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Changes to evaluation system (August 2013)

New fertility and stillbirth haplotypes and changes in haplotype status

By Paul VanRaden, Dan Null, Jana Hutchison, and Tabatha Cooper (AIPL-USDA)

Several changes were introduced regarding recessive factors affecting fertility and stillbirth. Four new haplotypes HH4, HH5, BH2, and AH1 were discovered within the Holstein, Brown Swiss, and Ayrshire breeds, respectively. The loss-of-function (LOF) mutation within Jersey haplotype 1 (JH1) is now tested directly, and the LOF mutation within Holstein haplotype 3 (HH3) was discovered. Haplotype tests for Bovine Leucocyte Adhesion Deficiency (BLAD), Complex Vertebral Malformation (CVM), Deficiency of Uridine Monophosphate Synthase (DUMPS), Mulefoot, Weaver, Spinal Dismyelination (SDM), and Spinal Muscular Atrophy (SMA), Red hair color, and Polled were developed and reported. Specific information on each of these changes follows.

The HH4 carrier frequency is 7.2% in France (Fritz et al., 2013 PLoS ONE 8:e65550), but is only 0.7% for Holsteins genotyped in North America. The earliest known carrier bull is FRA4486041658 Besne Buck born in 1986. No homozygous HH4 animals were found in the French genotype database even though 49 were expected; 0 were found in U.S. genotypes but < 1 was expected. The conception rate loss estimated from >100,000 carrier matings in France is similar to losses estimated for previous fertility haplotypes. Fritz et al. (2013) initially identified HH4 using a haplotype on chromosome 1 in the range of 1.9-3.3 Mbase on the UMD3.1 map, and then identified a mutation at position 1,277,227 in the GlycinAmide Ribonucleotide Transformylase (GART) protein as the probable cause. In cooperation with Sébastien Fritz and AIPL, French and U.S. haplotype tests were matched and found to be consistent for about 99.5% of 7,861 French animals across all chips.

The HH5 carrier frequency has increased rapidly from < 1% before 2000 to 5% in currently genotyped Holsteins because of 1 recent popular carrier bull, Picston Shottle (GBR598172). Pedigree analysis and additional genotyping traced most carriers of HH5 to Canadian bull 264804 Thornlea Texal Supreme born in 1957. The estimated -3.5%±0.6% effect on conception rate in carrier sire by carrier maternal grandsire matings is similar to effects of previous haplotypes, and the HH5 fertility loss all seems to occur before 60 days of gestation. The effect on stillbirth was not significant. The number of expected homozygous HH5 genotypes was 7, and none were found except a genotyped embryo that was implanted, but no pregnancy was detected 28 days later. Jacques Chesnais and Nicolas Caron of the Semex Alliance assisted with this research. HH5 is located on chromosome 9 in the range of 91.8-93.8 Mbase.

The BH2 carrier frequency gradually increased from 4% before 1980 to 20% today. Nearly all carriers trace to U.S. Brown Swiss bull 144488 Rancho Rustic My Design born in 1963. Schwarzenbacher et al. (2012 EAAP meeting) discovered BH2 (which they labeled 19-1) on chromosome 19 at a range of 10.6-11.7 Mbase. The effect of BH2 is significant in both U.S. and Austrian data for stillbirth (not fertility), and the rate of calf loss is similar to the previously known defect SMA. No homozygotes for BH2 were found in U.S., Austrian, or Intergenomic Brown Swiss genotypes even though 29 were expected. Swiss and Austrian researchers recently identified 2 BH2 homozygous calves born with low birth weight that died from poor immune response, and are now using sequence data to locate the mutation causing the calf loss.

The AH1 carrier frequency has been high and steady at about 20% for many generations. Nearly all carriers trace to U.S. Ayrshire bull 117936 Selwood Betty's Commander born in 1953. The -4.4%±2.5% effect of AH1 on conception rate is slightly larger than for previous fertility haplotypes, but not highly significant because of fewer observations. No homozygous genotypes were found even though 14 were expected. AH1 is located on chromosome 17 in the range of 65.9-66.2 Mbase. Further information is available from Cooper et al. (2013 ADSA abstract).

An exact test of the LOF mutation within JH1 is now used to determine heterozygous (carrier) status for genotyped Jerseys. The LOF mutation in the *CWC15* spliceosome-associated protein homolog gene was discovered by Sonstegard et al. (2012, *PLoS ONE*, 8:e54872) at the Bovine Functional Genomics Laboratory (BFGL), ARS, USDA, Beltsville, MD, and animals genotyped with GeneSeek Genomic Profiler version 2 (GP2) and GeneSeek High Density (GHD) are tested for the mutation. As of July, 4,265 Jerseys were tested directly, and other genotyped Jerseys also have their carrier status improved indirectly by use the LOF test results to impute which crossover haplotypes contain the mutation. Concordance of haplotype tests with LOF mutation tests was 98.9% from 50K chips but was 96.5% overall for JH1 including the lower density chips; 2.9% of Jerseys previously listed as noncarriers are now detected as heterozygous for JH1 by the LOF mutation test, and another 0.6% previously listed as carriers are now detected to be free. Further information on combining LOF mutation tests with haplotype tests is available (VanRaden et al., 2012, poster presentation, annual meeting of the American Dairy Science Association).

The LOF mutation within Holstein haplotype 3 (HH3) was also discovered independently by Hayes et al. (2013, Plant Animal Genome XXI, Abstr. W150) and by McClure et al. (2013, draft publication) at BFGL. The exact location (95,410,507) within the SMC2 gene is now used instead of the 0.4 Mbase fine-mapped region of chromosome 8 to determine HH3 carrier status; an LOF mutation test is not yet available on a chip.

Carrier status for Holstein haplotypes containing the BLAD mutation (HHB), the CVM mutation (HHC), the DUMPS mutation (HHD), and the Mulefoot mutation (HHM), the Red mutation (HHR), and the Polled mutations (HHP) will also be reported. Brown Swiss haplotype tests for Weaver (BHW), SDM (BHD), and SMA (BHM) [NOTE: corrected haplotype abbreviations] are also provided but these tests do not directly include the causative mutation as an additional SNP because too few bulls were previously tested. Codes in the XML files are 0 for normal animals, 1 for heterozygotes, and 2 for homozygous animals such as Red. Most females were not tested for these known conditions because individual mutation tests were expensive and were not included on SNP chips until recently. The frequency of BLAD and Mulefoot are low and DUMPS is very low, but the cost of providing haplotype status to monitor these defects is also very low. Official BLAD test results for >11,000 bulls and DUMPS test results for >3,000 bulls were used to improve the accuracy of the imputed haplotypes. Only 87 bulls were officially tested for Mulefoot status, but 1,000 other high reliability U.S. Holstein bulls were also assumed to be non-carriers to improve the accuracy of HHM status. Fritz et al., 2013 PLoS ONE 8:e65550 attempted to track CVM using 2 haplotypes that they called HH5 and HH6 (not the same as HH5 above), but we use 1 haplotype HHC including additional information from official CVM mutation tests. Haplotype tests for CVM are less accurate without pedigree information, and retesting of valuable animals detected as carriers for any of these conditions is recommended because haplotype tests are not quite as accurate as LOF mutation tests.

Version 2 of GeneSeek Genomic Profiler chip

By George Wiggans, Tabatha Cooper, and Paul VanRaden (AIPL-USDA)

Since May, the GeneSeek Genomic Profiler (GGP) was replaced by a new version (GP2) containing a superset of the markers included previously. For imputation to 50K or to 90K, the new GP2 chip is almost no different than the previous GGP because the added SNPs are not from the 50K or GHD, but are only from the HD. Many customers now refer to all chips by 3K, 6K, 8K, 50K, etc., and the new chip contains 19K but only 8K can be used from it. The chip number is 9 in formats 38 and 105. The GP2 is missing 691 SNP from the GGP, but only 305 of those were usable SNPs. For each other chip, numbers of usable and total SNPs in common with the GP2 are:

Chip	Usable	Present_On_Both
HD	11,358	19,491
GHD	8,824	9,218
50K	8,128	8,278
GGP	7,727	8,071
LD	6,835	6,907

Foreign and genomic information in parent averages

By Paul VanRaden (AIPL-USDA)

Beginning August, multi-trait across country evaluation (MACE) files are received a week earlier, allowing use of current instead of 4 month old MACE to compute marker effects. Parent averages (PA) for young bulls are now calculated using the genomic PTAs of parents instead of traditional PTAs. Genomic PTAs already were used for PA of females reported on format 105 but used 4 month old MACE, whereas PAs of young bulls matched those reported in the XML files and included the latest MACE from Interbull but not the genomic PTAs of parents. With additional processing, PAs for young bulls and genotyped females are recalculated to include both the latest available foreign and genomic information.

Six digit cow control numbers

By Leigh Walton (CDCB)

The largest herds now require using 6 digit cow control numbers. In May, to accommodate the reporting of these larger numbers, AIPL-CDCB changed the interpretation of the cow control number and barn name fields in the format 4 (lactation) record. The format 105 also requires change in August to report these numbers. Since there are no unused 6 character areas in the format, AIPL-CDCB added a field at the end (columns 408-413) for storing the number. The current field “Last animal control number” (columns 82-86) will be set to 5 zeros and indicated as “reserved for future use” in format 105.

For reporting data to AIPL-CDCB in formats 4, 5, and 6, use the following procedures:

Format 4 coding to report 6 digit cow control number:
1. Use barn name field (columns 221 – 227) ONLY if cow control number is > 5 digits
2. Blank cow control number field (columns 115 – 119)
3. Right justify 6 digit cow control number in the barn name column (columns 221 – 227). Leave column 221 as 0 or blank.

Formats 5 and 6
1. For 6 digit cow control numbers ONLY, leave the cow control number field blank, just as in the format 4! Do not report a truncated cow control number in format 5 or 6, it will negate the special handling in the formats.