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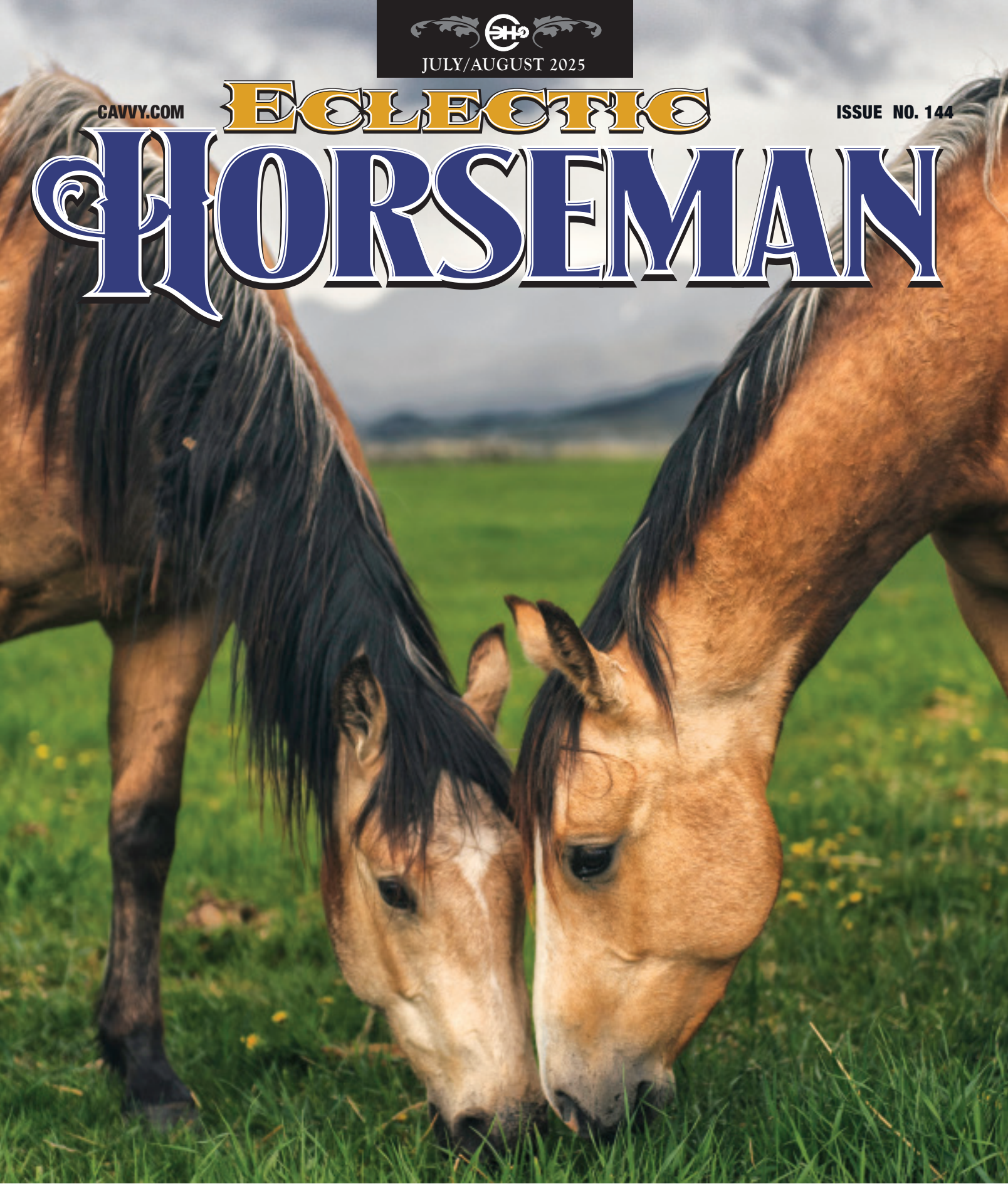

Communicating Equine Science

GENETIC DISEASES

By Siobhán Watkins, Ph.D., Skeleton Key Equine, LLC

A couple of years ago, I was fortunate to meet an incredible mare. She was a Kentucky-bred Thoroughbred, that came to the racehorse rescue I was working at with a broken sesamoid bone.

You could tell that her nervous system was pretty shot—she was sensitive and couldn't take much sensory stimulation. During recovery, in her box stall, she loved to kick water out of her trough, and could successfully empty a 30-gallon trough in a couple of minutes. Later, during turnout in the paddocks, she would play with the hose as I filled the larger tanks and would ask me to turn the water on her. As time went on, it was clear to us that the mare had serious suspensory problems in all four legs. Her fetlocks dropped lower and lower, and she found it harder and harder to amble around the paddock. Despite this, she was the boss and lived with two other girls who she moved around, wonky legged and stumbling. Those girls were present, and so was I, when Gertrude was peacefully euthanized after diagnosis and ongoing progression of degenerative suspensory ligament desmitis (DSLD).

Each article I write here is inspired by a particular horse—I'm thinking about them as I write. Originally, I had planned to write about DSLD, with Gertrude in mind. I loved her, after all, and I was heartbroken when we euthanized her. But, when I started pulling the research on DSLD, I got distracted by a tangential pathway. So, with apologies for anyone who feels cheated out of a juicy essay about tissue, in honor of Gertrude, I'm moved to write about genetic diseases instead.

Gertrude had a beautiful head, a deep chest, and a short back. She also had very long pasterns and fine, delicate limbs. While, of course, there was all sorts going on with her suspensory ligaments, which were stabilizing those fetlock joints as best they could (we saw sesamoid fractures on every other horse at that rescue, it seemed like). The tricky thing with genetics is that, it's hard to breed for a specific characteristic and not make concessions in other areas, particularly over time. Generations of selective breeding might give you nice conformation, but you can never be sure what else you might be breed into a line.

I used to teach college-level genetics and luckily, as a microbiologist (therefore working with comparatively small genomes), I could just about manage it. But as a theoretical subject, genetics can seem impenetrable, particularly when you upgrade to mammals. As for plants? Forget it. Plant genetics is bananas. Genomes, genetic blueprints of living organisms, contain units of heredity known as genes. Genes come in different flavors, which we call alleles. Alleles are variants of the same gene. The study of genetics and genetic information becomes extraordinarily complicated very quickly. This is, in part, due to an exciting phenomenon known as mutation. Mutation, truly, is the spice of life. Often a word used in association with something negative, mutation has truly allowed for all the genetic diversity we enjoy in the world today.

Horses have around 22,000 genes and 32 pairs of chromosomes (64 in total). Foals get half of their genetic complement from their dam and half from their sire, they have two copies of every gene, and one from their father, one from their mother. Genes are defined sections of DNA within a chromosome. The copies of specific genes that a baby receives from his parents might not be identical, and alternate versions of the same gene are called alleles. When a horse inherits the same allele from both parents, he is referred to as being homozygous for that allele. When they're different, the individual is heterozygous for that allele. The full genetic complement of an individual, encompassing all of that variability, is the horse's genotype. The physical expression of the genotype, including coat color, is the horse's phenotype.

In 1992, the first mutation for the disease hyperkalemic periodic paralysis (HYPP) was discovered and linked to the lineage of the Quarter Horse stallion Impressive. The entire equine genome was sequenced in 2007—all the genes of a specific horse were mapped out to produce, base pair by base pair, the order of her DNA. This dramatically sped up the course of research into genetic disease, and that year, genome mapping was used to identify two new mutations: for hereditary equine regional dermal asthenia (HERDA) and polysaccharide storage myopathy (PSSM). Prior, progress was hindered in horses by factors such as long gestation period, and giving birth to single foals. Many genetic diseases present with delayed onset, or variable symptoms, and horses tend to be dispersed after weaning, so it's difficult to keep track of them.

Diseases caused by a mutation in a single gene are referred to as "single gene" or "simple genetic" diseases, also known as monogenic diseases. Polygenic diseases are caused by mutations in more than one gene, plus the combined effect of environmental factors. Monogenic diseases in horses have, in

part, developed because of selective breeding. Generally speaking, selective breeding reduces genetic diversity and therefore increases the risk of inherited disorders, because many breeds start with a small group of founder animals. If a popular stallion produces 2,000 offspring over the course of his breeding career, that popularity leads to the predominance of his genetic material in the breed gene pool. If he carries a disease-causing allele, depending on the disease's mode of inheritance, predominance can be very difficult to breed away from once it's bred in.

In genetics, dominance describes how an allele is expressed physically. In diseases with a recessive mode of inheritance, both copies of a gene must have the mutant (disease-causing) allele in order to produce the disease phenotype. In this situation, most of the time we are breeding carriers of a disease who don't demonstrate symptoms. Recessive disorders include HERDA, lavender foal disease, severe combined immunodeficiency (SCID) and glycogen branching enzyme deficiency (GBED). However, in diseases with a dominant mode of inheritance, only one copy of the mutant allele is needed to cause the disease, and offspring have a much higher chance of actually suffering from a disease rather than being a carrier. Dominant disorders include HYPP, PSSM, and malignant hyperthermia (MH).

We know a great deal more about monogenic diseases than we do polygenic. Polygenic diseases are harder to figure out; they're more challenging to identify by nature—lots of factors affect how they present and progress. For some time DSLD has been suspected to be genetic in origin due to strong breed disposition.

Despite this tendency, other breeds are also affected, and no single gene mutation has ever been identified as being a culprit. It's also difficult to definitively diagnose DSLD due to the potential for catastrophic damage to tissue structures related to the disease if they're sampled directly. Research published this year approached the problem using genome-wide association study (GWAS) and polygenic risk scores (PRS) methods. A PRS, or genetic risk score, is a number assigned to reflect the risk of an individual developing a disease based on the cumulative effect of many genetic elements. This analysis makes use of thousands of variables that may contribute a small influence on whether a disease develops. Statistically, each element is weighted for the impact it is likely to have. During this study, scientists identified 151 single nucleotide mutations associated with DSLD. So, if our DNA code is put together with a series of bases (ACGT), there are 151 single A's, G's, C's, or T's implicated in the development of DSLD. Based on these analyses, the authors were able to design a model which could predict if a Peruvian horse was likely to develop the disease. They concluded that DSLD, in this study, demonstrated "moderate heritability and a clear polygenic disease architecture." Roughly translated, that means, "there appears to be a genetic link, but there's also a whole lot of other stuff happening which affects whether or not a horse gets this disease."

As genomics-based technology has advanced and become less expensive, previously unidentified illnesses are being reported in the literature. A study published in 2024 describes a novel disease identified in 12 young Quarter Horses. All the foals appeared healthy and normal for the first month or so of their lives, but shortly after became neurologic and developed a tendency to move their limbs beyond the intended placement (hypermetria). Eleven of the 12 were ultimately humanely euthanized, and the remaining one died without intervention. After performing a pedigree analysis, authors noted that six of the foals were related on the sires' side within four to five generations, and related on the dams' side within four to six generations since both sexes were affected and two healthy parents produced affected foals, they concluded an autosomal recessive mode of inheritance. A subsequent paper, published in 2025, implicates a mutation of a gene leading to neurodegeneration. (The 2025 paper is unfortunately paywalled.) The disease described in these two publications has been named Equine Juvenile Spinocerebellar Ataxia (EJSA), and University of California, Davis, now offers testing for it.

As technology advances and breeding practices continue to develop, we will likely witness many future discoveries and many alleles to test for. In a world searching hard for perceived deficiencies, and subsequent fast fixes to repair those deficiencies, oversimplification of the realities of what genomic information can actually provide by way of explanation and recovery is rife. As ever, the science of it all guides our way.

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