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Review Article

Review on Animal Diseases Resistance and Adaptation Improvement through Molecular Genetics

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Abstract

This review is conducted to highlight the application of molecular genetics for improvement of diseases resistance in livestock. Diseases prevention is a serious issue to restrict economic damage due to economically important diseases outbreaks worldwide. Over the last decades, the excessive use of drugs has been criticised because of the possible development of drug-resistant zoonotic organisms and the potential dangers of drug residues in food animal products for human consumption. To prevent this problem following the ways for host resistance improvement to disease is a low cost and sustainable approach. So, this literature review was done on the theory of how to use molecular markers to select for quantitative trait loci (QTL) in genetic improvement programs, both within populations and for introgression of QTL from one population to another. If the effect of each marker is known, then an animal with no available phenotype for disease can be genotyped and its direct genomic value can be estimated based on its genotype only. The advantage of such a method is that accurate estimates of genetic merit can be achieved exploiting knowledge of the genotype of the animal even if the animal is very young. So, it is possible to put recommendation for further research on the generation of phenotypes that are resistant to diseases and development accurate bio-markers that can be readily measured in large numbers of animals at a relatively low cost.

Keywords: *Adaptive, Diseases resistance, Livestock, Molecular genetics*

Introduction

Significant losses caused by livestock diseases continue to restrict livestock industries despite traditional control measures. Over the last decade, the excessive use of drugs has been criticised because of the possible development of drug-resistant zoonotic organisms and the potential dangers of drug residues in food animal products for human consumption. These problems and concerns suggest that other measures for the control of infectious disease should be sought to enhance animal health management programmes. To increase the overall level of resistance at herd and population levels newer strategies are expected to contribute significantly in this regard (Adams & Brandon, 1984; Van Der Zjipp, 1983).

Natural resistance to infectious diseases was first observed over one hundred years ago as familial tendencies in resistance or susceptibility to diphtheria in humans (Jacobi, 1880) but the genetic implications of this observation were not appreciated at the time, and another twenty years passed before the rediscovery of the studies performed by Gregor Mendel. With the renewed appreciation of the genetic principles proposed by Mendel, experimental animals were bred in the 1920s specifically to study natural resistance to a variety of infectious diseases. The fact that disease manifestations

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rarely occur in all members of the population exposed to bacterial pathogens had long been observed in domestic livestock, and studies of resistance to *Salmonella pullorum* in poultry and *Brucellasuis* in swine confirmed a major role for genetic control. Subsequent research on tuberculosis in twins confirmed the importance of genetics in determining the variability of susceptibility, while other studies have clearly differentiated the influence of genetics as compared to environment on premature death caused by infectious and non-infectious diseases (Sorensen *et al*, 1988).

The immune system has thousands of genes at its disposal (Breuer *et al*, 2013). Immune system provides protection from a wide range of microbes as well as tumours (Mallard *et al*, 2015). Livestock species have been selected for production traits but little attention was given to health traits, including immune response. Now a day it is possible to identify and selectively breed livestock with an inherent ability to make superior immune responses that can reduce disease occurrence, improve milk production and increase farm profitability (Thompson- Crispi *et al*, 2014).

Animal Disease Resistance and Adaptation Improvement

Until recently livestock species have been largely selected for production traits, little attention was given to health traits, including immune response. With several notable exceptions, particularly from the Nordic countries, breeding programs of the past selected aggressively for increased milk production. However, the current international breeding goals generally include functional traits such as fertility, udder health, type traits and functional survival (Miglior *et al*, 2005). So, it is possible to identifying and selectively breeding livestock with an inherent ability to make superior immune responses that can reduce disease occurrence (Thompson-Crispi *et al*, 2014). Healthier animals also may be expected to demonstrate improvements in other traits, including reproductive fitness and growth (Mallard & Wilkie, 2007; Thompson-Crispi *et al*, 2012; Hine *et al*, 2014; Aleri *et al*, 2015).

Knowledge of immune-genomics such as the quantitative trait locus (QTL), mapping of the combination of DNA variations, immune response by the host and the transcriptome can be used to identify disease resistant genes. Disease resistant genes are those encoding antibodies, microRNA and other materials that help the host to resist the damage caused by pathogens. Advances in the field of molecular biology have led to the discovery of many disease resistant genes. Genes such as major histocompatibility complex (MHC) genes, the Natural resistance-associated macrophage protein 1 (Nramp1) gene, Interferon (IFN) genes, Myxovirus-resistance (Mx) genes, anti-Avian leucosis virus genes and the Zyxin gene have been linked to disease resistance (Jie & Liu, 2011).

In most of the multicellular organisms single-nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variations (CNVs) are the major sources of genetic and genomic structural variations (Freeman *et al*, 2006). These genetic variations may be exploited to study the diseases resistance levels in different organisms. Genetic enhancement of the immune response can increase vaccine efficacy and disease resistance, thereby reducing drug residues in food. In order to reduce the drug residues in the food and introduce the genetic breeding programs for improving the disease resistance we need to have a better understanding of the disease resistant genes. Also, breeding for disease resistance requires tools such as indicator traits or genetic markers that can be used for selection.

Most studies discussed an antagonistic correlation between both animal health and resistance to disease and milk production implying that placing selection pressure on health and disease resistance will reduce genetic gain in milk production. So, selection on a balanced breeding goal will increase genetic gain in overall profitability if each of the traits is weighted appropriately by their respective economic values. Routine access to accurate phenotypes is vital to achieving sustainable genetic gain in animal health and disease resistance. However, for rare diseases in particular, a cost-benefit analysis of generating sufficient data to estimate breeding values and then incorporate these values into a breeding programme should be evaluated relative to embarking on a project to control the disease through other means. An expected response to genetic selection will take a long time to develop. Furthermore, when evaluating the economic benefit of breeding for disease resistance, some account must be taken of the impact of selection on its effects on the transmission of disease through the population and, therefore, the challenge faced by all animals including those not selected for resistance (MacKenzie & Bishop, 1999).

Studies aimed at detecting QTL for disease resistance will generally identify several or many QTL with various effects on different disease phenotypes. For example, studies conducted by Vallejo *et al* (1998) and Yonash *et al* (1999) identified 14 QTL associated with various indicators of resistance to Marek's disease, including the proliferation of tumors, survival and viremia. Similarly, Hanotte *et al* (2003) detected 16 QTL for various indicators of tolerance of trypanosomosis in a cross of N'Dama and Boran cattle. A critical question for the implementation of a breeding program is which of these QTL would be most effective in helping to control the disease? Another example of MAI in livestock is reported by Hanset *et al* (1995) on the successful introgression of the halothane normal allele into a Pietrain line that had a high frequency of the halothane-positive allele. Yancovich *et al* (1996) used marker-assisted background selection to speed up the recovery of the broiler genome when introgressing the naked-neck gene from a rural low-BW breed into a commercial broiler line.

Marker-assisted selection, combining the traditional genetic evaluation of an animal with its genotype at several loci, was originally proposed as a method of incorporating genomic information into genetic evaluations. However, few markers have been commercialized based on associations with quantitative traits related to animal health. The use of genetic markers for pre-screened animals for single gene genetic disorders or traits has, however, been successfully used in animal breeding (Dekkers, 2004).

Miniaturized genotyping platforms with individual detection elements capable of simultaneously assaying up to 777,000 distinct SNP genetic markers, which are evenly distributed across the bovine genome are now commercially available. However, whole genome sequencing on large numbers of animals will soon become feasible increasing the number of useful markers dramatically. Once each marker effect is known, then an animal with no available phenotype (e.g., a disease free newborn calf) can be genotyped and its direct genomic value (DGV) estimated based solely on its genotype. This is usually integrated with the traditional genetic evaluation of the animal to generate a genomic-estimated breeding value (GEBV). The advantage of such a method is that accurate estimates of genetic merit can be achieved exploiting knowledge of the genotype of the animal even if the animal is very young. Reliability estimates of up to 50% have been reported in the Irish genomic selection breeding programme for Holstein-Friesian dairy cattle in which no phenotypic data were available, which are higher than the approximate 30% reliability achieved previously using traditional methodology (Berry *et al*, 2009).

Applications

There are opportunities for using molecular genetics to identify genes that are involved in variety of traits. The first task is to understand the genetic control of the trait of interest and then to identify the genes involved. The main reasons why molecular genetic information can result in greater genetic gain than phenotypic information is:

1) Assuming no genotyping errors, molecular genetic information is not affected by environmental effects and, therefore, has heritability equal to 1;

2) Molecular genetic information can be available at an early age, in principle at the embryo stage, thereby allowing early selection and reduction of generation intervals;

3) Molecular genetic information can be obtained on all selection candidates, which is especially beneficial for sex-limited traits, traits that are expensive or difficult to record, or traits that require slaughter of the animal (carcass traits) (Naqvi, 2007).

Host resistance to disease is a low cost and usually sustainable approach to control of disease. Increasingly, other disease control measures are failing due to evolution of resistance of the pathogen to chemical or vaccine control measures. Important examples include the evolution of resistance to anthelmintic by nematodes in all major sheep producing countries, the evolution of resistance to antibiotics by bacteria, and the evolution of resistance to vaccines by the virus. Also, legislative changes in many countries are increasingly restricting the use of therapeutics in animal production systems. There are also examples of Governments dictating breeding strategies to farmers, such as the program to limit clinical expression of scrapie in sheep flocks in Western Europe, using selection for PrP genotypes associated with resistance to scrapie (Barton & Keightley, 2002).

For almost every disease that has been intensively and carefully investigated, evidence for host genetic variation in either resistance or tolerance has been found. Well-known examples include Marek's disease in chickens, F4 and F18 E. coli infections in pigs, and nematode infections, mastitis, dermatophilosis, trypanosomosis and theilerioisis in ruminants. In most cases, breeding programs exist that aim to select animals for enhanced resistance (or tolerance) to these diseases (Maillard *et al*, 2003).

Multiple techniques, including QTL mapping and linkage disequilibrium mapping methods, exist for mapping genes underlying adaptive traits based on marker-trait associations (Mackay, 2001; Phillips, 2005). In QTL mapping, loci controlling trait variation between two individuals are mapped to specific genomic regions. Initially, individuals that differ in traits of interest are crossed, and their progeny are inbred and backcrossed to generate populations of recombinant inbred lines (RILs). These RILs are typically homozygous throughout the majority of their genomes with different genomic regions being descended from each parent. When grown in a controlled setting or a common garden, phenotypic differences can be mapped back to the genome based on trait associations with parental markers. QTL mapping has played a prominent role in mapping genomic regions that control phenotypic variation in many species.

Linkage disequilibrium (LD) is the non-random association of polymorphisms within a population (Pritchard & Przeworski, 2001). Because polymorphisms that are in LD with a functionally important polymorphism will also be associated with any phenotypic differences caused by that polymorphism, LD can be exploited to map the genomic regions that underlie adaptations. In practice, LD mapping requires a sample of genotyped and phenotype individuals taken from a natural population or from a family with a known pedigree. Correlations between observed genetic variants and trait variation in this sample can then be measured, leading to the identification of specific polymorphisms or haplotypes that explain adaptive trait variation. In LD mapping, the mapping resolution is primarily influenced by the rate of LD decay.

Either cDNA- or oligonucleotide based whole genome microarrays are available for many species. Whole genome transcriptional analysis with these microarrays can be used to identify loci that control transcriptional differences between individuals. One increasingly used method is to analyse the transcriptomes of RILs in order to define expression QTLs (eQTLs), marker intervals correlated with transcriptional variation (Gibson & Weir, 2005). Such screens allow for the differentiation of cis and transeQTLs based on the position of the significant marker relative to the transcribed gene. In conjunction with genetic mapping, gene expression analysis provides a powerful tool for connecting genetic variation to adaptive trait differences. Not only will this technology help in the identification of evolutionarily important genes and polymorphisms, but it may also help to determine the functional molecular basis of adaptive trait changes.

Conclusions

Excessive use of antibiotics has been criticised because of the possible development of antibiotic-resistant zoonotic organisms and the potential dangers of residual antibiotics in food animal products for human consumption. Animal breeding for improved animal health or resistance to disease is constrained due to the necessity of routine access to accurate phenotypes (i.e., measurements) of health traits. Therefore, there are opportunities for using molecular genetics to identify genes that are involved in variety of traits. Armed with this information it would be possible to select improved livestock on the basis of their genetic makeup. There are many potential target diseases for the genetic improvement. Well-known examples include Marek's disease in chickens, F4 and F18 E. coli infections in pigs, and nematode infections, mastitis, dermatophilosis, trypanosomosis and theilerioisis in ruminants. Studies aimed at detecting QTL for disease resistance will generally identify several or many QTL with various effects on different disease phenotypes. Miniaturized genotyping platforms with individual detection elements capable of simultaneously assaying up to 777,000 distinct SNP genetic markers, which are evenly distributed across the bovine genome are now commercially available. So, it possible to put recommendation for further research on the generation of phenotypes that are resistant to diseases and development accurate bio-markers that can be readily measured in large numbers of animals at a relatively low cost. Furthermore, increased collaboration between veterinarians and animal breeders on the definition and collection of the relevant phenotypes, as well as the most appropriate statistical model, based on biological soundness, is vital to achieving genetic gain.

Conflict of Interest

There is no conflict of interest.

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