

# Discovering Genetic Anomalies from Genotyping

Genotyping a single animal has direct advantages in terms of providing a genomic evaluation for genetic selection and mating as well as confirming its parentage for herdbook integrity. Accumulating thousands of genotypes for a population of animals in a breed has become an excellent source for identifying various genetic anomalies, which are usually undesirable. Although the discovery of an undesirable gene in a breed is initially viewed negatively, the new knowledge provides an opportunity to monitor the frequency over time and eventually eradicate it from the active population, especially among A.I. sires.

## Haplotypes Impacting Fertility

Due to the growth of genotyping in North America since it began in 2008, the Canadian Dairy Network (CDN) database now includes over 800,000 Holstein genotypes and more than a million across all dairy breeds. This extensive database of DNA profiles allows scientists to follow the transmission of short sections of DNA strands, called haplotypes, from parent to progeny across generations. To date, given the number of genotyped animals in each breed, various “Haplotypes Impacting Fertility” have been identified including five in Holsteins (HH1 to HH5), two in each of Jersey (JH1 and JH2) and Brown Swiss (BH1 and BH2) and one in Ayrshires (AH1). The impact of these haplotypes in each breed, which generally cause early embryonic death, depends on the frequency of the associated gene in the population and especially the percentage of active A.I. sires that are carriers. Any negative impact of these genetic anomalies can be eliminated by avoiding the mating of carrier sires to carrier heifers and cows, which is best achieved using computerised mating programs offered by A.I.

## New Holstein Haplotype Discovered

Very recently, a group of research scientists in Germany discovered a new haplotype in the Holstein breed. Unlike the previously found “Haplotypes Impacting Fertility”, this particular genetic anomaly was found to be associated with calf survival in the first months of life. For calves that inherited the undesirable gene from both parents, it was found that they had an increased incidence of chronic/prolonged diarrhea that was untreatable, as well as other illnesses. Examination of blood samples from affected calves showed a cholesterol deficiency that prevented the normal deposition of fat in body tissues. Over the course of months after birth, the affected calves lost all body reserves and it appears that all eventually died.

In an attempt to identify the specific gene responsible for this newly identified genetic anomaly, the German scientists were successful in showing the inheritance pattern and the gene location being on chromosome 11. While the specific gene has not yet been located, a short series of SNPs, referred to as a haplotype, has been identified that is consistently present in the genotypes of carrier animals. Pedigree analysis of carriers has shown they all trace back to Maughlin Storm, born in 1991, as the oldest common genotyped sire. The popularity of Storm, as well as several of his outstanding sons and grandsons that are carriers, eventually spread the associated gene to many Holstein populations globally, which explains this discovery in Germany. Since the negative impact of this genetic anomaly, namely early calf death, only happens for calves that inherit the gene from both parents (i.e.: two descendants of Storm mated together), it takes multiple generations of breeding to discover.

## A Complicating Factor

Unfortunately, without having an exact gene test for this genetic anomaly, determining the carrier status can be complicated for some animals. The haplotype identified in Storm and his carrier descendants also exists in Willowholme Mark Anthony (born in 1975) but he does not carry the specific undesirable gene. The presence of the common haplotype stems from the fact that Mark Anthony's sire, Fairlea Royal Mark, is also the great maternal grandsire of Storm. It appears that somewhere in the transmission of genes from Fairlea Royal Mark down through the three generations to Storm a form of mutation occurred that caused this genetic anomaly. Without knowing the exact gene, the only tool available for identifying carriers is by using the defined haplotype. This means, however, that animals with both Storm and Mark Anthony in their pedigree may have the defined haplotype but could be falsely identified as a carrier of the responsible gene. Table 1 provides a list of the A.I. sires that are known carriers of this undesirable gene and have more than 5,000 registered daughters born in Canada to date. An animal with any of these sires in its pedigree may also be a carrier and genotyping such animals will help to clarify the carrier status.

Table 1: HCD Carrier Sires with over 5,000 Registered Daughters Born in Canada		
Relationship to Maughlin Storm (HOCANM5457798)		
Sons	Grandsons	Great Grandsons
PURSUIT SEPTEMBER STORM	BRAEDALE GOLDWYN	GILLETTE WINDBROOK
COMESTAR STORMATIC	GILLETTE FINAL CUT	COMESTAR LAUTHORITY
HARTLINE TITANIC-ET	DUDOC MR BURNS*	GILLETTE STANLEYCUP
LADINO PARK TALENT-IMP-ET	KERNDT STALLION	LIRR DREW DEMPSEY
		COMESTAR LAVANGUARD
		GOLDEN-OAKS ST ALEXANDER-ET
		GILLETTE WINDHAMMER

*\* Dudoc Mr Burns carries the haplotype with the undesirable gene from Storm as well as the haplotype sourced through Mark Anthony. Therefore, genotyping his progeny will not lead to conclusive results about the carrier status of the undesirable gene.*

## Carrier Probability Values

Since the initial discovery of the first "Haplotypes Impacting Fertility" CDN has been calculating and publishing "Carrier Probability" values for every animal in the CDN database. Regardless of the breed, the haplotype Carrier Probability values are displayed on the "Pedigree" link from each animal's "Genetic Evaluation Summary" page on the CDN web site ([www.cdn.ca](http://www.cdn.ca)). A displayed probability of 99% identifies animals that are expected to be "Carrier" while a value of 1% indicates they have been identified as "Free" based on the haplotype analysis. Animals not genotyped receive an estimated Carrier Probability that can vary from 99% to 1% depending on the probability values for its parents and other relatives.

In North America, this newly discovered haplotype in Holsteins will be labelled as HCD, meaning "**H**aplotype associated with **C**holesterol **D**eficiency". CDN has developed methodology for assigning a Carrier Probability value for HCD based on existing genotypes as well as tracking the source of the undesirable haplotype through pedigree analysis. This strategy allows some genotyped animals that have both Storm and Mark Anthony in their pedigree to be properly identified as "Carrier" or "Free" but for other animals, where this distinction is not possible, a Carrier Probability between 99% and 1% will be published by CDN.

## Summary

In addition to genomic evaluations and integrity of pedigrees, accumulating thousands of genotypes for a given breed results in the discovery of new genetic anomalies. Scientists in Germany recently discovered a new "**H**aplotype associated with **C**holesterol **D**eficiency" (i.e.: HCD) in Holsteins, which traces back to Maughlin Storm as the oldest genotyped sire of origin. Without the presence of an exact gene test to identify carriers, the current haplotype analysis

can result in some animals being falsely labelled as a carrier if they have both Storm and Willowholme Mark Anthony in their pedigree. The methodology used by CDN to calculate the HCD Carrier Probability values (varying from 99% for “Carrier” to 1% for “Free”), reduces this problem by combining the haplotype test with pedigree analysis. Now that this undesirable anomaly is known, an industry effort can easily be made to reduce the frequency that carrier animals are mated together, thereby lowering the frequency that homozygous calves are born and subsequently die within months. The discovery of this genetic condition also demonstrates the value and importance of producers reporting to DHI the date and reason for every animal leaving the herd, including young calves.

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