WHFF Monogenetic Traits Working Group Report – May 2023

Current committee members: Lindsey Worden (WHFF Council representative), Alex Baranco, Laszlo Bognar, Christa Kuhn, Linda Markle, Tom Lawlor & Jiri Motyca

The Monogenetic Traits Working Group has had two videoconferences so far this year, on February 1 and March 10, 2023. A third meeting was desired to be held later in the spring, but WG members' travel schedules did not allow for documents to be updated and reviewed in a timely fashion or a meeting date to be selected. The WG will pick up these discussions again this summer.

Major topics discussed include:

1. **Selection of new chair** – As Linda Markle wished to step down as chair of this WG, a new chairperson must be selected. All of the committee members were asked if they would like to serve as chair, and nobody volunteered. As such, Lindsey Worden has agreed to serve as chair for the time being.
    a. ACTION: The WHFF Council must approve Lindsey Worden as new chair of the Monogenetic Traits WG.
2. **Discussion on classes of genetic traits** – With the evolution and adoption of genomic testing around the world, it is expected that new genetic conditions are going to come to light, and our current categorization system of recognizing traits has been determined to be inadequate. Below, you can see the proposal that the WG has been reviewing and discussing, the basis of which was written by Dr. Tom Lawlor. A similar version was seen by the WHFF Council at the October meeting, and the document has undergone revisions based on committee member feedback since that time. This document will be discussed thoroughly and hopefully finalized for approval by the WHFF Council at our next WG meeting, this summer.
3. **Information on BLIRD was reviewed and discussed.** The WG feels at this time that there has not been sufficient scientific documentation (such as published journal articles) presented on this trait to take further action on it at this time. It sounds like more evidence on this condition will be made available this summer, and at that time, the WG can decide on a course of action.
4. **A new potential undesirable genetic condition is being investigated in the United States, originally referred to as Calf Recumbency, and now being termed Early Onset Muscle Weakness Syndrome.** Holstein Association USA is currently working to gather more information on this condition, and it will be discussed at a future WG meeting to make a recommendation on further action.

These last three items will be discussed at length at the next Monogenetic Traits WG meeting, which will be held this summer (in June or July).

****DRAFT prepared by Dr. Tom Lawlor – May 2023****

WHFF guidelines for interpreting new evidence on potential monogenic traits.

WHFF is a federation of Holstein breed associations around the world. In this role, WHFF draws upon a pool of resources to review and evaluate the science and discovery of new genetic traits. Cooperatively they work to review the literature; evaluate the data's accurary and soundness of interpretation. WHFF harmonizes nomenclature, coding and descriptions of genetic traits; and helps ensure transparency and public disclosure of test results.

As genetic testing of humans and animals has increased more DNA sequence variants are being identified as potential monogenic markers. For example, the Online Mendelian Inheritance in Man (OMIM) database is a catalog of human genes, genetic disorders, and traits. As of 2022, there were over 6,000 monogenic diseases with more than 200,000 pathogenic variants described. This database is constantly being updated as the genetic basis of most of the rare disorders remains to be determined.

The scientific significance of any given sequence variant falls along a gradient, ranging from those in which the scientific evidence is complete and convincing to those where substantial uncertainty remains. It is important to keep in mind that inclusion on the WHFF Master List of monogeneic traits will lead to certain actions including a substantial change in the potential usage of an animal and their market value. Placing a genetic condition onto the WHFF Master List has severe consequences to international trade and commerce.

The WHFF has established the following guidelines whereby variants will be classified into five classes describing their phenotypic expression. A set of criteria (e.g., population, predictive, functional, and segregation data) is used to judge soundness of the evidence and the severity of the condition to determine its eligibility for inclusion on the WHFF Master List of monogenic traits.

WHFF Classes of genetic traits:

Class 1 — Traditional: Traits with distinctive characteristics

- Breed characteristics: such as Color, horns, etc.
- Physical deformities: such as Complex Vertebral Malformation (CVM), Brachyspina (BY), etc.

Class 2 — Haplotypes Impacting Fertility

- Embryonic death due to a genetic variant causing loss-of-function
- 90% or more of the associated deaths associated occur prior to birth
- Examples: HH1, HH2, etc.

Class 3 — Desirable traits

- Examples: variants associated with beneficial cheese making properties, improved digestibility eg. A2, certain kappa casein alleles, etc.

Class 4 Reduced Fitness and Health

- Non-specific: Poor health, lack of vigor, etc.
- Late onset: Vision loss, heart malformations

Class 5: No Known Impairment

- Impact on production, reproduction or health is little to none.

Genetic traits included in Classes 1, 3 and 4 must meet or exceed the WHFF criteria for being added to the WHFF Master List. Traits, that qualify, will be identified by a three-letter expression code, e.g. MFC = tested carrier of Mule foot. Class 2 traits, categorized as haplotypes impacting fertility, will also need to meet or exceed the WHFF criteria for being added to the WHFF Master List. Their expression code follows the international rules of sequentially numbering each new haplotype as they are added to the WHFF Master List. Class 5 genetic traits do not qualify for inclusion in the WHFF Master List.

Rules for inclusion on WHFF Master List and the appropriate expression code:

Class	Master List	Expression Code
1	Must meet criteria	Three-letter code
2	Must meet criteria	Follows haplotype nomenclature, HH1, HH2, etc.
3	Must meet criteria	Three-letter code
4	Must meet criteria	Three-letter code
5	No	None

Criteria to be used in determining if a new genetic trait should be added to the WHFF Master List.

1. Frequency of defective variant to be greater than 5% in 2 or more countries.
2. Description and location of the variant must be provided.
3. Diagnostic SNP(s) should be included on one or more of the commercially available SNP Chips.
4. Explains 5% or more of the genetic variation for a polygenic trait such as health or production.
5. Acts independent of environmental conditions.
6. Free of epistasis, i.e., acts independent of other genes.
7. High penetrance, a “high-penetrance” variant is defined as a variant that segregates in a Mendelian pattern and in which 50% or more of the carrier individuals develop features of the condition.

Genetic traits not meeting the above criteria will be deemed as **Under investigation.** This would allow each country, region, or group of researchers to construct a list of U haplotypes that they are investigating or monitoring. For example, the U.S Holstein population is currently monitoring 32 monogenic conditions, where the anomaly is not at a high enough frequency, lacks a complete genetic profile or its severity does not warrant the notification of the respective international breed association. If one of these HU haplotypes, e.g. HU21, increased in frequency or other information became

available so that it now meet the criteria to be added to the WHFF Master List, haplotype HU21 would be sequentially submitted to WHFF for further review. If it met all WHFF criteria, it would be added as HH7 or the next appropriate sequential number.

Haplotypes Under Investigation may be further categorized by the amount of evidence pointing to a monogenic form of inheritance, for example, conservative or weak. In the case of a haplotype with conservative evidence, although there may be a lack of sufficient evidence about its mode of inheritance and functional behavior, there may be enough evidence to warrant the sharing of the genotypes as it directly pertains to the risk of an animal suffering from an undesirable genetic condition. Designating a new genetic variant as having conservative evidence may allow for further and quicker collection of phenotypic data from the industry. For example, owners of young recumbent animals would be more inclined to genotype them if they knew they would receive back a diagnostic result on a suspected genetic condition.

Publication

All countries are encouraged to publish the WHFF three-letter expression code close to the animal's name on all official documents. WHFF recognized haplotypes should be made publicly available and easily obtained on all animals. Information on animals for genetic traits under investigation can be handled in two ways:

HU with Conservative Evidence: genotypes of HU conditions may be sent to the owner of the animal. This information can be used for diagnostic purposes, but publication of individual results is strongly discouraged.

HU with Weak Evidence: will not be publicly displayed nor will they be included in the routine reporting of genomic information to the owners. Genotypes with HU with Weak Evidence will be kept on file by the national genetic evaluation center, the respective breed association and/or the genotyping lab and only made available to qualified researchers upon formal request.

Conclusions:

In our rapidly evolving world, WHFF needs to be adaptive to new and more information coming from genomic research. Recently, our Class descriptions of Monogenic traits have been updated and criteria for inclusion in the WHFF Master List has been initiated.

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Example of WHFF guidelines for a new trait (XXXX) with limited information:

Currently, there is not enough information to declare XXXXX as a WHFF monogenic trait. However, we should work to collect more information and resolve outstanding questions. We're recommending that genetic test results on XXXXX be identified as a Haplotype Under Investigation with conservative evidence. This would be the first genetic condition identified as such and made available for public release. Therefore, genotype information related to XXXXX should be labeled as **HU1**. It's recommended that **HU1** genotype test results be sent to the owner of the animal as a part of the routine genomic test results. **HU1** test results should utilize the same interpretation

codes as previously established for haplotype information (Table 1). **HU1** test results can be used for diagnostic purposes, but publication of individual results is strongly discouraged.

HU1: **H**aplotype **U**nder Investigation Number **1**	
Code	Interpretation
0	Tested Free / non-carrier
1	Tested Carrier / Heterozygous / Confirmed with pedigree info.
2	Tested Homozygous / Confirmed by both sides of pedigree
3	Unconfirmed / Status of one suspected haplotype could not be confirmed.
4	Unconfirmed / Status of two suspected haplotypes could not be confirmed.