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Faculty of Veterinary Medicine and Animal Science
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Control of inbreeding in dairy cattle in the genomic era

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Kontroll av inavel hos mjölkkor i den genomiska eran

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Abstract

This review evaluates the effects of inbreeding and inbreeding depression on the productivity of dairy cattle (*Bos taurus*), how genomic selection can control and decrease inbreeding and lethal inherited diseases related to the inbreeding. The relatedness and inbreeding have increased within populations since only a few elite sires are used in today's dairy cattle breeding practice. An increase of inbreeding results in an increased level of homozygosity, and thereby inbreeding depression and inherited diseases which influence production, reproduction and health traits negatively. Through molecular genetics and analysis of haplotypes that are common in the population but are never found as homozygotes, lethal recessive alleles can be identified. Publishing the test result of animals used in breeding allows for avoidance of at-risk matings with otherwise severe consequences.

Sammanfattning

Denna litteraturstudie utvärderar effekterna av inavel och inavelsdepression på produktivitet hos mjölkkor (*Bos taurus*), och hur genomisk selektion kan användas för att kontrollera samt minska inavel och förekomsten av ärftliga, dödliga sjukdomar relaterade till inaveln. Medelsläktskapet och inavelsgraden har ökat inom mjölkkopopulationer då endast ett fåtal elittjurar används i dagens mjölkkoavel. En ökad inavel resulterar i en ökad nivå av homozygositet, inavelsdepression och ärftliga sjukdomar, vilka påverkar produktion, reproduktion samt hälsoegenskaper negativt. Med molekylärgenetiska metoder och analyser av vanligt förekommande haplotyper som aldrig återfinns som homozygota kan man identifiera dödliga recessiva alleler. Genom att publicera provsvar från avelsdjur kan riskfyllda parningar, som annars ger allvarliga konsekvenser, undvikas.

Introduction

Selective breeding has been used by humans since the early domestication of animals in order to change their characteristics. Today, artificial selection is widely used in our food production with the main goal of producing enough food to sustain the growing population. By selecting animals exhibiting desirable traits and breeding them, the expression of the trait (i.e. the performance) will increase in subsequent generations. This is called genetic gain. The level of genetic gain in a population is the result of the accuracy of the estimated breeding value (EBV), the generation interval, the selection intensity and the additive genetic standard deviation. Daetwyler *et al.* (2007) suggest that the change in the genetic progress mainly comes from increasing the selection intensity or the accuracy of the EBV, since the additive genetic variance for traits is considered a constant in the short term. The selection intensity will increase by reducing the number of individuals selected to provide the next generation. However, breeding fewer individuals leads to an increase in inbreeding and thereby an increased risk for inbreeding depression. The preferred

way to maximize genetic gain is, therefore, to increase the accuracy of the breeding values or decrease the generation interval (Daetwyler *et al.*, 2007).

Breeding values estimated with traditional best linear unbiased prediction (BLUP) are based on phenotypic observations of the individual and/or observations from its closest relatives. Thus, BLUP-selection increases the accuracy of the EBV by including observations from known relatives (Meuwissen *et al.*, 2001; Daetwyler *et al.*, 2007). This also results in an increased rate of inbreeding per generation (Daetwyler *et al.*, 2007) as selected individuals with the best breeding values are likely related and co-selected (unless constraint for inbreeding and optimal minimum selection is used). Furthermore, elite sires have historically been overused with the aid of artificial insemination (AI), which has led to an increased relatedness and higher levels of homozygosity within the population and thus further decreasing the health status of several commercial breeds (Thompson *et al.*, 2000a).

Meuwissen *et al.* (2001) introduced the concept of genomic selection (GS) as a further development of BLUP. As shown in figure 1, a reference population is evaluated based on phenotypic observations and genotyping in order to calculate genomic estimated breeding values (GEBV). Samples from the selection candidates are then genotyped and breeding values are calculated using information from the reference population. Parents of the next generation are then selected based on these GEBV (Meuwissen *et al.* 2001).

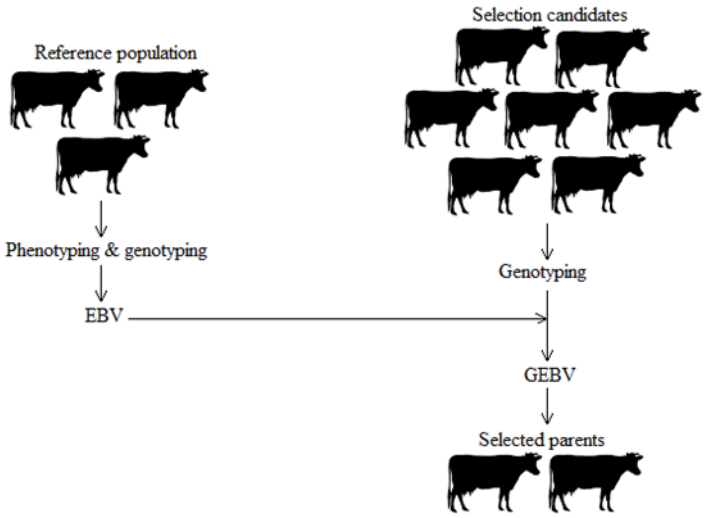

Figure 1: Schematic overview of genomic selection.

Compared to BLUP, GS increases the accuracy over several generations by using genetic markers (Meuwissen *et al.*, 2001; Daetwyler *et al.*, 2007; Habier *et al.*, 2007; Schierenbeck *et al.*, 2011) and by being able to better predict the Mendelian sampling term of breeding values. A better distinction between siblings is possible due to the better prediction of the Mendelian sampling term, which in turn will decrease the co-selection of sibs and, thus, decreasing the rate of inbreeding per generation (Daetwyler *et al.*, 2007; Schierenbeck *et al.*, 2011). Using GS will

also allow for better estimation of within-family variance and make it easier to distinguish between family variance (Daetwyler *et al.,* 2007; Sonesson *et al.,* 2012). In addition, GEBV with high accuracy are available early on in the individual's life due to large reference populations, which means that phenotypic observations from progeny testing become less important. As shown in figure 1, only the reference population will have both phenotypic and genetic observations rendering progeny test results unnecessary outside the reference population. Due to the faster selection process with GS in conjunction with AI, a further decrease of the generation interval is possible which will allow for higher rate of genetic gain (Meuwissen *et al.,* 2001; Daetwyler *et al.,* 2007; Habier *et al.,* 2007; Pryce *et al.,* 2012). However, a shorter interval will also enable more intensive breeding, which can further increase the rate of inbreeding and the frequency of diseases in the population (Daetwyler *et al.,* 2007; Pryce *et al.,* 2012).

The aim of this review is to understand the occurrence and consequences of inbreeding in dairy cattle (*Bos taurus*), and how genomic selection can be used to control and possibly decrease inbreeding and inherited diseases related to inbreeding.

Literature

Inbreeding and inbreeding depression

Inbreeding lowers the mean phenotypic performance in the inbred animal and increases homozygosity levels in the population (Miglior *et al.,* 1995; Falconer & Mackay, 1996a; Smith *et al.,* 1998; Thompson *et al.,* 2000a, 2000b), which in turn increases the risk of deleterious effects and lethal recessive genes being exhibited (Miglior *et al.,* 1995). Furthermore, traits associated with fitness and survival (such as reproduction, fertility, and health) are in general more susceptible to inbreeding depression (Miglior *et al.,* 1995; Cassell *et al.,* 2003) where greater depression is often associated with rapidly increasing inbreeding (Falconer and Mackay, 1996b).

According to Smith *et al.* (1998), Thompson *et al.* (2000a, 2000b) and Mc Parland *et al.* (2007) inbreeding decreases the total milk production, including total protein and fat content in milk during the first lactation as well as during the lifetime of dairy cattle. Length of lactation can also be affected by high rates of inbreeding, resulting in decreased days in milk (DIM) (Smith *et al.,* 1998; Thompson *et al.,* 2000a). While inbreeding causes significant losses in production, it has a larger effect on the lifetime profit rather than on a single lactation trait in dairy cows due to the cumulative effect of inbreeding (Smith *et al.,* 1998).

The daily production in the Holstein and Jersey breeds seemed to be weakened especially at early ages, where greater losses at younger ages seems to be linked with the amount of inbreeding (Thompson *et al.,* 2000a, 2000b). However, it has been found that low levels of inbreeding (1 to 5 %) can at certain ages (22 months to 55 months in the Holstein and after 36 months in the Jersey) prove favorable for milk production and DIM, or at least without negative impact on the

production compared with non-inbred dairy cows (Thompson *et al.,* 2000a, 2000b). Furthermore, Thompson *et al.* (2000b) found no significant effect of inbreeding on daily milk production with inbreeding coefficient less than 7 % after peak production in Jersey cows. Low levels of inbreeding seemed to have a small but insignificant effect after peak yield (Thompson *et al.,* 2000b). The effect on daily milk production after peak yield in the Holstein was small for inbreeding levels higher than 6 % (Thompson *et al.,* 2000a).

Inbreeding also affects some important non-production traits negatively; mainly fertility, survival rate, age at first calving and first calving interval (Smith *et al.,* 1998; Thompson *et al.,* 2000a, 2000b; VanRaden & Miller, 2006; Mc Parland *et al.,* 2007). Thompson *et al.* (2000b) found that the effect on fertility was greater in younger individuals, which was also concluded in the study by Cassell *et al.* (2003). Furthermore, the survival rate decreases for all lactations in both Holsteins and Jerseys as inbreeding increases (Thompson *et al.,* 2000a, 2000b). VanRaden and Miller (2006) also found that the negative impact on conception and survival up to 70 days after first insemination increased with level of inbreeding. No effect on age at calving could be observed at low levels of inbreeding. However, more than 10 % inbreeding is associated with increased age at calving for lactations one through four (Thompson *et al.,* 2000a, 2000b) and the deleterious effect accumulates over parities (Mc Parland *et al.,* 2007).

Smith *et al.* (1998) found no effect due to inbreeding on conformation traits such as rump angle, thurl width, foot angle, udder conformation and attachment. The effect of inbreeding on ease of milking or temperament was not significant either (Mc Parland *et al.,* 2007). Furthermore, Smith *et al.* (1998) reported inbred Holstein to be smaller, while Mc Parland *et al.* (2007) found inbred Irish Holstein-Friesians to be taller and more angular compared with non-inbred individuals.

How the udder health is affected by inbreeding is less well known (Mc Parland *et al.,* 2007). While Smith *et al.* (1998) and Thompson *et al.* (2000a, 2000b) found no significant effect on udder health traits, a later study performed by Mc Parland *et al.* (2007) showed a (small) deleterious effect where udder traits had an increased score. Furthermore, if inbreeding has an effect on somatic cell count, and thereby an effect on the incidence of mastitis, is still not settled (Mc Parland *et al.,* 2007). Neither Smith *et al.* (1998) nor Thompson *et al.* (2000a) found a significant effect on somatic cell score (SCS) due to inbreeding, in contrast to Miglior *et al.* (1995) who found a tendency of higher lactation mean of SCS for inbred individuals compared to non-inbred animals. The study of Miglior *et al.* (1995) suggests that inbreeding is related to disease incidence in large purebred dairy cattle populations and that more research is necessary in order to fully explain the relationship between inbreeding and fitness traits.

Inherited diseases

Although selection and artificial reproduction can be used to increase genetic gain, it can also cause an increase in inbreeding and coancestry which in turn can lead to an increase of recessive

defects (Charlier *et al.*, 2008). Prior to the development of modern molecular technologies, abnormalities that somehow caused lethal effects (such as losses during conception, gestation and stillbirth) were difficult to find, even with large sets of data (VanRaden & Miller, 2006; VanRaden *et al.*, 2011). At the time, the best way to confirm such suspicions and to look into previously unknown defects were through pedigree analysis, segregation analysis and subsequent test matings (Nicholas, 2010c, 2010d).

VanRaden and Miller (2006) estimated the effect of carriers on embryonic mortality where genetic causes of embryo loss included chromosomal defects, individual genes, and genetic interactions. In contrast to lethal recessives that cause defects visible at birth, genetic defects that cause losses early in gestation are difficult to detect. Such losses generally leave no physical trace and are therefore not reported by breeders (VanRaden & Miller, 2006).

Lethal recessive defects are often suspected when a homozygote is missing in a population. With today's molecular technologies it is possible to find these recessive lethal gene variants with genetic markers. Furthermore, haplotype testing is ideal for detecting lethal recessives since it only requires samples from supposedly normal individuals and phenotypic observations are not necessary (VanRaden *et al.*, 2011). Moreover, the distribution of haplotypes within the population will be representative when testing numerous individuals and, therefore, the lack of homozygous haplotypes is most likely not a coincidence (VanRaden *et al.*, 2011). The inheritance of a disorder can also be studied more easily when genetic methods are used (Leipold *et al.*, 1990; VanRaden *et al.*, 2011). However, several other lethal defects may exist within a breed but remain undetectable, for instance due to the lack of molecular technologies or due to disease frequencies being too low for detection (Van Doormaal & Kistemaker, 2008; VanRaden *et al.*, 2011).

Charlier *et al.* (2008) studied five new recessive defects in cattle; congenital muscular dystonia 1 (CMD1), congenital muscular dystonia 2 (CMD2) and crooked tail syndrome (CTS) in the Belgian Blue, renal lipofuscinosis (RL) in Holstein-Friesian and Danish Red cattle, and ichthyosis fetalis (IF) in Italian Chianian cattle. While CTS and RL only causes economic losses due to growth retardation and reduced longevity; CMD1, CMD2 and IF are lethal. Charlier *et al.* (2008) analyzed DNA samples with single nucleotide polymorphism (SNP) arrays and mapping; and they were able to identify the genes and causal mutation for CMD1, CMD2 and IF. Although the dog (*Canis lupus familiaris*) is the preferred model animal for human medicine (Karlsson *et al.*, 2007), Charlier *et al.* (2008) also determined the human diseases corresponding to CMD1, CMD2 and IF – Brody myopathy, hyperekplexia and harlequin ichthyosis.

Likewise, VanRaden *et al.* (2011) studied marker genotypes and haplotypes with high frequency that were never found homozygous from 58453 Holsteins, 5288 Jerseys, and 1991 Brown Swiss in the North American database. For instance, they reported a reduction in harmful recessive alleles expressed in the Holstein over time. They suggest that the trend in carrier frequency for

these haplotypes can be explained by selection for higher daughter pregnancy rate and other traits important for fitness. This type of breeding would then select against the haplotypes causing embryo loss and abnormal calves (VanRaden *et al.,* 2011).

VanRaden *et al.* (2011) also found that the estimated effects on stillbirth rate were positive for most haplotypes, i.e. number of stillbirth increases as the haplotype frequency increases. They suggest this might indicate that some lethal effects occur in the middle of, or at late, gestation, which would increase the economic losses due to the risk of longer calving intervals and/or culling. By identifying different lethal recessives in each breed, VanRaden *et al.* (2011) also showed that crossbreeding may improve fertility, compared to pure breeding. Since crossbred animals in general exhibit greater fitness than the parent breeds, which is seen in commercial poultry (*Gallus gallus domesticus*) and pig (*Sus scrofa*) populations, crosses of different breeds are of interest for improving the reproductive efficiency in dairy cattle (VanRaden & Miller, 2006).

In today's practice, only a limited number of elite sires are used worldwide for breeding by the means of AI. Since there is a high frequency of carriers among our popular breeding animals, the population can suffer a serious increase in frequency of harmful recessive alleles (Smith *et al.,* 1998; Thompson *et al.,* 2000a; VanRaden *et al.,* 2011). However, this can be managed to a certain degree with genomic selection (Van Doormaal & Kistemaker, 2008; VanRaden *et al.,* 2011).

Control of inbreeding using GS

Pedigree-based versus genomic relationships

Traditional BLUP-selection uses pedigree information to construct relationship matrices and to constrain the progeny inbreeding (Smith *et al.,* 1998; Meuwissen *et al.,* 2001; Habier *et al.,* 2007; Pryce *et al.,* 2012). The development of molecular genetics has enabled genotyping of animals (Meuwissen *et al.,* 2001; Habier *et al.,* 2007; Pryce *et al.,* 2012) and using genomic relationships in the selection process (Habier *et al.,* 2007; Pryce *et al.,* 2012). Genomic relationships will in general obtain more information than pedigree-based relationships, even when compared to deep and thorough pedigrees (Pryce *et al.,* 2012), due to the use of genetic markers, such as SNPs. A more accurate relationship matrix will also allow for a higher accuracy than EBV from BLUP and relationships based solely on pedigree information (Habier *et al.,* 2007; Sonesson *et al.,* 2012). However, data from one generation is not sufficient for predicting GEBV from markers with high accuracy since the accuracy will decline due to linkage disequilibrium breaking up over time (Habier *et al.,* 2007). SNPs also describe the coancestry between individuals more precisely than pedigree information does, as long as enough SNPs are used (Pryce *et al.,* 2012).

Sonesson *et al.* (2012) studied the consequences of inbreeding on genetic variability across the genome through simulations. They measured genetic gain, rates of inbreeding based on pedigree

and genome, and local inbreeding across the genome in order to quantify the consequences from the use of GS. Sonesson *et al.* (2012) showed that the approach used to estimating breeding values and to control inbreeding can have severe influences on the final outcome if not combined properly. Both Schierenbeck *et al.* (2011) and Sonesson *et al.* (2012) found that the resulting rates of genomic inbreeding correspond to desirable values when the same source of information is being used, whereas values will deviate when using different methods to estimate breeding values and to control the inbreeding. Therefore, control of inbreeding (to manage the rate of inbreeding per generation) should be managed using the same method as used for estimating the breeding values, i.e. genomic selection should be used with genomic control of inbreeding and, similarly, inbreeding should be managed with pedigree-based inbreeding control when using traditional BLUP-selection (Schierenbeck *et al.*, 2011; Sonesson *et al.*, 2012).

Pryce *et al.* (2012) used a pedigree relationship matrix (consisting of 6019 animals) and two genomic relationship matrices (42115 SNPs and 3123 SNPs respectively), in order to control progeny inbreeding levels in Holstein dairy cattle. They found that both of their genomic matrices could decrease inbreeding at somewhat similar rates. Ultimately, the most efficient means to decrease the anticipated progeny inbreeding was to use the 42115 SNP matrix when the inbreeding of the progeny was measured using this method, followed by the other genomic relationship matrix and lastly the pedigree matrix. Similarly, expected inbreeding measured with the 3000 SNP matrix and the pedigree matrix respectively, should be evaluated primarily using the same method as originally measured. They also mention that high-density SNP chips might be unnecessary for commercial practice when the smaller amount of SNP data gives sufficient results, especially considering the increased cost for a denser SNP panel (Pryce *et al.*, 2012).

From their study of Holstein dairy cattle, Schierenbeck *et al.* (2011) concluded that breeding programs need to pay attention to the constant increase of inbreeding, genetic defects and inbreeding depression in order to maximize genetic gain. It is also necessary to minimize genetic relationships within breeding populations as this will have a positive effect in the long run (Schierenbeck *et al.*, 2011). Furthermore, Pryce *et al.* (2012) also showed that when using information from genomic relationship matrices, a reduction in inbreeding in the offspring can be achieved with only minor changes to the breeding objective. However, these changes are not made clear.

Gene tests

In the case of a new defect, the animal where the first mutation occurred can be identified via a gene test (Van Doormaal & Kistemaker, 2008). However, in most cases the causative mutation happened generations ago and, although important carrier ancestors can be traced, the source animal cannot be identified. With today's technology and large databases, it is possible to avoid at-risk matings, i.e. carrier-carrier matings, by testing and profiling the breeding population (VanRaden *et al.*, 2011). With the health status of commercial breeds decreasing, several

breeding companies and breed associations have implemented policies for proper testing and documentation as a way of controlling and eventually eliminating harmful disorders (Van Doormaal & Kistemaker, 2008). Although this process is expensive today, the added cost and work of genotyping can pay off over a short period of time. For instance, Sattler (2002) report that from 2001 to 2002 the amount of complex vertebral malformation (CVM) carriers had dropped from 18 % to less than 1 % in the US Holstein population simply by testing most bulls suspected to be carriers and thus avoiding carrier matings. Likewise, CMD1 and CMD2 in Belgian Blue were nearly eradicated from the population within a few months after the causative mutation was uncovered (Charlier *et al.*, 2008).

Although gene tests can be used to prevent carrier matings, it is also important to know the risk of some animals being mislabeled and used in at-risk matings (Leipold *et al.,* 1990; VanRaden *et al.*, 2011).

By designing and using gene tests, all breeding animals can be profiled and the data published (Charlier *et al.,* 2008; VanRaden *et al.,* 2011). If the initial allele frequency of a recessive defect is relatively high, selection against it will rapidly reduce the frequency within the population. However, selection against the recessive trait will be limited when frequencies are lower, since the recessive allele is concealed from selection in heterozygotes (Nicholas, 2010a). Since all carriers have a 50% risk of passing on their defective allele to their offspring, these individuals should not be allowed to mate with other heterozygotes. This would, theoretically, result in homozygosity for the defect, the lethal combination, in ¼ of the offspring, while the rest would be 50% heterozygous and ¼ homozygous for the normal allele. Due to the nature of heterozygotes, these individuals should only be allowed to mate with homozygotes for the normal allele, which will result in progeny 50% carriers and 50% homozygous for the normal allele (Nicholas, 2010b). This problem is the main reason why so much research is aimed at detecting heterozygotes; by distinguishing between carriers and non-carriers, selection could be made more efficient (Nicholas, 2010a).

If no carriers are ever used in breeding, the allele frequency in a population will decline and reach zero immediately and thus, new recessive alleles that arise will never be inherited and will not remain in the population. Although this could be used to delete all recessive alleles, the approach is neither practical nor necessary (Nicholas, 2010a). For instance, preventing heterozygotes from mating would result in substantial loss of genetic variance (Charlier *et al.,* 2008; VanRaden *et al.,* 2011) and the effect of mutation must also be considered. Over time, mutations will occur all over the genome building up new recessive alleles in all populations rendering deletion of them useless. Furthermore, a reduction of (lethal) recessive diseases can be reached easily by preventing at-risk matings by ensuring heterozygotes are always mated to homozygotes. Consequently, the disorder will not be eliminated, but at least it will not occur again since individuals homozygous for the recessive gene does not exist (Nicholas, 2010a).

Although the desirable approach is to perform strong selection against the carriers of defective alleles, studies show that the true improvement on the trait is only minimal. VanRaden *et al.* (2011) explored the possibility to improve future fertility when a carrier was mated at random within the breed. They found that the conception rates will only increase by carrier frequency divided by 4. For instance, with a conception rate of 31 % and carrier frequency of 5 % it would only yield 0.39 percentage points, that is "conception rates will increase by <1 percentage point by eliminating any of the haplotypes from the population" (VanRaden *et al.*, 2011). But although carriers will inherit defective alleles to 50 % of their offspring, they can still possess other profitable genes and, thus, get positive evaluations (Van Doormaal & Kistemaker, 2008; VanRaden *et al.*, 2011).

Discussion

It is important to control inbreeding and to minimize the inbreeding depression due to the consequences they have in high levels on the production, reproduction and health status of a breed (Sorensen *et al.*, 2005). According to Thompson *et al.* (2000a, 2000b) increased inbreeding appeared to correspond to greater production losses at younger ages in both Holstein and Jersey. This could indicate that inbred individuals experience a slower growth and maturation. Furthermore, the disagreement of whether or not udder health traits and somatic cell score are affected by inbreeding also reflects the need for more research (Smith *et al.*, 1998; Thompson *et al.*, 2000a, 2000b; McParland *et al.*, 2007). It might also be easier to counteract the effect of inbreeding and inbreeding depression with a better understanding of how it affects important properties, both production and vitality traits (Miglior *et al.*, 1995). Interestingly though, low levels of inbreeding (1 to 5 %) can have a favorable effect on production in early ages, which indicates that the animal is not affected to a large extent of these levels and/or that they are able to somehow compensate and still produce relatively normal (Thompson *et al.*, 2000a, 2000b).

Due to the overuse of elite sires with AI and the pure breeding idealization over the past few decades, today's dairy cattle are exhibiting increasing inbreeding and vitality issues. Today, some breed associations insists upon proper testing and documentation with regard to certain genetic recessives in order to monitor the incidence of these diseases "with the goal of full elimination" (Van Doormaal & Kistemaker, 2008). It is possible to reduce an allele frequency to zero through selection; however, all of the harmful alleles cannot be removed from a population for several reasons. Firstly, every individual carries multiple mutations located throughout the genome. It is simply a matter of if and when the genes will be expressed and what consequences they will have on the animal at expression. Secondly, due to the replication of DNA through meiosis and mitosis, new and recurring mutations will also happen in the future, bringing back mutations in the genome and rendering removal of them useless. Thirdly, recessive alleles can "hide" from selection in heterozygotes, which means that every carrier must be excluded from breeding (Nicholas, 2010a). However, due to the heavy use of AI and a few elite sires, today's dairy cattle population has a small breeding population with an effective population size of only 50-100. This

means that the alleles of a few ancestors are quite common in the population, thus completely forbidding carriers to breed will have severe implications on the genetic variance of the breed as well as the selection intensity (Charlier *et al.*, 2008; Van Raden *et al.*, 2011). Furthermore, excluding animals that, apart from inheriting one defect allele, are otherwise healthy and might also be high yielding can have a negative effect on future genetic gain and the economy. Finally, selection against a carrier is relatively ineffective since the real improvement of the trait is only minimal, which further reinforces the importance of working with sustainable and responsible animal breeding (Van Raden et al., 2011).

Although crossbreeding risk decreasing the short-term genetic gain found in purebred individuals, like high milk yield, crossbred animals will in general exhibit better fitness than the parent breeds due to heterosis. This should be used to help improve traits where commercial pure breeds are depressed, like fertility and reproductive efficiency. Furthermore, different breeds rarely exhibit the same mutations which mean that the offspring will only inherit the trait from one parent, thus the progeny will never exhibit the harmful recessives found in each of the parent breeds (Van Raden & Miller, 2006; Van Raden *et al.*, 2011).

With molecular technologies it is possible to find known recessive lethal gene variants with genetic markers; however, a flawless method to measure inbreeding and to predict inbreeding in future progeny does not exist. Although today's methods can provide adequate results, a lack of information and errors in pedigrees are limiting the accuracy of BLUP-selection. Likewise, GS is highly reliant upon accurate sampling and processing of SNPs for calculating genomic relationships in order to calculate breeding values (Pryce *et al.*, 2012). Furthermore, developing more sensitive methods will allow for earlier detection of defects, which in conjunction with more research into genetic defects with the goal of designing more gene tests and larger databases, can reduce the economic losses associated with carrier matings, early embryo losses and unnecessary culling (Van Doormaal & Kistemaker, 2008; Van Raden *et al.*, 2011). Researching inherited diseases in animals have also made it possible to identify the causative mutation of corresponding human diseases using dense SNP arrays and fine-mapping. Thus, developing effective molecular technologies and researching animal genetic defects have, and will continue to, benefit human medicine (Charlier *et al.*, 2008).

Conclusion

Instead of working for full elimination of harmful alleles, animals used for breeding should be tested for their breed's most common lethal recessives and by publishing the data, at-risk matings can be avoided. It is obvious that this approach pays off as the incidences of several lethal diseases, like CMD and CVM, have successfully been decreased to lower levels. The industry also needs to look more favorably upon crossbreeding as a means to increase the fitness of commercial populations. In addition, this might also help with the poor image of today's dairy cattle production due to the inbreeding problematics.

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