Harmful haplotypes in dairy cattle

Technote 16

HIGHLIGHTS

- Haplotypes (or genetic mutations) that have undesirable effects have been identified in several breeds of dairy cattle. Several affect fertility and calf health.
- Haplotypes are breed specific and those available are published on DataVat.com.au
- Managing inbreeding (to avoid mating carriers) is important strategy to reduce the impact of harmful haplotypes.

The study of haplotypes is relatively new as it's been made possible by advances in genomic technologies in the past 15 years.

A haplotype is a stretch of DNA (containing one or more genes) that is inherited intact or as a block from a single parent. Because of their genetic origin, haplotypes are breed-specific.

Also referred to as genetic mutations, haplotypes may have desirable or undesirable effects on specific traits; for example, there is a haplotype for polledness.

Examples of haplotypes with undesirable effects include several that affect fertility in Holsteins and Jerseys. In addition, researchers have detected haplotypes associated with cholesterol deficiency (HCD), early onset muscle weakness (HMW), lymphocyte defect (BLIRD) in Holsteins as well as Jersey neuropathy (splayed limbs).

Haplotypes on DataVat

The haplotype status of animals can be looked up on DataVat.com.au or on the Good Bulls App. There is a search function under "Reports and Tools" that allows you to find haplotype results for tested animals.

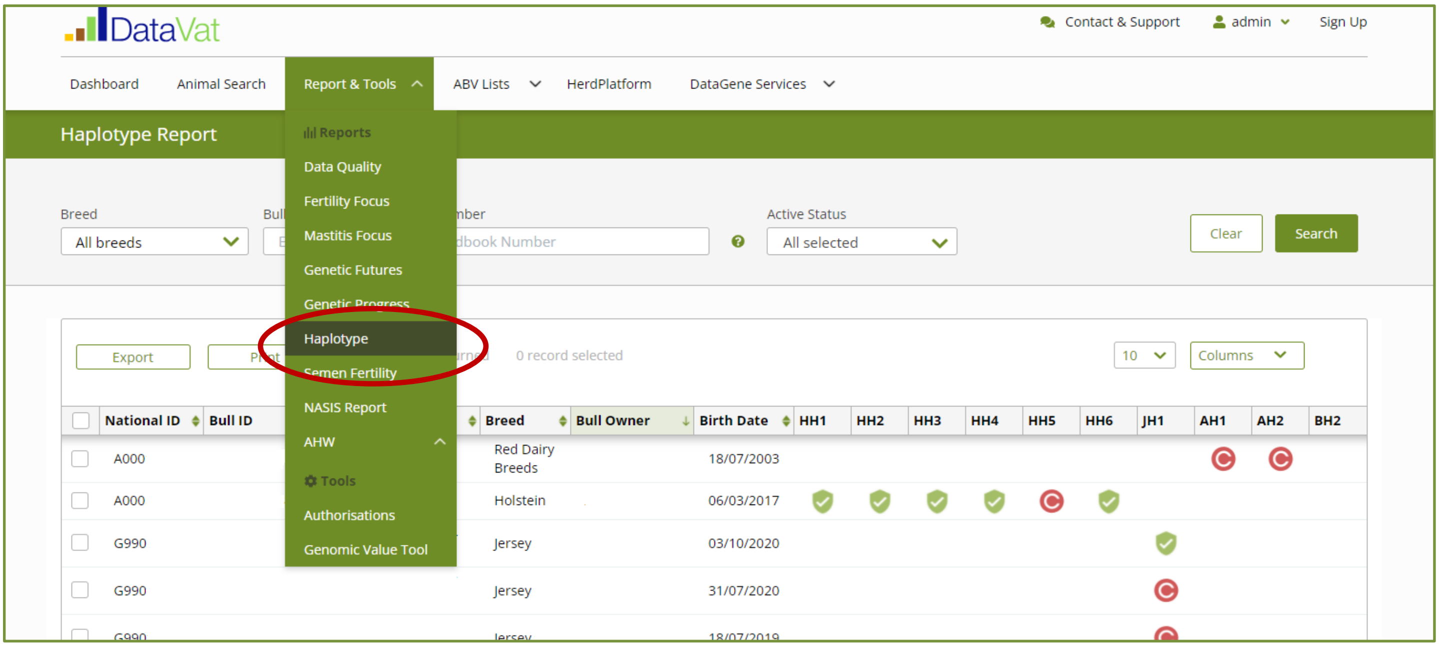
The haplotype information is based on CDCB calls on bulls, updates from bull companies, information provided by genomic service providers, or DataGene calls based on the genotype received. Female haplotypes will only come from the last two sources.

Implications for your breeding program

Attempting to eradicate every animal with an undesirable genetic mutation is not recommended because these animals may carry desirable genes for other traits. Also, it is not practical because it is likely that more undesirable genetic mutation will be found in further investigations.

The use of inbreeding reports is a very important risk management strategy. Where haplotypes are known for your cows and potential bulls, mating programs can be used to avoid haplotype carrier to carrier matings.

In the case of fertility haplotypes, the Daughter Fertility Australian Breeding Value (ABV) remains the most useful tool for selecting bulls to improve fertility. The Daughter Fertility ABV captures the effect of all genes affecting fertility, not just the ones tracked by the haplotypes.



Eary Onset Muscle Weakness

Early onset muscle weakness is a calf recumbency affecting Holsteins where otherwise healthy animals are unable to stand at birth or lose the ability to stand shortly after birth. Most calves do not survive beyond six weeks of age but a few recover. Given the animal welfare implications, farmers may euthanise affected calves. Similar symptoms in calves have been reported by dairy farmers in Australia and overseas since 2021. It was first reported in scientific literature by Dechow et al. in 2022. So far, Holsteins are the only dairy breed affected.

There are two types of testing available. One is a reliable gene test which has been used by bull companies to test their bull teams. The second test is a haplotype test that can identify probable carriers in genomically tested animals.

Since December 2023, DataGene's counterpart in the US, the CDCB, has included this haplotype in its genetic evaluations. Animals are reported as either:

- Noncarrier
- Carrier (1 copy of the recessive haplotype)
- Probable carrier
- Homozygous (2 copies of the recessive haplotype)
- Probable homozygous

At the time of publishing, early onset muscle weakness was not reported on DataVat either as a haplotype or a genetic condition. DataGene is working with bull companies and its counterparts overseas to report the haplotype status as soon as possible. Contact bull companies for information relating to individual bulls.

Read more

DataGene Fact Sheet: Early onset muscle weakness

Recumbency in Holstein Calves, CDCB industry statement April 2023

Understanding recumbency in Holsteins calves: Genex update (April 2023)

Dechow, C.D et al (2022) Identification of a putative haplotype associated with recumbency in Holstein calves, Journal of Dairy Science Communications 2022; 3:412–415

Al-Khudhair, A. et al (2024) New mutation within a common haplotype is associated with calf muscle weakness in Holsteins, Journal of Dairy Science Volume 107, Issue 6, 3768 - 3779

Fertility haplotypes

In dairy cattle, fertility haplotypes have been identified that involve a recessive mutation. If an animal inherits the recessive mutation from both parents, the effect is lethal, causing early embryonic loss or stillbirth. This translates to apparent reduced fertility of the parents that carry the associated haplotype.

At the end of this Tech Note is a quick overview of the principles of genetic inheritance which may be useful background.

Genes affecting fertility

Daughter Fertility is a very complex trait and is influenced by many genes, found on a variety of chromosomes. The Daughter Fertility Australian Breeding Value (ABV) accounts for all the genes influencing dairy cow fertility.

Haplotype genes

Unlike daughter fertility, the genetics of lethal haplotypes is relatively simple, involving a short stretch of DNA located on the same chromosome. Although the actual mutation within each haplotype is not always known, gene markers can pick up the presence of the haplotype in the animal's genome with high accuracy.

Lethal haplotypes

The lethal effect of haplotypes is expressed only in homozygous recessive individuals. Because these individuals die as embryos, none are found in the live animals when genotyped.

Let's use the example of the Holstein haplotype HH1. The progeny from a mating between a carrier sire and a carrier dam will result in the following combinations (Figure 1):

- Homozygous non-carrier (HH): 25% of progeny
- Heterozygous carrier (Hh): 50% progeny
- Homozygous recessive – lethal (hh): 25% of progeny, lost as embryos.

Example mating between heterozygous haplotype carriers

		Carrier Sire Heterozygous	
		H	h
Carrier Dam Heterozygous	H	HH	Hh
	h	Hh	hh (lethal)

Impact of haplotypes on fertility

Haplotypes explain a very small amount of the variation in dairy cattle fertility. Currently, they occur at such a low frequency in Australian dairy cattle that their impact on overall conception rates is minor.

A carrier (sire or dam) can still have daughters that are more fertile than the national average because they carry other good genes that affect fertility. A good example of this is the Holstein bull 7H6417 commonly known as "Oman". This bull had an enormous effect on daughter fertility globally and still has a Daughter Fertility ABV of 115. He is also a carrier of the HH1 haplotype.

Overall, the effect of the haplotype at a population level will depend on the frequency of the carriers in the population.

Semen fertility
The impact of the fertility haplotypes on a carrier bull's semen fertility will be determined by the frequency of the haplotype in the general population. In general, bulls carrying haplotypes will have slightly lower semen fertility because half the embryos produced will inherit the lethal mutation from the bull and, if they inherit another copy from their dam, the embryo will die, and the mating will be recorded as a failure.

Breed differences

Lethal haplotypes affecting fertility are breed specific. They have been identified in many dairy breeds, including Holsteins, Jerseys, Ayrshires and Brown Swiss.

The table below lists fertility haplotypes most relevant to Australian dairy herds.

Haplotypes affecting fertility of relevance to Australia	
Holstein	HH1, HH2, HH3, HH4, HH5, HH6
Jersey	JH1
Ayrshire	AH1, AH2
Brown Swiss	BH2

Haplotype frequency

Van den Berg et al (2024) published the frequency of carriers in Australian Holsteins and Jerseys (see table).

Haplotype frequency in the Australian female population			
Breed	**Haplotype**	**Chromosome**	**Frequency %**
Holstein	HH1	5	1.5%
	HH2	1	1.8%
	HH3	8	3.7%
	HH4	1	2.3%
	HH5	9	4.8%
	HH6	3	1.1%
Jersey	JH1	15	8.1%

Impact on actual fertility

The impact of haplotypes on fertility depends on the frequency of the particular haplotype within the dairy population.

Where the frequency is low (for example 1%), the semen fertility of carrier bulls is predicted to be reduced by about 0.13% (see box). The conception rate of the daughters of carrier bulls is predicted to be reduced by half this (0.07%) because about half the daughters would themselves be carriers.

In cases where the frequency is higher, say 6.5% the semen fertility of carrier bulls is predicted to be reduced by 0.8% and the conception rate of the daughters of carrier bulls was predicted to be reduced by 0.4%.

Acknowledgement

Calculating impact of haplotypes on semen fertility

The impact of a haplotype on semen fertility is influenced by the frequency of the haplotype, conception rate (assume 50%) and the chance of inheriting the haplotype (one in four).

$$\frac{\text{Haplotype frequency} \times 0.5}{4}$$

Example low frequency

$$\frac{1.0 \times 0.5}{4} = 0.13\%$$

Example high frequency

$$\frac{6.5 \times 0.5}{4} = 0.8\%$$

Updates to haplotypes have relied on work undertaken by DairyBio researchers. DataGene also acknowledges the help and support of the CDCB and bull companies for use of their data.

DairyBio is a joint initiative between Agriculture Victoria, Dairy Australia and the Gardiner Dairy Foundation. Thanks also to the farmers who provide tissue samples from affected calves and software providers for data used in genetic research and evaluations.

References

1. van den Berg I 2024 Imputation accuracy and carrier frequency of deleterious recessive defects in Australian dairy cattle *J Dairy Sci*

Inheritance basics

Simple inheritance traits

Simple inheritance traits are traits largely controlled by one major gene. These are ‘yes’ or ‘no’ characteristics that are either present or absent in an animal. In some cases, simple inheritance traits may involve more than one gene however the pattern of inheritance remains fairly simple. Testing for these genes allows breeders to effectively select for or against the trait/disease.

Dominant vs recessive?

Most simple inheritance traits can be divided into either ‘dominant’ or ‘recessive’. We’ll use coat colour as an example. The dominant gene is black (B), and the recessive gene is red (b).

Animals carry two copies of every gene – one is inherited from the dam and the other from the sire. The different variants of a gene are known as alleles (in this example, the alleles are for black or red coat colour).

The combination of alleles determines how a trait is expressed. Where the allele controlling a trait is dominant the animal only requires one copy for that trait to be expressed. Conversely a recessive trait requires both alleles (one from each parent) to be expressed.

Example mating between heterozygous coat colour

		Sire Heterozygous black	
		B	b
Dam Heterozygous black	B	BB	Bb
	b	Bb	bb

Allele combinations are be described as either:

- Heterozygous: one allele is dominant and one recessive (Bb). In the case of coat colour, this will be expressed as a black coat because black is the dominant gene)
- Homozygous: both alleles are the same eg BB, bb), In the case of coat colour, a homozygous dominant animal (BB) will have a black coat while a homozygous recessive animal (bb) will be expressed as a red coat.

Simple maths can be used to predict the proportion of offspring with a particular trait. In the following example both parents are heterozygous black (Bb) ie they are black cattle who carry both the black and red alleles.

When these two animals are mated there are three possible outcomes:

- Homozygous black calf (BB): 25% of progeny,
- Heterozygous black calf (Bb): 50% progeny
- Homozygous red calf (bb): 25% progeny

Multi-gene traits

Multiple gene traits are controlled by a larger number of genes. This group includes many economically important traits such as daughter fertility and kilograms of protein. In these cases, Australian Breeding Values (ABVs) are used to identify superior/inferior animals as it much more difficult to clearly identify animals with the favourable variants of each gene.

Haplotype inheritance

While overall daughter fertility is a multi-gene trait, recessive haplotypes affecting fertility are controlled by specific genes, so the principles of simple inheritance can be applied.

More information

Ph 1800 841 848
E: enquiries@datagene.com.auu
www.datagene.com.au.

Updated October 2024

About DataGene

DataGene is an independent and industry-owned organisation responsible for driving genetic gain and herd improvement in the Australian dairy industry. DataGene performs pre-competitive herd improvement functions such as genetic evaluation, herd testing and herd improvement software development and data systems. DataGene is a Dairy Australia and industry collaboration.

www.datagene.com.au Ph 1800 841 848 E: enquiries@datagene.com.au