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Potential Use of Molecular Markers in the Genetic Improvement of Livestock

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Abstract: Recent developments in DNA technologies have made it possible to uncover a large number of genetic polymorphism at the DNA sequence level and to use them as markers for evaluation of the genetic basis for the observed phenotypic variability. The use of DNA markers to define the genetic makeup (genotype) and predict the performance of an animal is a powerful aid to animal breeding. Molecular markers are a tool to study the diversity on the genetic level. The ultimate use of DNA markers would be to identify Quantitative Trait Loci (QTL) in order to practice genotype selection. In recent years different marker systems such as RFLP, RAPD, STS, AFLP, SSR, SNP and other have been developed and applied to livestock. This study provides a brief overview of the current application of these markers in animal breeding.

Key words: Molecular markers, genetic diversity, QTL, Marker Assisted Selection (MAS), livestock

INTRODUCTION

To date, most genetic progress for quantitative traits in livestock have been made by selection on phenotype or on estimates of breeding values derived from phenotype without any knowledge of the number of genes that affect the trait or the effects of gene (Zakizadeh *et al*., 2007). The development of molecular techniques has been created new possibilities for the selection and genetic improvement of livestock. The discovery of the PCR had a major impact on the research of eukaryotic genomes and contributed to the development and application of various DNA markers (Gholizadeh and Mianji, 2007). Molecular techniques allow detecting variation or polymorphism exists among individuals in the population for specific regions of the DNA. These polymorphism can be used to build up genetic maps and to evaluate differences between markers in the expression of particular traits in a family that might indicate a direct effect of these differences in terms of genetic determination on the trait. More probably, they can prove some degree of linkage of the QTL effecting the trait and the marker. For genetic analysis, molecular markers offer several methodological advantages that are both attractive as well as amenable. For example: (1) the DNA samples can not only be isolated very conveniently from blood of live individuals but can also be isolated from tissues like sperm, hair follicle and even from archival preparations, (2) the DNA samples can be stored for longer periods and can readily be exchanged between the laboratories, (3) the analysis of DNA can be carried out at an early age or even at the embryonic stage, irrespective of the sex, (4) once the DNA is transferred on to a solid support, such as filter membranes, it can be repeatedly hybridized with the different probes and moreover, heterologous probe and *in vitro*-synthesized oligonucleotide probes can also be used and (5) the PCR-based methods can be subjected to automation (Mitra *et al*., 1999).

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APPLICATIONS OF MOLECULAR MARKERS

Genetic Diversity

Breed characterization requires knowledge of genetic variation that can be effectively measured within and between populations (Gholizadeh *et al*., 2007). Extinction of endangered farm animal breeds leads to an irreversible loss of genetic diversity. The need to conserve genetic diversity is widely accepted for biological, economic and cultural reasons (Oldenbroek, 1999). A main reason is that an abundant resource of genetic diversity within each livestock species is the prerequisite of coping with putative future changes in livestock farming conditions (Bennewitz *et al*., 2006). The maintenance of high levels of genetic variability and low levels of inbreeding are major objectives in conservation programs. Genetic variation is a prerequisite for populations to be able to face future environmental changes and to ensure long-term response to selection, either natural or artificial, for traits of economic or cultural interest (Frankham *et al*., 2003). Also, inbreeding levels should be kept as low as possible in order to avoid deleterious effects on fitness related traits which could compromise the viability of the populations (Fernandez *et al*., 2005). Three factors are considered as being largely responsible for the declining genetic diversity of livestock:

- Destruction of the native habitats of livestock breeds.
- The development of genetically uniform livestock breeds.
- Farmer and/or consumer preferences for certain varieties and breeds (and changes in these consumer preferences over time).

Of these, commercial interests are considered as the most important pressure on livestock diversity. Important factors in determining the direction and nature of change include: growth performance (productivity), pest and disease resistance, ease of handling, adaptation to current levels of technology and to a relatively minor extent consumer choice. A more reliable measure of differences among breeds is genetic distance, which can be estimated from the differences in the frequencies of different genetic variants (alleles) at a number of marker loci. From the patterns of within-population genetic variation at marker loci, it is possible to deduce demographic factors important to the conservation of domestic cattle diversity (Malevieiute *et al*., 2002) The primary aim of studying genetic diversity is to understand the extent of differentiation of populations within species. Population-specific genetic markers (alleles) can be generated using a range of methods available for detection of polymorphic loci (Gwakisa, 2002). Measuring diverse attributes of a population is important to its characterization, taking into account phenotypic traits, reproduction, geographic distribution, origin and habitat (Gholizadeh *et al*., 2006). The genetic characterization of populations, breeds and species allows evaluation of genetic variability, a fundamental element in working out breeding strategies and genetic conservation plans. Molecular markers have been comprehensively exploited to access this variability as they contribute information on every region of the genome, regardless of the level of gene expression (Pandey *et al*., 2006). Lynch *et al*. (1995) showed that small populations might decline in fitness due to the accumulation of detrimental mutations. Hedrick *et al*. (1996) suggested that low genetic variation in a species might be indicative of a recent population bottleneck and such a bottleneck did potentially indicate vulnerability to extinction. In small populations, genetic drift tends to reduce genetic variation, leading eventually to homozygosity and loss of evolutionary adaptability to environmental changes (Lande, 1988). Low genetic variation in a species may be an indication of a recent population bottleneck and such a bottleneck could result in inbreeding depression. Species with low genetic variation may be more vulnerable to environment change and consequently is vulnerable to extinction (Zhang *et al*., 2002). A variety of different molecular techniques are being used in various laboratories for the study of inter-and intra-specific

genetic variation at the DNA level. The most widely used techniques are restriction fragment length polymorphism of nuclear DNA and mitochondrial DNA, minisatellites, randomly amplified polymorphic DNA (RAPD), microsatellite, amplified fragment length polymorphism and sequencing of mitochondrial DNA (Gwakisa, 2002). Among these, microsatellites have quickly become the favourite agents for population genetic studies as they offer advantages which are particularly appropriate in conservation projects (Canon *et al*., 2001). For the analysis of genetic diversity in Lithuanian cattle breeds Malevieiute *et al*. (2002) chose the analysis on microsatellite markers. Microsatellite markers have also important qualities that make them very practical as molecular markers:

- They are variable and exhibit a high level of allelic variation.
- They are co dominantly inherited.
- All co dominantly inherited alleles in an individual are visible, which is not the case for dominant markers, such as blood groups.
- They are very versatile in their application; they may be used to detect genetic variability and population structure differentiation among populations, phylogeny; they allow paternity testing and evaluate recent genetic and demographic history, such as population bottleneck.
- They are easily analyzed and occur regularly throughout the genome, making them especially suitable for genetic analysis.

When a population goes through a bottleneck rare alleles tend to be lost and the average number of alleles per locus, allelic diversity, is reduced. Heterozygosity, however, is not reduced proportionally, because rare alleles contribute little heterozygosity. The difference between allelic diversity and heterozygosity is used as the basis for statistical tests detect presence of recent genetic bottleneck (Piry *et al*., 1999)

Marker Assisted Selection (MAS)

The idea behind marker assisted selection is that there may be genes with significant effects that may be targeted specifically in selection. Some traits are controlled by single genes but most traits of economic importance are quantitative traits that most likely are controlled by a fairly large number of genes. However, some of these genes might have a larger effect. Such genes can be called major genes located at QTL. Although the term QTL strictly applies to genes of any effect, in practice it refers only to major genes, as only these will be large enough to be detected and mapped on the genome. Following the pattern of inheritance at such QTL might assist in selection (Van Der Verf, 2000). For MAS to be effective, reliable estimates of QTL positions and effects are required. An adequate power, precision and accuracy of QTL analyses can only be expected from large, well suited mapping populations, using a marker set with good genome coverage and phenotypic values based on multi-environment field trials (Van Ooijen, 1992; Utz and Melchinger, 1994; Beavis, 1998). Close linkage between marker loci and QTL is required not only for minimizing the bias of estimated QTL effects but also for maximizing the frequency of the desired QTL genotypes under MAS. The importance of close linkage is even higher, if MAS is continued in recurrent cycles with intercrossing the selected progenies after each cycle (Geiger and Welz, 1999). The linkage disequilibrium, genome scan approach using anonymous molecular markers is one of the major strategies used to identify QTL affecting economic traits. Many studies have mapped QTL affecting several economic important traits in farm animals and meat-type chickens (Zhou *et al*., 2003). Molecular marker analysis allows to identify genome segments, so-called QTL, contributing to the genetic variance of a trait and thus to select superior genotypes at these loci without uncertainties due to genotype by environment interaction and experimental error. Selecting for favorable QTL effects based on marker data therefore has great

potential for improving quantitative traits (Geiger and Welz, 1999). The earliest form of Deoxyribonucleic Acid (DNA) marker used to construct the first true genomic maps was the restriction fragment length polymorphism (RFLP). The development of the Polymerase Chain Reaction (PCR) technique has revolutionized molecular genetics. The localisation of QTL provides markers linked to the trait genes that could be used in breeding programs to improve the selection for a particular trait. However, to be applied in this way it is first necessary to determine the phase of the alleles at the markers and trait gene (Williams, 2005). Potential benefits from marker assisted selection are greatest for traits that:

- Have low heritability (traits with observed or measured values that are a poor predictor of breeding value).
- Are difficult or expensive to measure (disease resistance).
- Can not be measured until after the animal has already contributed to the next generation (carcass data).
- Are currently not selected for as they are not routinely measured (tenderness).
- Are genetically correlated with a trait that you do not want to increase (most likely because associated genes affects one trait of the pair but not the other) (Van Eenennaam, 2007). One of the best examples of the application of MAS within population is the selection of young sires before their induction for actual progeny testing (Kashi *et al*., 1990a; Weller and Fernando, 1991). Inclusion of marker information for selection of young sires in progeny-testing programmes may lead to an increase of genetic gain by 15-30% (Piper and Bindon, 1982).

Molecular Approaches to Disease Resistance

Genetic resistance to infectious diseases has been a subject of many controversies. One of the tasks of genetic improvement is to select animals resistant to infectious diseases, especially those difficult and expensive to eradicate, in order to obtain healthy animals in which endogenous potentiality is optimized and therapeutic events reduced (Zanotti *et al*., 2002). Infectious diseases are responsible for major economic losses in livestock production. Although control of the environment by sanitation and isolation and massive use of vaccination and drugs, reduces the incidence of many diseases, the problem has not been eliminated (Heller *et al*., 1992). The linkage disequilibrium, genome scan approach using anonymous molecular markers is one of the major strategies used to identify QTL affecting economic traits. Many studies have mapped QTL affecting several economic important traits in farm animals (Zhou *et al*., 2003). To achieve sufficient power to identify linkage between marker loci and QTL with low to moderate effects requires a large sample of animals to be genotyped (Darvasi *et al*., 1993). The relatively high cost of marker genotyping limits these applications for genetic analysis and genetic improvement. The DNA pooling, also called bulk segregant analysis, is an efficient method to reduce costs in marker-QTL linkage determination by pooling DNA from selected individuals at each of the two phenotypic extremes, which are the most informative individuals (Darvasi and Soller, 1994). To identify a DNA marker for a disease gene animal material from a few related families should exist, comprising around 50 offspring of which at least 15 have the disease. When linkage has been found, it is natural to continue using markers between the two markers providing the linkage. The final goal will always be to identify the real disease gene. When linkage has been found, comparative studies can also be initiated. Candidate genes for the disease might be found by looking at the corresponding chromosome areas in other species, which are already known. An alternative to the classic marker analysis might be a careful study of the disease and thereby finding a candidate gene from another species. A candidate gene is a gene with a fair chance of causing the disease when comparing the aetiology of the disease. If one or more candidate genes exist, the analysis starts by typing these. If it is the right gene, complete association is found.

Parentage Determination

Breeding programs have been of considerable importance to improve productivity in the animal industry. In dairy cattle, progeny testing is the method of choice; however, this method presents two drawbacks limiting its use: high cost and increased generation intervals. These obstacles can be overcome when large numbers of progenies are obtained by artificial insemination (Baron, 2002). Since the breeding value of an animal is generally estimated using the information available from its relatives, the knowledge of correct parentage is therefore a prerequisite. Parentage identification in segregating populations generally takes place by means of the exclusion principle. That is, presence at some genetic locus in the offspring of an allele not found in either of the putative parents effectively excludes the particular parental pair from biological parenthood. The effectiveness of DNA fingerprints for parentage identification derives from the fact that over an entire population, each minisatellite locus exhibits a wide range of alleles, differing in their fragment lengths. As a result, over the population as a whole, numerous bands, differing in fragment length, can be identified, but only a few of these bands will be present in any one individual. There is thus only a small probability that two randomly chosen individuals will share all, or even a large proportion of the bands in their respective DNA fingerprints (Kashi *et al*., 1990b). DNA testing is the most accurate and reliable genetic analysis available for parentage testing. However, the accuracy or specificity of the DNA testing depends on the sample and procedure that the DNA laboratory has used. Since we utilize the most advanced genetic testing procedure, we are able to achieve at least specificity of 99.9%. In most cases, DNA testing will result in specificities of 99.99% or greater. If DNA patterns between the child and the alleged father do not match on three or more genetic markers, then the alleged father is excluded with 100% certainty. Parentage testing using molecular markers yields much higher exclusion probability (> 90%) than the testing with blood groups (70-90%) or other biochemical markers (40-60%) (Geldermann, 1990). Glowatzki-Mullis *et al*. (1995) demonstrated that using two triplex microsatellites, wrong parentage can be excluded with almost 99% accuracy.

Measuring Effective Population Size

Effective population size is one of the key parameters in population genetics. It is analogous to different measures of genetic variation within a population, which is a function of mutation rate, gene flow and population size (Kimura and Ohta, 1971). Several factors affect the prediction of effective population size, including sex ratio, mating system, selection, pattern of inheritance, changes in the population size over generations and population subdivision (Caballero, 1994). Intuitively one might expect the effective population size to be close to the adult population census size, but parameters such as reproductive failures, skewed sex ratios and substantial reproductive skews caused by specific mating systems can bias Ne up to several orders of magnitude below census size (Frankham, 1995a). Two advances in molecular genetics hold great promise for the application of genetic markers to the estimation of N_c or N_e of wildlife populations. These are: (1) the development of highly polymorphic DNA markers and (2) the ability to amplify these markers with the Polymerase Chain Reaction (PCR) from low-quality, low quantity DNA samples (Schwartzl *et al*., 1998) The effective population size (Ne) plays a central role in how a population evolves because Ne affects the degree to which a population can respond to selection, as well as its sensitivity to inbreeding effects (Crow and Kimura, 1970; Lande, 1995; Lynch *et al*., 1995). N_e can be estimated from genetic data in one or more samples (Waples, 1991). Most one-sample estimators use associations among alleles at different loci to infer N_e (Hill, 1981; Vitalis and Couvet, 2001). Multiple-sample methods infer N_e from temporal changes in allele frequencies or the rate of coalescence of alleles between sample periods (Nei and Tajima, 1981; Wang, 2001; Berthier *et al*., 2002). Accurate estimates of effective population size (Ne) are central to the development of appropriate conservation strategies in any species as Ne predicts the rate of loss of neutral, genetic variation, the fixation rate of deleterious and favourable alleles and the rate of

increase of inbreeding experienced by a population (Frankham *et al*., 2002). Importantly, the Ne of a population is often many times smaller than the census size (N) of the population, the Ne/N ratio averaging just 0.11 in a survey of vertebrate species (Frankham, 1995b). While estimates of Ne can be gained using direct methods based on field data (estimates of sex ratio bias, offspring production, variation in family size etc.), obtaining such data can be very cumbersome in many wild populations, especially in aquatic species. Hence, indirect methods for Ne estimation based on molecular marker data have also been developed. From a practical viewpoint, these methods can be broken down into two categories: those that require data from a single population sample (single generation methods: e.g., Hill, 1981; Pudovkin *et al*., 1996; Beaumont, 1999; Luikart and Cornuet, 1999) and those requiring samples from the same population collected at least one generation apart (temporal methods: Waples, 1989; Anderson *et al*., 2000; Wang, 2001; Berthier *et al*., 2002). An important recent advance has been the development of methods which take into consideration the effects of migration on Ne estimation. The major limitation to use of these methods is that double the sampling effort is required. The change in allele frequencies (F) between sample periods is an inverse function of Ne. Therefore, Ne can be derived from the amount of change in allele frequencies (Nei and Tajima, 1981; Waples, 1991). However, this estimator uses only the first two moments of the allele frequency distribution to obtain Ne and a number of approximations are made in its derivation. Several studies have noted that it is often biased high.

DISCUSSION

The development of molecular markers for genetic analysis has led to great increase in our knowledge of livestock genetics and our understanding of the structure and behaviour of animal genomes. For example, Selection of bulls for artificial inseminations is a very large contributor to decisions affecting genetic progress in current dairy cattle improvement with increasing knowledge of position and effects of major loci for quantitative variation, modification of traditional selection procedures based only on phenotypes will be needed. Molecular data will help eliminate undesirable alleles and increase favorable alleles (Rahimi *et al*., 2006). In recent years, the demonstration of genetic polymorphism at the DNA sequence level has provided a large number of marker techniques with variety of applications. However, utilization of marker-based information for genetic improvement depends on the choice of an appropriate marker system for a given application. For example, different types of markers have been used in paternity testing. In recent years, microsatellite markers have been used, because of their large polymorphism information content, widespread distribution in the genome, the type of samples that can be used the possibility to process several samples at the same time and the fact that the results are easy to interpret (Baron, 2002). Marker assisted selection is starting to be implemented in nucleus breeding programs. Trait heritability is the most important factor influencing the effectiveness of MAS. MAS seems to be most promising for traits with low heritability. But trait heritability is also of major importance for accuracy in the mapping of QTLs. Low heritability reduces the power of detecting QTLs, which is based on correlation between phenotype and marker genotype. This could mean that for well-mapped QTLs MAS may add little to phenotypic selection, while for traits with a very low heritability the underlying QTLs cannot be identified. It is the area in between these two extreme cases that looks most promising for application of MAS. If QTLs can be mapped for a trait having a low heritability the accuracy of the QTL position may not be very high, which is reflected in a large QTL support interval on the genetic map (Lee, 1995).

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