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Considering genetic characteristics in German Holstein breeding programs

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ABSTRACT

Recently, several research groups have demonstrated that several haplotypes may cause embryonic loss in the homozygous state. Up to now, carriers of genetic disorders were often excluded from mating, resulting in a decrease of genetic gain and a reduced number of sires available for the breeding program. Ongoing research is very likely to identify additional genetic defects causing embryonic loss and calf mortality by genotyping a large proportion of the female cattle population and sequencing key ancestors. Hence, a clear demand is present to develop a method combining selection against recessive defects (e.g., HH1–HH5) with selection for economically beneficial traits (e.g., polled) for mating decisions. Our proposed method is a genetic index that accounts for the allele frequencies in the population and the economic value of the genetic characteristic without excluding carriers from breeding schemes. Fertility phenotypes from routine genetic evaluations were used to determine the economic value per embryo lost. Previous research has shown that embryo loss caused by HH1 and HH2 occurs later than the loss for HH3, HH4, and HH5. Therefore, an economic value of €97 was used against HH1 and HH2 and €70 against HH3, HH4, and HH5. For polled, €7 per polled calf was considered. Minor allele frequencies of the defects ranged between 0.8 and 3.3%. The polled allele has a frequency of 4.1% in the German Holstein population. A genomic breeding program was simulated to study the effect of changing the selection criteria from assortative mating based on breeding values to selecting the females using the genetic index. Selection for a genetic index on the female path is a useful method to control the allele frequencies by reducing undesirable alleles and simultaneously increasing economical beneficial characteristics maintaining most of the genetic gain in production and functional traits. Additionally, we applied the genetic index to real data and found a decrease of the genetic trend for the birth years 1990 to 2006. Since 2010 the genetic index has increased due to a strong increase in the polled frequency. However, further investigation is needed to better understand the biology to determine the correct time of embryo loss and the economic value of fertility disorders.

Key words: genetic index, lethal recessive, genomic evaluation, dairy cattle

INTRODUCTION

Routine genotyping of a large proportion of the dairy population for genomic evaluation and sequencing of key ancestors provide the opportunity to discover and monitor recessive genetic disorders. VanRaden et al. (2011a) was one of the first research groups who used the genotype pool from routine genomic evaluation to screen for recessive fertility haplotypes. They showed that 3 different Holstein haplotypes (HH1, HH2, and HH3) may cause embryonic loss in the homozygote state. Studies from Denmark (Sahana et al., 2013), the United States (Cooper et al., 2013), and France (Fritz et al., 2013) confirmed these results and identified additional haplotypes (among others, HH4 and HH5). These were also associated with a decrease of fertility due to a potential embryonic loss. Researchers have already found the causal mutation for HH1 (Adams et al., 2012), HH3 (Daetwyler et al., 2014; McClure et al., 2014), and HH4 (Fritz et al., 2013) by using whole genome re-sequencing data of the populations key ancestors (Jansen et al., 2013). However, the causal mutation for HH2 and HH5 is still unknown (McClure et al., 2014). Since the introduction of genomic selection, average inbreeding level increases more than linearly. This increases the risk of potentially many new genetic disorders. In general, for mating decisions and publication, a clear demand is present to combine this potentially large number of disorders with economically beneficial genetic characteristics. Detection and management of genetic disorders will have an effect on genetic gain for fertility traits, animal welfare, and the overall image of the breed (Egger-Danner et al., 2014). Furthermore, economically beneficial traits such as polled (Medugorac et al., 2012; Rothammer et al.,

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2014) should be expanded in the dairy populations to avoid dehorning young calves.

In the past, allele frequencies of genetic disorders such as complex vertebral malformation (Agerholm et al., 2001), bovine leukocyte adhesion deficiency (**BLAD**; Shuster et al., 1992), deficiency of uridine monophosphate synthase (**DUMPS**; Shanks et al., 1984), and brachyspina (Agerholm et al., 2006; Charlier et al., 2012) were drastically decreased by excluding carrier bulls from AI. Superior bulls were excluded from mating irrespective of their genetic merit and the frequency of the genetic disorder in the population. This results in lower genetic gain for production and functional traits (Van Eenennaam and Kinghorn, 2014). An example by VanRaden et al. (2014) showed that the famous key ancestor Pawnee Farm Arlinda Chief carries the HH1 haplotype. This sire contributed 14% of his gene variants to the current Holstein population, which increased the milk yield by $25 billion. In contrast the costs for mid-term abortions due to HH1 were only $0.4 billion.

For each genetic characteristic, comprehensive investigation including allele frequencies, inheritance, economic value, and causal mutation are needed to find the best way of handling the genetic characteristics in breeding programs. In most cases, the carrier frequency can be managed by finding the appropriate mating partner (e.g., mating a carrier sire only to noncarrier dams).

The aim of this study was to derive the economic values for the most important genetic characteristics segregating in German Holsteins and to develop an index of genetic properties summarizing the genetic characteristics and their economic values.

MATERIALS AND METHODS

Identification of the Considered Genetic Characteristics

In this study, we used the information of 5 recessively inherited disorders of fertility (HH1 to HH5) and one economically beneficial trait (polled) segregating in the German Holstein population. The characteristics BLAD and DUMPS were not considered because the carrier frequencies are very low in the current German Holstein population (BLAD 0.2%; DUMPS <0.1%). This means that the probability of mating 2 carriers is very low. The disorders complex vertebral malformation and brachyspina could not be considered based on their patent protection (Georges et al., 2010; Bendixen et al., 2014).

To investigate the development of the carrier frequencies over time, all Holstein animals (143,511) from routine German Holstein genomic evaluation (February 2015) were chosen. The genotype states for HH1 to HH5 were derived by the haplotype based missing homozygosity approach from VanRaden et al. (2011a). Haplotypes were derived using the Beagle (Browning and Browning, 2007) software package. Table 1 shows the used location and the mean minor allele frequency for the birth years 2012 to 2014. Since the end of 2014, the custom Illumina chip (EuroGenomics10KV4) is used for routine genotyping. This chip contains the known causal mutation for HH1, HH3, and HH4, facilitating the validation of the genotyped status with the derived haplotype status for 7,032 animals. Each causal mutation was added twice to the custom chip. This enables a comparison between the 2 genotype calls and allows to estimate the reproducibility for the identical genome position. The polled state was derived by a method described by Segelke et al. (2013). Briefly, this approach uses for the imputation reference population the polled entries from the herdbook as an additional marker within the polled region (Table 1). For animals with unknown polled state, the additional marker is set to "missing" and afterward imputed using the Beagle (Browning and Browning, 2007) software package. Segelke et al. (2013) showed that the allele error rate for the imputation of the polled state compared with the herdbook entry was 0.2%.

Effects of the Haplotypes on Fertility and Definition of the Economic Values

The economic value of the fertility defects were indirectly quantified by analyzing the fertility and calving

Table 1. Location and allele frequency of the considered characteristics

Characteristic	Chromosome	Map location (bp)	Mean minor allele frequency (%), year of birth 2012–2014
HH1	5	62,394,447 to 63,983,082	0.88
HH2	1	93,172,083 to 98,133,752	0.94
HH3	8	95,003,606 to 96,266,647	3.29
HH4	1	2,128,924 to 2,942,947	1.26
HH5	9	92,350,052 to 93,910,957	2.76
Polled	1	845,494 to 4,052,161	4.06