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Review Article

GENOME WIDE ASSOCIATION STUDIES FOR MILK PRODUCTION TRAITS IN DAIRY CATTLE: A REVIEW

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Abstract- The selection of animals using molecular information is more reliable with increased accuracy of selection and higher genetic gain. Hence, there is need to use selection methods that are based on genomic studies. Genomic selection (GS) is a variant of marker-assisted selection method used for predicting genomic breeding values (GEBVs) of animals using high density genetic markers, such as single nucleotide polymorphisms (SNPs). The utility of genomic information in dairy cattle breeding schemes has now reached the level of accuracy that enables dramatic changes and improvements to breeding schemes. GS can increase the accuracy of selection, shorten the generation interval by selecting individuals at the early stage of life, and accelerate genetic progress. The application of GS in dairy cattle has been reported in many countries, including USA, Canada, Australia, Norway, New Zealand, Netherland, Denmark, Germany and Ireland with very promising results. Published results indicates that for dairy cattle approximately 1000 bulls are required in the reference population to obtain GEBVs with accuracies that compete with the accuracies of EBVs based on progeny testing for all traits. Use of genomically evaluated young bulls can accelerate the breeding cycle and increase genetic gain per unit time beyond what is possible with phenotypic selection. With denser marker panels, more sophisticated statistical tools and in the longer term, sequencing, it is expected that the accuracy of GEBVs will continue to improve and breeding schemes will utilize genomic information further at the expense of progeny testing. Current application of genomic selection is only the start of the genomic era in livestock production. To fully capitalize on the benefits provided by GS, breeding programmes may need to be redesigned substantially.

Keywords- Genomic selection, Accuracy of selection, Genetic gain, Genomic estimated breeding values.

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Introduction

Genetic improvement of livestock began thousands of years ago with the development of a variety of livestock species and their adaption of specific climate and production system. The further development of breeds beginning in the late 18th century followed by emergence of science of Animal Breeding and Genetics in the 20th century with landmark assignment and improvements in livestock around the world. Further genetic improvements were made possible with the advent of Molecular Genetic Techniques. The application of quantitative trait loci (QTL) identification and mapping in livestock produced a number of DNA markers that were incorporated into selection programmes in many species. The 21st century has been marked with the use of molecular markers in genomics including whole genome sequencing and employing genomic selection in dairy cattle breeding programmes [1]. Genomic selection has the potential to revolutionize dairy cattle breeding because young animals can be accurately selected as parents, leading to a much shorter generation interval and higher rates of genetic gain. Genomic selection (GS) refers to genetic improvement of animals through selection based on genomic breeding values (GEBVs). GEBVs are computed using a reference population of animals that have a high diversity genotype as well as phenotypic information [2]. Genetic improvement programmes in many animal species will benefit from applying genomic selection. Advantages may be highest for breeding programmes because the generation interval in traditional progeny testing schemes is long and selection of young bulls for progeny testing is inaccurate [3]. The animal breeding industry is currently adapting selection procedures in each species to include this innovative tool. In the future, GS might be helpful to close the gap between countries with greater and lesser production. During these years, genetic selection also incorporated new computer technologies and animal reproduction discoveries to improve the identification of superior animals. The genome sequencing and development of chips that are able to genotype thousands of SNPs across the genome may be a breakthrough for breeders and scientists in animal breeding. The rapid adoption of this technology has caused profound changes in the dairy cattle industry.

SNP chips available for Genome Wide Association Studies

Genomic selection (GS) in dairy cattle started in 2006 [4], when high-density single nucleotide polymorphism (SNP) panels became affordable for application to livestock and plants [5]. The first official direct genomic values (DGV) were provided to dairy farmers in January 2009. Despite the improvement in reliability of young selection candidates achieved with genome enabled evaluations [6], the commercial price of high density SNP chips may limit their use to males and elite females in many populations. Currently in cattle, the most commonly used chip is the Bovine SNP50.v2 Bead chip (Illumina Inc., San Diego, CA) and imputation strategies are focused on imputation from 6K to 50K. The availability of the 80K SNP BovineHD BeadChip (Illumina Inc., San Diego, CA) opens the chance of imputation from 50K to this higher density panel. Genotyping a large reference population at extra-large high density would be cost prohibitive. However, genotyping a subset of this reference population, and then imputing the rest of the genotypes may be an efficient strategy if the predictive ability of subsequent

genomic evaluations exceeds that obtained before imputation. In addition, imputed SNPs from low density 3K and 6K platforms to high density must be assessed in terms of predictive ability. Recently, technological advances in molecular genetics have greatly improved our ability to use information on DNA polymorphisms to select livestock. Genome-sequencing efforts have resulted in the availability of a reference genome sequence for most livestock species (cattle, sheep, chicken, pig, horse, buffalo). This has also resulted in the discovery of many thousands, and even millions of single-nucleotide polymorphisms (SNPs), which are single–base pair variations of individuals from the reference genome. The most common SNP chip used for cattle is from the company, Illumina (Illumina Inc., San Diego, CA). SNP chip identifies nearly 50000 SNPs and is thus called a 50K SNP chip. Approximately 40K of these SNPs are reasonably useful for a variety of reasons. Much larger and more expensive SNP chips are used for studying the genetic basis of disease in human populations and much smaller and cheaper SNP chips are being planned for cattle. The current cost to researchers for one 50K SNP chip plus analysis is nearly US$200; smaller chips could cost as little as US$20–50 [7]. Currently available whole genome SNP-chips used in GS in dairy cattle are given in [Table-1].

Table-1 *Currently available whole-genome SNP-chips*

Identification	Classification	Provider	Consortium	SNP No.
Bovine HD	Commercial	Illumina	Various	7,77,962
Bovine HD	Commercial	Genesleek	Various	80,000
Bovine HD	Commercial	Genesleek	Various	90,000
BovineSNP50v2	Commercial	Illumina	Various	54,609
BOS 1	Commercial	Affymetrix	Various	6,48,000
Bovine LD	Commercial	Illumina	Various	6,909

[1]HD=high density, LD=low density; [2]Illumina Inc., San Diego, CA; Affymetrix, Santa Clara, CA.

Genome Wide Breeding Value Estimation

In the terms of sources of information, the simplest model to predict genome wide breeding values only uses genotypic and phenotypic data, where genotypic data in recent commercial applications nearly always consist of SNP genotypes. This allows deriving an additive relationship matrix and incorporation of polygenic breeding values in the model. Whenever pedigree information is not available, the additive relationship matrix can be constructed directly from the genotypic information. In terms of pre-processing data, pedigree information can be compared with SNP information to discover possible genotype or pedigree errors, while pedigree and SNP information may be used jointly to derive marker haplotypes [8]. De Roos, *et al*. [4] showed that in order to accurately predict GEBVs for Jerseys, using prediction equations based on a Holstein–Friesian reference population, at least 300000 SNPs are needed, while the current available SNPs (approximately 50000) are sufficient for accurate predictions within the same breed. Since within the Holstein–Friesian breed, the average r^2 between adjacent SNPs at a marker density that resembles the used 50000 SNPs is between 0.15 and 0.20, it is expected that panels that may be used to predict breeding values across breeds or lines should capture at least the same level of LD across those breeds or lines. Eggen [12] diagrammatically summarized the process of genotyping reference population by using a whole-genome SNP array. The first step in the genomic selection process is the assessment of reference or training population with accurate phenotypes for the trait(s). Then, genotyped this population using a whole-genome SNP array the resulting data then serve as a reference to develop a statistical model estimating the effect of each SNP with the trait(s) of interest. This result is a predictive equation to calculate a genomic estimated breeding value (GEBV). After validation step, genomic breeding value of new animals can be computed using prediction equation, based on their genotypes from the SNP array and in absence of accurate phenotypes for these animals.

World-wide use of genomic selection in dairy cattle breeding schemes

To date, genomic selection has only been implemented in a few countries and mainly in connection with breeding programmes of Holstein cattle [13]. This breed was a good case study for developing genomic selection because it has been intensively selected for decades, hence strengthening statistical associations between markers and QTL. Furthermore, many large breeding programmes have been set up world-wide, facilitating the constitution of large reference populations. Thus, international collaborations to exchange genotypes allowed further improving the accuracy of genomic predictions [6]. The first genomic evaluations were officially released for a few Holstein populations in 2009. Different strategies have since been adopted to integrate genomic selection into existing breeding programmes. Focusing on the Holstein breed, Pryce and Daetwyler, [13] summarized the strategies adopted in eight countries by April 2011. Advancements have been rapid and a few countries such as Italy and the United Kingdom have now released GEBV for large populations of Holstein bulls. Utilization of genomic selection has accelerated among Holstein breeders. For example, in France, genomically tested bulls without milking daughters represented 39% of market shares in 2011. In most countries, PT continued to be carried out during this transition period. France was an exception, with PT officially ceasing in 2009 [13]. However, the number of AI sires used each year was increased, their diffusion was constrained to a few thousand straws per sire and farmers were encouraged to use teams of at least five young bulls. In other dairy cattle breeds, several difficulties have impeded the integration of genomic selection into breeding programmes. First, breeding programmes are generally of smaller size than Holstein programmes, which makes it more difficult to gather large reference populations. Several initiatives have, however, been created to exchange genotypes across countries, for example, the Inter Genomics consortium for the Brown Swiss breed [14] and the collaboration between breeding schemes of the Nordic Red Dairy cattle in Denmark, Sweden, Finland and Norway. Second, some of these breeds may have larger effective population sizes, resulting in weaker associations between markers and QTL. Both of these factors tend to reduce the accuracy of genomic predictions, which are generally lower than in Holstein populations. The recent use of high-density SNP panels [e.g. Illumina Bovine HD (777K)] was a promising option to increase GEBV accuracy in such populations. Having large densities in SNPs reduces the physical distance between markers and QTL, and hence should strengthen the statistical association between them. At such marker density, associations between markers and QTL may be also maintained across breeds, making it possible to build across-breed prediction equations and to capitalize on reference populations of several breeds. However, preliminary analyses of high-density chips with the genomic BLUP evaluation model only resulted in marginal gains within breeds and across breeds [15]. Szyda, *et al.* [16] studied statistical modeling of candidate gene effects on milk production traits in dairy cattle. The Phenotypic records were daughter yield deviations for milk, protein, fat yields, and, obtained from a routine national genetic evaluation. Out of all analyzed polymorphisms, DGAT1 K232A had a much larger effect on milk production traits than the other SNPs considered. Estimates of the additive genetic effect of K232A expressed as half of difference between Lys and Ala encoding variants were 107.4 kg of milk, 5.4 kg of fat, and 1.6 kg of protein at first parity, as well as 120 kg of milk and 6.8 kg of fat at second parity. Bionaz and Loor, [17] studied gene networks driving bovine milk fat synthesis during the lactation cycle. Marked up regulation and/or percent relative mRNA abundance during lactation were observed for genes associated with mammary; Hayes, *et al.* [18] reported the progress of genomic selection in Australian HF and Jerseys dairy cattle using a Bayesian method. They reported larger increases in accuracy for the Jersey animals when using a Bayesian method than when using a GBLUP method and the largest gain was observed for fat yield, which might be explained by a better ability to estimate the effect of the DGAT1 mutation in the combined dataset. Beecher, *et al.* [19] reported associations of polymorphisms in bovine immune genes with milk production traits in dairy cow. TLR4-2021 associated with both milk protein and fat percentage in late lactation. No association was found between this polymorphism and either yield or composition of milk within the bull population. CXCR1-777 significantly associated with fat yield and CD14-1908 A allele was associated with increased milk fat and protein yield. A *SERPINA1* haplotype with superior genetic merit significantly associated for milk protein yield and milk fat

percentage. Jiang, *et al*. [20] reported genome wide association for milk production traits in dairy cattle population. The majority of the significant SNPs is located within the reported QTL regions and some are within or close to the reported candidate genes. ARS-BFGL-NGS-4939 and BFGL-NGS-118998, are located close to the *DGAT1* gene and *GHR* gene, respectively. These findings herein not only provide confirmatory evidences for previously findings, but also explore a suite of novel SNPs associated with milk production traits, and thus form a solid basis for eventually unraveling the causal mutations for milk production traits in dairy cows. Pryce, *et al.* [21] studied a validated genome-wide association study in two dairy cattle breeds for milk production traits and fertility traits using variable length haplotypes. QTL mapping increased with haplotype length as did the number of validated haplotypes discovered, especially across breed. Bouwman, *et al.* [22] studied genome wide association of the milk fatty acids in Dutch dairy cows. The two-step single SNP association analysis found a total of 54 regions on 29 chromosomes that were significantly associated with one or more fatty acids. *ABCG2* and *PPARGC1A* on BTA 6; *ACSS2* on BTA 13; *DGAT1* on BTA 14; *ACLY*, *SREBF1*, *STAT5A*, *GH*, and *FASN* on BTA 19; *SCD1* on BTA26 and *AGPAT6* on BTA 27 Olsen, *et al.* [23] studied genome wide association mapping in cattle identifies QTL for fertility and milk production on BTA12. Genotyping costs were minimized by genotyping the sires of the cows recorded and by using daughter averages as phenotypes. The genotyped sires were assigned to either a discovery or a validation population. Associations were only considered to be validated if they were significant in both groups. Strong associations were found and validated on chromosomes 1, 5, 8, 9, 11 and 12. Several of these were highly supported by findings in other studies. The most important result was an association for non-return rate in heifers in a region of BTA12 where several associations for milk production traits have previously been found. Fuyong, [24] studied Genome-wide association analysis for 305-day milk production traits in dairy cattle. Totally, 1659 cows were genotyped resulting in 44668 effective SNPs in lactation 1 (LA1) and 1333 cows were genotyped resulting in 44054 effective SNPs in lactation 2 (LA2). The single SNP association analyses were conducted in the animal model, and all relationships between individuals in the pedigree were taken into account. 232 SNPs in LA1 and 125 SNPs in LA2 were identified as being significantly (false discovery rate < 0.05) associated with 305-day milk production traits. For 305D-MY, 128 SNPs distributed on *Bos taurus* autosome (BTA) 2, 4, 5, 6, 9, 10, 14, 15, 16, 21, and 28 were significant in LA1; and 49 SNPs distributed on BTA 4, 6, 7, 10, 11, 14, 22, and 25 were significant in LA2. For 305D-PY, 4 SNPs distributed on BTA 3 and 16 were significant in LA1; and 2 SNPs distributed on BTA 1 and 11 were significant in LA2. For 305D-FY, 159 SNPs distributed on BTA 2, 3, 4, 5, 8, 9, 12, 14 and 28 were significant in LA1; and 117 SNPs distributed on BTA 1, 2, 4, 10, 11, and 14 were significant in LA2. The majority of detected significant associations (231/232 in LA1 and 125/125 in LA2) were located within known quantitative trait loci (QTL) for the traits of interest; 1 SNP on BTA 2 (at 12.80 Mbp) that does not appear to be located within a known QTL region for MY, was identified as being significantly associated with 305D-MY, suggesting that this region is a new and unique QTL for 305D-MY in the Dutch dairy population. Region 2a, region 9, region 10b, region 11, region 14, 5 single SNPs and 2 unmapped SNPs showed significant associations with 2 studied traits; region 6, region 14 and 2 unmapped SNPs showed significant associations in both LA1 and LA2. Region 14 was the major genome region for 305D-MY and 305D-FY in both 2 lactations. Regions for 305D-PY had relatively small effects and we did not find regions with major effects on 305D-PY. The proportion of genetic variance explained by the SNP showing the strongest association per region ranged from 2.46% for 305D-MY in LA1 on BTA 9 to 33.50% for 305D-FY in LA2 on BTA14. The proportion of phenotypic variance explained by the SNP showing the strongest association per region ranged from 0.66% for 305D-MY in LA1 on BTA 9 to 5.98% for 305D-FY in LA2 on BTA14. Above all, the results of this study revealed genome regions for 305D-MY, 305D-PY and 305D-FY in the Dutch dairy cattle population, and the QTL identified in this study should be further studied to identify the causal mutations and candidate genes underlying the QTL. Gray, *et al.* [25] studied effectiveness of genomic prediction on the milk flow traits in dairy cattle. Milk flow measures for total milking time, ascending time, time of plateau, descending time, average milk flow and maximum milk flow were collected on 37 213 Italian Brown Swiss cattle. The Reliabilities from a validation dataset were estimated and used to compare accuracies obtained from the parental averages with genome enhanced predictions. The genome enhanced breeding values evaluated using two stage methods had similar reliabilities with values ranging from 0.34 to 0.49 for the different traits. Across two stage methods, the average increase in reliability from parental average was approximately 0.17 for all traits, with the exception of descending time, for which reliability increased to 0.11. Maxa, *et al.* [26] studied Genome-wide association mapping of milk production traits in Braunvieh cattle. Five hundred and fifty-four progeny-tested bulls and 36,219 autosomal single nucleotide polymorphism (SNP) markers on 29 *Bos taurus* autosomes (BTA) were included in the analysis. A principal component analysis was conducted to adjust for the effect of population stratification in the analyzed data set. For the principal component analysis, genome-wide relationships between individuals were calculated. Three different criteria (Horn's test, Kaiser's criterion, and Jolliffe's criterion) were tested to determine the number of significant principal components. Estimation of putative associations between SNP and milk production traits was carried out using a linear regression model in R software (R Foundation for Statistical Computing, Vienna, Austria). Significant principal components, adjusting for population stratification separately for each criterion and family relationships and genotypes at individual SNP were included as fixed effects in the model. The inflation factor λ and quantile-quantile plots were calculated to compare how the different criteria deal with stratification in our mapping population. Based on the analyses on all of the aforementioned criteria, we can conclude that Jolliffe's criterion deals the best with population stratification. Two SNP had an effect on milk yield on BTA4, 2 SNP affected fat yield on BTA14 and BTA23, and 1 SNP was associated with fat percent on BTA1. Meredith, *et al.* [27] reported genome wide associations for milk production traits in dairy cattle. Significant associations were detected for milk yield, fat yield, fat percentage, protein yield, protein percentage and somatic cell score. These associations were detected using two separate populations of HF sires and cows. In total, 1,529 and 37 associations were detected in the sires using a single SNP regression and a Bayesian method, respectively. Crepaldi, *et al.,* [28] studied associations of *ACACA*, *SCD*, and *LPL* genes with dairy traits in goats. *ACACA,* the major regulatory enzyme of fatty acid biosynthesis; *SCD*, involved in the biosynthesis of monounsaturated fatty acids in the mammary gland; and lipoprotein lipase (*LPL*), which plays a central role in plasma triglyceride metabolism. An approach somewhat similar to the granddaughter design for detecting quantitative trait loci in dairy cattle was followed. Effects of genotypes of a sample of 59 Alpine bucks on phenotypes of their 946 daughters raised in 75 flocks were investigated. Data comprised 13,331 daily records for milk yields (L/d), fat and protein yields (kg/d), and fat and protein contents (%) of 2,200 lactations. Population genetics parameters were calculated and associations between milk production traits and 10 single nucleotide polymorphisms (SNP) at the 3 genes were tested. Two markers at the *ACACA*, 1 for the *SCD* and 1 at the *LPL* locus, deviated significantly from the Hardy-Weinberg equilibrium, with an observed heterozygosity lower than expected. Flock, age of the goat, kidding season, and stage of lactation affected all traits considered, except fat percentage. Three SNP were found to be significantly associated with milk production traits. The SNP located on the *ACACA* gene showed an effect on milk yield. The marker on the *LPL* locus was highly associated with milk yield, with the largest values for CC daughters. Fang, *et al.* [29] studied a Multiple-SNP Approach for Genome-Wide Association Study of Milk Production Traits in Chinese Holstein Cattle. A fast method called MEML (Mixed model-based Expectation-Maximization Lasso algorithm) was developed for simultaneously estimate of multiple SNP effects. A series of simulation experiments were conducted to validate the proposed method, and the results showed that compared with SMMA, the new method can dramatically decrease the false-positive rate. Mai, *et al.* [30] studied a genome-wide association study for milk production traits in Danish Jersey cattle using a 50K single nucleotide polymorphism chip. QTL for milk production traits in Jersey cattle were mapped by a genome wide association analysis using a mixed model which incorporated 1,039 bulls and 33,090 SNP and resulted in 98 detected combinations of QTL and traits on 27 BTA. These QTL comprised 30 for milk

index, 50 for fat index, and 18 for protein index. The evidence presents 33 genome wide QTL on 14 BTA, of these 7 had effects on milk index 21 on fat index and 5 on protein index.

Conclusions

India is changing rapidly in aspects of life. The effect of westernization is one of the main factors responsible for societal changes, mostly related to living standards, changing diets, and accordingly a change of product lines in the retailers. The utility of genomic information in dairy cattle breeding schemes has now reached the level of accuracy that enables dramatic changes and improvements to breeding schemes. With denser marker panels, more sophisticated statistical tools and in the longer term, sequencing, it is expected that the accuracy of BVs will continue to improve and breeding schemes will utilize genomic information further at the expense of progeny testing. Current applications of genomic selection are only the start of the genomic era in livestock production. To fully capitalize on the benefits provided by GS, breeding programmes may need to be redesigned substantially.

Application of review: Genomic selection (GS) refers to genetic improvement of animals through selection based on genomic breeding values (GEBVs). GEBVs are computed using a reference population of animals that have a high diversity genotype as well as phenotypic information

Review Category: Milk production traits

Abbreviations:

GS : Genomic selection
QTL : Quantitative trait loci
SNP : Single nucleotide polymorphism
BTA : *Bos taurus* autosomes
GEBV : Genomic estimated breeding value
DGV : Direct genomic values

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