways for calcium regulation and mitochondrial oxidative stress in Standardbreds[59] and Thoroughbreds.[60]

Treatment and management of RER can be found in Stephanie J. Valberg's article, "Sporadic and Recurrent Exertional Rhabdomyolysis," in this issue.

SUMMARY

A summary of where each genetic mutation affects skeletal muscle is provided in **Fig. 4**. With the continued advancement of genetic tools for investigation of genetic diseases in the horse, additional DNA tests are likely to become available for inherited muscle disorders across breeds. Appropriate validation of these tests is a critical step prior to commercialization to guard against misdiagnosis. Genetic and phenotypic heterogeneity should be considered during these genetic investigations, and genetic counseling will become an essential part of the equine practitioner's tool kit.

CLINICS CARE POINTS

- Many recurring muscle diseass have an underlying genetic basis.
- To date, DNA testing exists for five validated inherited muscle disorders.

DISCLOSURE

A portion of proceeds from the genetic testing for MYHM that is performed at the UC Davis Veterinary Genetics Laboratory is returned to Dr C.J. Finno's laboratory to support ongoing genetic research.

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