

## Haplotypes & Fertility: Common Sense

Genomic predictions have proven to be a great tool for the AI industry, and the dairy industry in general. With genomics we have “turned the cow inside out” and can look at the actual genes inherited that have an impact on overall genetic merit. For example, we have found SNP’s that increase milk production, while we have also found SNP’s that decrease milk production. With this exciting tool we can make progress much more quickly because we discover good and bad parts of the genome.

### What is Discovered?

Recently, USDA-AIPL discovered 5 new Haplotypes (a group of SNP’s inherited together) that exist normally as Heterozygotes but do not exist as expected in one homozygous form, thus having a negative effect on fertility. These haplotypes will be called **HH1** (Holstein Haplotype 1), **HH2** (Holstein Haplotype 2), **HH3** (Holstein Haplotype 3), **JH1** (Jersey Haplotype 1), and **BH1** (Brown Swiss Haplotype 1). These groups of SNP’s do not exist in one homozygous state, but exist normally in the heterozygous form. The inheritance of these Haplotypes is very similar to Black and Red coat color.

### Key Points:

- *New haplotypes for HO, JE, and BS have been discovered.*
- *When heterozygote animals are mated together, an overall reduction in CR of ~4% in CR for these animals (example 33% - 29%)*
- *ConceptPlus and DPR evaluations already include this effect in the published sire proof.*
- *Pedigree mating with AltaMate is an effective tool to manage and/or minimize impact in your herd.*
- *The economic value of a sire should still be judged on total genetic merit relative to your genetic plan.*

### Definitions:

Haplotype: The simplest ‘Haplotype’ is an individual SNP, but ‘Haplotype’ generally refers to a group of SNP’s that are always inherited together.

Homozygote: This is the definition of an animal that got the same gene, Haplotype, or SNP from both sides of the pedigree. In coat color, we would say that “RR” would be homozygous black, and ‘rr’ would be homozygous red.

Heterozygote: This is the definition of an animal that got a different gene, haplotype, or SNP from both sides of the pedigree. In coat color, we would say that “Rr” is the heterozygote.

For simplicity, a simple example is shown below. Although a haplotype is a group of SNP’s inherited together, the mechanism of inheritance is the same as coat color. Each cell in the table is an outcome of a mating and each outcome has a 25% (divide by 4) chance of occurring. Pregnancies are either not created or suffer early pregnancy loss in only one of the two homozygous states.

Coat Color Example

	R	r
R	RR (Homozygote-Black)	Rr (Heterozygote)
r	Rr (Heterozygote)	rr (Homozygote-red)

Haplotype Example

	A	T
A	AA (Homozygote)	AT (Heterozygote)
T	AT (Heterozygote)	<b><u>Does not exist</u></b>

In this example the one homozygote (TT) does not exist because no sustainable pregnancy can exist, however both heterozygotes (AT) are completely normal. Although the inheritance is similar, these haplotypes are not considered recessives because no specific gene mutation has been found and calves are never born alive. Conception rates are the only affected trait by this discovery.

Putting this new finding into perspective, heterozygotes of each of the three Holstein Haplotypes have a frequency of between 4.5 and 4.7% in the population today, which means if a heterozygote bull was used randomly across an entire population, the impact on conception rates would be ~0.4% - a very small impact compared to normal variation between animals.

It is important to recognize these are all separate haplotypes and mating a heterozygote of different haplotypes has no impact whatsoever. For example, mating a bull which is a heterozygote of HH1 with a cow which is a heterozygote for HH2 will result in no reduction in fertility, as each Haplotype functions independently.

### What is the Effect on Genetic Evaluation?

With no calves born, and only an effect on fertility, the impact of these haplotypes is limited to sire fertility (ConceptPlus) and Daughter Fertility (DPR). As noted above, when heterozygotes are mated together, 25% of time a pregnancy will not occur. Fortunately, published proofs for DPR and ConceptPlus include these matings and therefore the published evaluation used to market Alta sires ALREADY reflects the genetic merit of both homozygote and heterozygote bulls. Therefore, this discovery will not have an affect beyond what is already officially included in an animal's proof.

### Haplotypes on Alta's Marketing Sires

All studs in the industry are affected by the discovery of these haplotypes. Known Marketing List sires from Alta and other popular sires which are heterozygotes are reported in the table below. The list is not comprehensive, and a complete list will be sent out after August evaluations.

	Marketing Sires	Other Popular Sires (not comprehensive)	Original Heterozygote
HH1	AltaSUEDE AltaCONSORT AltaFELIX	AltaFINELY AltaYANKEE AltaTHRONE AltaAARON AltaFORMATION Morty Leadman Marion Marsh Fortune	Pawnee-Farm Arlinda Chief
HH2	AltaASIDE AltaBAYSIDE AltaSLOAN AltaAZZURRI AltaRIC-RED	AltaROXSIDE Outside Million Colby	Willowhome Mark Anthony
HH3	AltaROSS AltaOMAX AltaMAXLIFE AltaROLLIN AltaJUPITER AltaCHAIRMAN AltaCONCISE AltaCANDOR AltaSAMOA AltaGENESEEE	Oman O-style Bogart Logan Bronco Hayden Junction	Glendell Arlinda Chief Gray-View Skyliner
JH	CELEBRITY LENCREST FOREST CARL	Sooner Beretta Hallmark Doc	Observer Chocolate Soldier

	SUNDANCE JESTER CARRIER FREEZE ARON CLEM VICTOR KARBALA	Legal Jace Valentino	
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Note: With OMAN being a heterozygote for HH3, the percentage of heterozygotes in top bull lists is approximately 20%, much higher than the average in the population.

### What Makes Common Sense?

Certainly it is easy to over-react this discovery – but that makes no common sense. We must realize that we are talking only about one small part of the genome. We can't forget about the rest of the genes an animal may have! You don't choose to buy a house because you love the front door; rather it is whole home that is important. Same for genetics – seeing the complete picture of value is critical.

With the effect of these haplotypes showing up in CP and DPR, we can see many examples of homozygotes that are not as good as heterozygotes for these traits! Consider the following example: AltaROSS is a known heterozygote for HH3 – yet he has a DPR of +2.0 and a CP rating of 5-stars! Meanwhile AltaOLIVER is a homozygote for all three Holstein Haplotypes and yet has a CP rating of 3-stars (average), and a DPR of -3.4. This is clearly an example where AltaROSS has superior genome at other locations which more than compensate for this small region where he is a heterozygote.

	DPR	ConceptPlus
AltaROSS	2.0	5-star
AltaOLIVER	-3.4	3-star

While AltaROSS has a comprehensive group of genes that add more for both sire and daughter fertility, AltaOLIVER has other traits which he excels in – like production. These bulls are just one case example drawn from many others available. Hundreds of other haplotypes exist that have negative effects on traits like production, type, SCS, longevity, etc., and some likely have greater economic impact than the five haplotypes reported. Therefore, all animals transmit undesirable haplotypes. Genomics allows us to find those animals that transmit the most desirable haplotypes for the combination of all traits, while minimizing those that have negative impact. The point is single trait selection was never our strategy before the discovered haplotypes – and they should not be after.

### Effectively using this new information

The challenge that we now face as an industry is what to do with this new information that genomics has provided. We learned long ago that single-trait selection resulted in decreased genetic gain in other traits, and that multiple-trait selection indexes resulted in the most economic gain from genetic selection. Genomics has taught us that the traits that we select for are controlled by many SNPs and haplotypes, with no single SNPs or haplotypes having major economic impact. GPTAs are an accurate and comprehensive summary of the effect of ALL haplotypes, combined into a single figure for each trait.

In the past, we found an undesirable genetic recessive, such as BLAD or CVM, every five years or so, and chose to eliminate these genes from the population. And we could take that route without a significant penalty on genetic gain, since these were few and far between. Genomics has changed that, however. The first genomic research has discovered five haplotypes that affect fertility, with more under current review. As we go to higher density genomic tests, we will find more haplotypes that affect fertility. And we know that all animals have haplotypes that have negative economic impact. It will be impossible to eliminate all haplotypes that have a negative effect, so the key is to

use this information to our advantage, and there exists a big opportunity with this finding with the use of AltaMate!

We know 25% of heterozygote matings have no chance to result in sustained pregnancy. Therefore the use of AltaMate for pedigree mating is highly recommended for those customers with complete and accurate identification, as AltaMate considers a comprehensive pedigree analysis to avoid any possible heterozygote matings. For those herds without sire identification, the use of heterozygotes should carefully be evaluated as part of each dairies genetic plan such that possible heterozygote matings can be avoided – in some cases to the extreme that heterozygote sires should not be used.

### **The Alta Mission: Create Value, Build Trust, Deliver Results**

Alta's strategy remains unchanged with this new information, as we strive to provide the highest level of both fertility and genetic merit to our customers. To do that, we must consider a comprehensive view of the entire genome to get the best measure of genetic merit – including, but not limited to fertility traits. We will continue to evaluate sire fertility through our own internal ConceptPlus measurement, and encourage all our customers and partners to keep good accurate identification, as an important part the ability to maximize genetic progress in your herd. Finally, we encourage all producers to use AltaMate to prevent matings of heterozygotes mentioned above, limit inbreeding, and prevent matings of previously discovered lethal recessive traits such as Brachyspina (BY), CVM, and others.

The excitement in our industry remains the same. Genomics has given us new to tools to work with the best genetics, and manage or eliminate the bad. Menatime, we have a lot of genetic improvement yet to be made and results to deliver our clients. It is predicted an animal with all the most desirable SNP's could have a NM\$ on today's base of >\$4,000! And we are staying focused on leading the industry in bringing this kind of exciting value to our progressive clients.

#### **Haplotypes & Creating Value for JERSEY dairies**

While JH1 functions exactly the same as the three Holstein Haplotypes, the incidence rate in the breed is different. It is estimated that approximately 23% of the Jersey breed is a heterozygote for JH1, as the popular sires SOONER and BERETTA were both heterozygotes.

Therefore the reduction in conception rate by using a heterozygote bull across a random sample the entire population is more substantial – yielding a reduction in conception rates by 2.2%.

While this is a much larger impact, it is still relatively small compared to normal variation between animals for sire and daughter fertility. AltaMate becomes an even more important tool for Jersey's, and consideration should be given to selection of homozygotes for any animals without known pedigree status.