Equine Genetic Disease: Who's At Risk?

by: Marcia King
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Many of today's scientific advancements are based on genetic technology, and medicine is at the cutting edge of gene discovery. Equine medicine is no different. Using the very information code for life in genes, scientists are working to:

- Prevent devastating or career-ending diseases through informed breeding;
- Gain new knowledge on conditions that contribute to disease severity;
- Monitor efficacy of treatments;
- Assess fitness expression;
- Identify at-risk horses;
- Map the horse genome in order to improve the search for specific genes responsible for traits of interest; and
- Utilize gene chip technology to study disease expression.

The goal is to control, treat, and even eliminate equine genetic disorders. This article will discuss how genetic research is helping our horses live better, healthier lives.

What is a Genetic Disease?

All of the physical characteristics a horse expresses, and likely many of his mental ones, are controlled by his unique combination of genes--arrays of DNA sequence that code for specific combinations of amino acids, which form unique functional proteins. Many DNA sequence variations are fine; they just give rise to the broad spectrum of colors, sizes, and other characteristics we see in the horse population. Some variations, however, cause problems. These might range from a genetic predisposition toward a particular limb conformation to overo lethal white syndrome, which is 100% fatal.

And you can't currently cure a genetic disease. You can treat the clinical signs, but you can't change the horse's DNA to completely get rid of the problem. However, we can identify many genetic diseases via DNA testing and avoid spreading the diseases by removing affected individuals from breeding programs. Thus, much of the genetic research today is focused on identifying the gene mutations that cause particular diseases and developing tests for them. Other researchers focus on ways to improve treatment and management of affected horses so they can live more comfortable, productive lives.

Mapping the Equine Genome

"A genome map is like a road map with a set of landmarks along the chromosomes that lets a person know where on the road they are," says James D. Murray, PhD, professor of animal science at the University of California, Davis.

"Another way of looking at it is if you are looking for a house you have never been to before, you start your search by finding out where it is close to (state, town, suburb, block, etc.)," he explains. "A genome map is used in the same way. By doing a linkage mapping study of a trait we are interested in--say, a coat color in a set of families derived from stallions that produce offspring of the trait we are interested in--we can determine which highway (chromosome) the trait is on and place the trait between two markers. At that point we know the trait is between marker A and marker B, and we can then target the region in between for more markers, to get closer to the genes there that might cause the trait. In this way we can zero in and eventually identify the gene and the mutation responsible for the trait."
This same method is used for locating the defective genes that cause disease.

Dozens of laboratories and scores of researchers are engaged in this project. At this point, researchers are developing the tools needed by scientists to help them locate the genes responsible for traits. "The tools include a good linkage map and physical map to provide a source of markers whose locations are known on the map," Murray says, "and a good comparative map so that we can link from the horse genome map (which is incomplete) to the human and mouse maps (which are complete) in order to help us find what genes are present in a region of interest."

In terms of disease control, after locating the gene(s) that cause a disorder, researchers can then develop diagnostic tests to determine whether horses are clear of, carriers of, or affected with a specific disease, and breeders can use that information to select away from a disease.

The Five Least-Wanted List

The names of several genetic diseases strike fear into the hearts of horse breeders and owners. Researchers have identified the responsible gene mutations and modes of inheritance for the following five diseases:

**Glycogen branching enzyme deficiency (GBED)** causes abortion, stillbirths, and foal deaths in affected Quarter Horses. "All foals with GBED studied to date have died or been euthanized due to weakness," says Stephanie Valberg, DVM, PhD, Dipl. ACVIM, professor of large animal medicine and director of the Equine Center at the University of Minnesota, who is studying several genetic disorders.

The disease is inherited as an autosomal (non-sex-linked) recessive trait, meaning that an affected horse received a copy of the defective gene from each parent (see "Dominant, Recessive, What's the Difference?" on page 38). (For more information on GBED, see [www.TheHorse.com/viewarticle.aspx?id=2419](http://www.TheHorse.com/viewarticle.aspx?id=2419).)

**Overo lethal white syndrome (OLWS)** is a fatal autosomal recessive disease in which foals cannot pass feces. The disease is seen in all-white or primarily white Paint foals. Horses carrying the OLWS gene usually have a frame overo coat color pattern, although occasionally carriers can be solid-colored Paint broodstock or horses with other white color patterns. Carriers are found rarely among miniature horses, half-Arabians, Thoroughbreds, and Quarter Horses that have associated white coat color patterns. The gene mutation has been identified, and owners can test breeding stock to avoid producing affected foals. There is no means to save affected foals. (For more information, see [www.TheHorse.com/viewarticle.aspx?id=3010](http://www.TheHorse.com/viewarticle.aspx?id=3010).)

**Hyperkalemic periodic paralysis (HYPP)** is a muscular disorder resulting in sudden episodes of uncontrollable muscle twitching, paralysis, and sometimes collapse or death. It is seen in Quarter Horse bloodlines (and some crosses breeding back to Quarter Horses), and it is inherited as an autosomal dominant trait (any horse with even one copy of the defective gene will express the disease).

Now that a DNA test exists for identifying HYPP horses, research efforts are directed toward disease management. "We have performed research as to why some horses are more symptomatic than others, in spite of having the identical mutation," says Sharon J. Spier, DVM, PhD, Dipl. ACVIM, Professor in the Department of Medicine and Epidemiology at the University of California, Davis. Investigators found horses that are more severely affected have an increased proportion of abnormal sodium channels in their muscle. "Veterinarians have observed that heavy sedation, such as occurs with modern dentistry and general anesthesia, precipitates attacks and even death," says Spier. "We continue to investigate other muscular and neuromuscular disorders that can cause similar signs or exercise intolerance."

Management, says Jeremy Powell, DVM, extension veterinarian at the University of Arkansas, should include dietary changes to decrease potassium levels. "Feeds with relatively high levels of potassium include alfalfa
hay, molasses, and wheat bran," he says. "Feeds such as cereal grains (corn, oats, barley), beet pulp, and vegetable oils contain lower levels of potassium."

Avoid electrolyte supplements containing potassium and analyze forages as potassium concentrations vary with maturity, Spier adds. Another management tool, says Powell, is to administer acetazolamide; this medication reduces episodes. (For more information, see www.TheHorse.com/ViewArticle.aspx?ID=725.)

**Severe combined immunodeficiency (SCID)** seen in Arabian horses is an autosomal recessive disorder in which affected horses can't produce immune responses sufficient for protection against infectious diseases. Explains Lance Perryman, DVM, PhD, Dean of the College of Veterinary Medicine and Biomedical Sciences at Colorado State University, "Affected foals don't produce antibodies after infection or immunization, and rarely live beyond five months of age unless the condition is corrected through bone marrow transplant."

Perryman collaborated with other scientists to locate the defective gene, and since 1997 breeders have been able to use DNA testing to identify carrier, clear, and affected horses. (For more information, see www.TheHorse.com/ViewArticle.aspx?ID=680.)

**Junctional epidermolysis bullosa (JEB)** is another autosomal recessive disease that causes skin lesions over pressure points of the body in newborn Belgian foals and results in large areas of skin loss. JEB is also seen in American Cream draft horses, Breton draft horses, and Comtois draft horses. The condition is untreatable, and foals die within 24 hours to 14 days after birth. A form of the disease also occurs in American Saddlebred newborns, although the mutation responsible is different from that in draft horses.

John D. Baird, BVSc, PhD, professor of large animal medicine in the department of clinical studies at Ontario Veterinary College, was part of the team that developed the test for identifying carriers of the mutation responsible for JEB in Belgian draft horses. (For more information, see www.TheHorse.com/ViewArticle.aspx?ID=4994.)

**Still Just Suspects**

There are quite a few other disorders that horse people suspect of having a genetic origin, but the specific mutations causing the diseases have not yet been unequivocally identified.

"Until you've got the gene, you just don't know for sure," says Valberg. "Research goals are to determine the underlying genetic defects, their mechanism of causing clinical signs, and the best way to alleviate those signs and make horses as comfortable and physically sound as possible," she says.

Following are seven diseases for which researchers are working to understand the genetics involved.

**Polysaccharide storage myopathy (PSSM)** causes tying-up in Quarter Horses, Paints, and Appaloosas; there is also a form that presents as muscle soreness, weakness, and tying-up in draft horses, draft crossbreds, and warmbloods. Horses affected by PSSM forms are managed by providing regular turnout, a gradually increasing exercise schedule that becomes a regular routine, and a low-starch/high-fat diet.

"We've done some pedigree analysis that suggests a dominant mode of inheritance for this disease," reports Valberg. Horses with PSSM should not be bred, as there is a 50% chance their offspring will be affected, she adds. (For more information, see www.TheHorse.com/ViewArticle.aspx?ID=4139.)

**Degenerative suspensory ligament desmitis (DSLD)** is a chronic, untreatable connective tissue disease that causes pain and abnormalities, primarily in limb tissues and to a lesser degree in other tissues of the body.
Initially identified in Peruvian Pasos, DSLD has also been diagnosed in Thoroughbreds, Quarter Horses, warmbloods, Standardbreds, Arabians, and draft horses.

Researchers at the Universities of Kentucky and Georgia have identified eight chromosomal regions where there are differences in the marker genotypes between affected and unaffected groups of horses, reports Jeanette L. Mero, DVM, associate veterinarian at Starland Veterinary Services in Romulus, N.Y., and an activist in promoting DSLD recognition and research. More work will be done to localize the specific gene on one of these chromosomes. Additionally, various clinicians and researchers are hoping to develop diagnostics for subclinical early cases and to further clinical understanding of DSLD.

Therapies including therapeutic shoeing, medications, surgeries, bone marrow injections, and extracorporeal shock wave therapy have been ineffective for curing DSLD or relieving clinical signs, Mero reports. (For more information, see www.TheHorse.com/ViewArticle.aspx?ID=4049.)

**Recurrent exertional rhabdomyolysis (RER)** is a form of tying-up in Thoroughbreds. Researchers have been working to identify a genetic mutation causing this disease, but have not yet located it.

RER-affected horses are managed by housing them in a quiet area of the barn, avoiding exciting situations, providing turnout, feeding a specially formulated high-fat/low-starch diet, providing warm-up exercises, and avoiding routines that promote tying-up. "In Thoroughbred racehorses," says Valberg, "this means avoid fighting to hold a horse back during galloping. In Standardbreds, limit jogging to 20 minutes per session. In riding horses, acclimate horses to new environments, horse shows, and speeds achieved during steeplechase phase of three-day events."

The disease "may be inherited as an autosomal dominant trait with variable expression," concludes a study published in 1999 in the American Journal of Veterinary Research. In other words, the appearance of clinical signs in RER-affected horses might be influenced by management—diet and exercise level/schedule. More work on the inheritance of this disease is forthcoming. (For more information, see www.TheHorse.com/ViewArticle.aspx?ID=3717.)

**Hyperelastosis cutis (HC) or hereditary equine regional dermal asthenia (HERDA)** is a rare condition occurring in some Quarter Horse bloodlines. In affected horses, the deep layers of skin are weak and thin, thus separating and tearing easily. The disorder is passed to offspring via recessive inheritance, which means that if both apparently normal parents carry the HC gene, the offspring has a 50% chance of carrying the disease without clinical signs and a 25% chance of expressing the disease. If only one apparently normal parent carries the defective gene, the foal has a 50% chance of carrying it without clinical signs, but will not express the disease.

While Cornell University's Nena Winand, DVM, PhD, searches for the defective gene, Ann Rashmir-Raven, DVM, MS, Dipl. ACVS, associate professor in the department of clinical sciences at Mississippi State University, is comparing skin biopsies, thermography, and biochemical studies of normal and affected foals to evaluate differences between the two.

There is no cure. "In most cases, horses are euthanatized or donated for research by the time they are four years old," Rashmir-Raven states. Occasionally, heavily managed horses with mild cases can be ridable. For them, Rashmir-Raven recommends dietary changes to include increased amounts of copper, vitamin C, calcium, and phosphorus, and good protein levels, along with sun restriction and very careful selection of saddles and pads to prevent skin rubbing and subsequent open wounds. (For more information, see www.TheHorse.com/ViewArticle.aspx?ID=5037.)

**Laryngeal hemiplegia (roaring)** is one-sided paralysis of the larynx, in which horses suffer from partial to nearly complete collapse of the airway during exercise and generate a subsequent loud "roaring" noise. In
searching for the gene mutation, Elizabeth Santschi, DVM, Dipl. ACVS, clinical associate professor of large animal surgery at the University of Wisconsin, looked at mouse data to see if there was a similar gene mutation (there wasn't). She is now screening genomic material for a gene sequence difference between affected and unaffected horses. Treatment is surgical, with varying degrees of success. (For more information, see [www.TheHorse.com/ViewArticle.aspx?ID=4589](http://www.TheHorse.com/ViewArticle.aspx?ID=4589).)

Colic-induced intestinal injury refers to colic-caused damage sustained by the intestine (twisting and loss of blood supply), the most common reason for colic fatalities.

For unknown reasons, some horses' intestines do a better job of repairing themselves than those in other horses. Using genetic sequencing (figuring out the genetic code), researchers at North Carolina State University (NCSU) and Virginia-Maryland Regional College of Veterinary Medicine are searching for the genes involved in intestinal repair. With that information, they hope to learn how to turn on or off genes that aid or hinder intestinal repair.

Reports NCSU researcher Anthony Blikslager, DVM, PhD (GI physiology), associate professor in equine surgery in the Department of Clinical Sciences at North Carolina State University, "We have sequenced a group of genes involved in regulating the connection between cells that line the intestinal tract; these cells stick together and re-seal damaged junctions in between the cells that line the intestine."

But in some horses, these cells contain reduced amounts of reparative proteins. "We want to understand the cause of these reduced amounts and then figure out a way to boost their production," he adds.

**Osteochondritis dissecans (OCD)** is a joint cartilage disorder. Studies have found differences in the gene expression of local hormones within cartilage associated with the disease process of OCD. "The premise has been that an underlying molecular abnormality leads to matrix and cell signaling changes in OCD cartilage," says Stacy A. Semevolos, DVM, Dipl. ACVS, assistant professor of large animal surgery at Oregon State University. "These changes ultimately result in areas of thickened cartilage that is weaker than its normal counterparts, making it susceptible to biomechanical damage. Determining normal gene expression lays the groundwork for understanding what happens in disease processes like OCD and osteoarthritis."

She is also investigating how growth hormones circulating in the bloodstream affect local hormonal signaling within OCD and normal cartilage. "This project will give us further clues on how OCD cartilage may respond differently than normal cartilage during rapid growth spurts," she says.

Arthroscopy is the treatment of choice for many OCD lesions, Semevolos states. "Most horses require six weeks (hock OCD) to six to 12 months (stifle OCD) of down-time after surgery," Semevolos adds. "Gradually increasing increments of hand-walking and controlled exercise are part of post-surgical care. Conservative treatment--decreasing the nutritional plane (grass hay only, reducing or eliminating grain and alfalfa from diet), balanced nutrients in the diet, decreased exercise level, and hyaluronic acid joint injections by a veterinarian--is recommended for young horses with mild OCD lesions." (For more information, see [www.TheHorse.com/ViewArticle.aspx?ID=4262](http://www.TheHorse.com/ViewArticle.aspx?ID=4262).)

**New Technologies**

The way scientists study these diseases and others is continually evolving; one exciting development is the gene chip.

The next wave of modern medicine, the gene chip is a 2.5-inch x 1.5-inch cartridge with a postage-stamp-sized glass window containing some 1.3 million DNA probes representing 3,000 unique equine genes. Drop a DNA blood sample on the glass wafer, and it gives information about the individual's gene expression (phenotype).
Alicia Bertone, DVM, PhD, Dipl. ACVS, Director of the Comparative Orthopedic Research Laboratories at The Ohio State University and developer of the chip, explains, "At any given moment, you express about 5% of your DNA make-up; that's your expression phenotype, and those phenotypes will change over your lifespan."

For example, foals express many growth and development genes not seen in adults. An overweight, under-exercised horse expresses a particular phenotype, but if conditioned will produce a different phenotype--muscle enzymes that represent fit muscles, genes that are turned on to make bones denser, etc. A horse at risk for--or in the very early stages of developing--cancer, osteochondrosis dissecans, colic, or other diseases will have a gene expression profile outside the norm. A horse that has an active infection, such as herpes or EPM (as opposed to just being exposed to a virus and raising an antibody response) will express genes indicative of active infection.

Because the gene chip can view thousands of genes at once, looking at a horse's phenotype will help us make earlier and more accurate diagnoses, and providing an objective way to determine fitness.

"Most of this is still in the future," says Bertone. "We've looked at five or six key diseases in horses--that data is not published yet--and have genes on the chip that represent acute herpesvirus infection and many other infectious diseases. We're hitting the most obvious ones first. Clearly this is something with tremendous potential."

Breeders Make the Difference

With new technologies promising to expand the range of veterinary advances, along with traditional clinical trials to evaluate treatments and identify contributing causes, the tools for breeding healthier, sounder horses increase every year--but breeders must utilize those tools.

Although it's been 13 years since a DNA test for identifying HYPP in carrier and affected horses was developed, the incidence of H/H, or severely affected horses, continues to rise, meaning that people are still breeding affected horses to affected horses, says Spier. "The market has not resolved the problem, as was predicted when the test became available in 1992," she states. "Gene frequency is increasing in the breed rather than decreasing. With all of the education, publications, web sites, brochures, and presentations by veterinarians regarding this disease, it is disappointing that figures remain what they are. I would hope that breeders would have a longer-term vision for what is good, sound breeding for the health of the horse."

"The same could be said for breeding horses with poor hoof conformation or soundness issues," she adds. "We can manage these for the short term (and shortened equine career), but should breeders continue to promote these horses as the best of the breed? I believe the problems that occurred in the Quarter Horse breed and other breeds over the past 20 years have been due to the over-specialization and over-use of inbreeding to produce 'carbon copy' images of what is considered ideal for that event."

Spier says there should be more emphasis placed on hoof and leg conformation, temperament, and soundness rather than bloodlines when breeding. "I wish breeders would take more chances and breed horses outside of their specialty to see if we can maintain what makes the Quarter Horse so popular--a healthy, versatile horse."

Santschi finds that attitudes about breeding decisions are sometimes ambivalent. "They all think genetic disease should be as limited as possible," she says, "but some get weaker-hearted when it involves their horses. It's also about money: The more valuable breeds are, the less interested some breeders are in talking about genetic defects."

It's hard to determine the percentage of breeders who are willing to make the tough decisions when it comes to the overall well-being of the breed versus the breeding career of their prized stallion or mare--and the
financial well-being of the breeding operation. Obviously, although some breeders are reluctant to embrace
the big picture, others are willing to move forward, particularly when it involves diseases that result in foal
death or young horse loss.

Along those lines, Baird notes, "The JEB test is now accepted as a useful tool by draft horse breeders, as it
prevents the financial losses associated with the birth of a foal with a lethal genetic disease."

Additionally, organizations including The American Quarter Horse Association, Morris Animal Foundation,
Grayson Jockey Club Research Foundation, Oak Tree Racing Foundation, and University of Minnesota
Equine Center contribute to and support genetic research. "Research into genetic diseases in horses is highly
dependent on the support of breeders through research funding and cooperation with veterinarians to identify
and allow affected and unaffected horses to be tested," states Valberg. "The cost of research is such that it
would be a rare instance that herds of horses of sufficient size could be kept by universities to study these
diseases.

"Progress," she adds, "will depend on the degree to which breeders work with the researchers and breed
associations to develop these genetic tests." And to the degree that breeders utilize them.

Take-Home Message

There have been many advances in genetic research, some of which have resulted in genetic tests to help
breeders avoid passing on disease-causing genes. However, there is still a lot to learn, and once learned,
breeders must put the tools into practice in order to breed healthier, happier horses.

Unlocking Genetic Secrets: How Research Works

How do scientists uncover the secrets of genetic disease? The search begins by looking for evidence that
suggests the disease is hereditary, says Stephanie Valberg, DVM, PhD, Dipl. ACVIM, professor of large
animal medicine and Director of the University of Minnesota Equine Center. One indicator is if the disease is
common in some families or lines, but not in others.

From there, approaches vary. Valberg describes one process:

- Develop a clinical diagnostic test to identify normal or affected individuals, then work with breeders
  and owners to test as many related individuals as possible in multigenerational families, classifying
  them as normal or affected. This could suggest the mode of inheritance--whether offspring need to
  inherit the defective gene from only one parent or from both to be affected, and whether the gene is
  passed from either or both sexes.
- Collect blood or tissue samples from all family members to isolate DNA and perform a comparative
  review of scientific literature to find any similar diseases described in other species. "If these
  comparative diseases have known genetic causes, this suggests a possible 'candidate' gene for the
  equine disease. An assay can be done to see if the gene is abnormal, then the gene would be sequenced
  to see if there is a mutation in the genetic code. If found, the mutation would be checked to ensure that
  it is consistently present in all the affected horses and consistently absent in the normal horses."
- If no candidate gene is suggested from other animal species, perform a genetic linkage analysis to look
  at the alleles (individual characteristics) of specific markers spread throughout all the equine
  chromosomes. "We look to see if alleles of key markers are consistently associated with the disease
  and not associated in normal horses. This provides an approximate location of the disease gene on the
  equine chromosomes."
- Study the human genome map, examine corresponding chromosomes in humans, and see if there are
defective genes that could produce the clinical signs seen in the affected horses. "These genes are then
selected and the genetic code sequenced to find a mutation. The equine genome map is now developed
to the point that linkage analysis can be performed in horses, and several groups are using this approach for PSSM, RER, and HERDA."--Marcia King

**Dominant, Recessive, What's the Difference?**

When you hear that a trait is dominant or recessive, does that confuse you? You're not alone. But it's not too complicated, and knowing how these diseases are passed can help you make breeding decisions that sidestep the problems entirely.

Many traits are controlled by a pair of genes; each single gene can be either dominant or recessive. If a dominant gene is present, it will be expressed (i.e., you will see that characteristic) regardless of whether the other gene is dominant or recessive. A recessive gene, however, is not expressed unless both members of the gene pair are recessive. The gene types are normally noted with capital letters for dominant traits and lowercase letters for the recessive version.

For example, let's say a brown eye color (written as "B") is dominant over blue (written as "b"). A horse would have brown eyes if he had either a BB (homozygous dominant, or having two copies of the dominant gene) or Bb (heterozygous, or having one dominant and one recessive gene) genotype, but he would have blue eyes if both copies of that eye color gene were recessive (bb, homozygous recessive).

The mating diagrams below show the outcomes of various crosses with recessive and dominant traits.--Christy West

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**RECESSIVE TRAITS**  
(example: Overo lethal white syndrome, or OLWS)

**MATING TWO CARRIERS (LlxLl)**

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- 25% normal (LL)
- 50% chance of carriers (Ll)
- 25% chance of an affected foal (ll)

**MATING A CARRIER TO A NORMAL HORSE (LlxLL)**

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- 50% chance of a normal foal (LL)
- 50% chance of carriers (Ll)
DOMINANT TRAITS
(example: Hyperkalemic periodic paralysis, or HYPP)

### MATING AFFECTED HORSES (NHxNH)

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- 25% normal (NN)
- 50% chance affected (NH)
- 25% chance of a severely affected foal (HH)

### MATING AN AFFECTED HORSE TO A NORMAL ONE (NHxNN)

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- 50% chance of a normal foal (NN)
- 50% chance affected (NH)