INDUSTRY-WIDE EFFORT BRINGS SOME CLARITY TO UNDERSTANDING THE INHERITANCE OF EARLY ONSET MUSCLE WEAKNESS

For the last couple of years, a new genetic condition known as early onset muscle weakness (MW) has been under investigation. First reported as recumbency by Dr. Chad Dechow of Penn State University, he observed that a genetic component was associated with calves who were unable to stand up or remain standing without assistance. Soliciting help from other researchers, a mutation was identified, located in the CACNA1S gene responsible for controlling muscle contraction, and traced back to the bull Southwind.

The evidence for this new undesirable genetic condition was very compelling and a gene test was soon developed by several genotyping labs. However, some troubling concerns quickly became apparent. The inheritance pattern of this trait came under question as several cows and two bulls with the homozygous lethal genotype showed little signs of muscle weakness.

Early haplotype tests had low accuracy due to the mutation being recent and located in a very common or popular haplotype. Validating the early research findings with traditional sources of information proved challenging as detailed information on calves is not routinely collected by farmers.

What was needed was an improved haplotype software program from USDA; lots of gene tests from dedicated breeders and breeding organizations; collection and assembling of the gene tests into a central database by Holstein Association USA; and sharing that data with the Council on Dairy Cattle Breeding (CDCB) and USDA-AGIL.

This industry-wide effort allowed the Holstein Association, breeders, researchers, and allied industry members to obtain the necessary information needed to determine if MW meets the criteria to be declared an undesirable genetic condition.

Improved accuracy

As of January 2024, over 12,000 gene tests are available for research and inclusion in the new haplotype software. Based upon these gene tests, the frequency of the deleterious allele in the Holstein breed is 5%. Although significant, with proper breeding practices and resolve, the incidence of MW will be rapidly reduced.

Haplotype tracking allows us to use a set of DNA markers to tag a specific chromosome segment and follow its inheritance over time. Given the large size of the cattle genome, the DNA markers are spaced about 40,000 base pairs apart. In the case of MW, the defective allele is located between two of these markers within a very common haplotype. The old software, with a limited number of gene tests, often had difficulty distinguishing the defective haplotype from the healthy one. When a clear answer wasn't possible animals were coded as suspect carriers or Code 3. The new haplotype results are more accurate. The percentage of Code 3 animals falsely labeled as "suspect" was reduced by 27%, providing more clarity for their owners.

Linking haplotypes on the millions of Holsteins participating in a genomic testing program with their phenotypic data provides a way to evaluate the severity of the MW defect.

The new data confirms that this disorder displays both incomplete penetrance and variable expressivity. This means that not all individuals who are homozygous for the MW defect are affected in the same way.

The trait Calf Livability measures the percentage of heifers alive at 2 days of age and surviving up to 18 months of age. The national average for Heifer Livability of Holsteins is 96%. Most heifers, who come through the birthing process alive

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and well, continue to survive. USDA researchers observed that 56% of heifers with a Code 2, confirmed homozygous for MW defect, did not survive to 18 months of age. The average age of death, for the Code 2 heifers who died, was 1.5 months.

Navigating challenges

The latest haplotype information also provides evidence of incomplete penetrance. With a completely lethal condition, one would expect few if any Code 2 confirmed homozygous heifers to be genotyped by their owners. An estimate of the penetrance is obtained by comparing the number of "missing" Code 2 heifers with the expected number. Our most recent year, i.e., heifers born in 2023, showed that 54% of the expected number of Code 2 heifers were missing. This latest measure of 54% penetrance is quite close to the earlier one of 56% by USDA.

The true level of penetrance is most likely higher. As some heifers would be genotyped or recorded into the DHI system at a very young age, prior to when some of them would be exhibiting severe MW symptoms. However, what is clear is that both studies illustrate a need to reduce the frequency of MW in the Holstein breed. Farmers need to avoid making carrier-to-carrier matings as it will often lead to an undesirable outcome. Recently, the World Holstein Friesian Federation (WHFF) defined a "high-penetrance variant as a variant that segregates in a Mendelian pattern and in which 50% or more of the carrier individuals develop features of the condition".

The exact cause of incomplete penetrance or why some animals exhibit varying levels of its onset and severity of muscle weakness is still not well understood. It may be partially explained by the action of, yet undiscovered gene modifiers and/or different environments or diets. Incomplete penetrance and variable expression are often seen with human diseases, where the same mutation is not always expressed in all individuals who carry it, nor is it always expressed in the same way. In Holsteins, another trait exhibiting incomplete penetrance is Cholesterol Deficiency. We routinely see Code 2 confirmed homozygous being genotyped. The highest year was 2013 with 69 heifers.

A review of the new haplotypes did uncover a problem in the current software whereby some gene tests were being overwritten by the haplotype result. The bug in the program was traced back to parent-progeny conflicts. This issue will be resolved by forcing the gene test to override the pedigree check in subsequent releases. Some genotyping labs will soon be incorporating the actual causative mutation for MW into their SNP chip. This makes the haplotype results 100% accurate and consistent with the stand-alone gene tests.

This latest review provides more evidence and support on the recent action taken by the Holstein Association USA Board of Directors to add Early Onset Muscle Weakness to the list of officially recognized genetic conditions in February 2024. Soon, we'll have MW in the rear view mirror as we move ahead with our genetic advancement of the Holstein breed.

Dr. Tom Lawlor
Executive Director of Research and Development, Holstein Association USA, Inc.

Starting in February 2024, direct gene test results for MW will be labeled on Official Holstein Pedigrees, and other products where officially recognized genetic conditions are displayed.

The following codes will be used to designate animals with official gene test results on file:

- **TE= tested free of MW**
- **MW= Heterozygous Carrier**
- **MW2= Homozygous Carrier**

Breeders can forward lab reports for MW test results to labresults@holstein.com to have them added to Holstein Association USA genetic conditions database.