Genomics Research: Livestock Production

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Abstract

The major emphasis of animal genomic research has been to increase the productivity and disease resistance ability of economically important farm animal breeds to meet the ever increasing demands of animal products. Traditionally, the approach of livestock improvement was based on the classical breeding where in the parents of the next generation were selected based on their phenotype without knowing the genetic variation underlying the traits of interest. To this end, genomic tools have helped to move away from this "Black box" approach and understand the complex genetic components of phenotypic variation. Through structural and comparative genomics it had become possible to identify the genomic regions/quantitative trait loci (QTL) harboring the performance altering genes. However, the QTL search followed by fine mapping could prove useful to a limited extent as detection of casual mutations underlying QTL's was time consuming and cost extensive. These limitations restricted the extensive implementation of marker assisted selection technology in the commercial breeds. Recent advances in genomic research including whole genome sequencing, expression array, and highly multiplexed and high throughput single nucleotide polymorphism (SNP) genotyping platforms have a large impact on the ability for genome mining and pinpoint genes that influence biological and economically important traits. In future, selection decision based on the genomic breeding values complemented with other quantitative genetic evaluation approaches can very well lead to improve genetic gain in livestock species. In this chapter, an effort has been made to describe the issues, scope and needs those confront the animal genomics community in today's industry driven era.

INTRODUCTION

Livestock science has an increased challenge to meet the food demand for an ever-expanding world population. Livestock production started ~8000–10,000 years ago with the domestication of various livestock species. Along with domestication, livestock improvement was attempted following a classical breeding approach where parents of the next generation were selected on the basis of their phenotypes. This was somewhat a black-box approach as nothing in specific (DNA sequence, gene, or underlying traits?) was known and thus, it had limitations to improve the livestock production. Simultaneously, with the rise in income and urbanization, the demand/consumption of milk and meat has been increasing tremendously (Table 1, Fig. 1). During the 1996/1998–2020 period, the projected growth rates in developing countries for milk and meat are projected to be 3.0 and 2.9% annually, respectively. In addition, by 2020–2030, world demand for meat and dairy products is expected to increase by 40–50%.[2] To increase the production of meat and milk, it is not recommended to add on the number of livestock because of the associated pollution risks. Hence, introduction of new technologies to meet the ever-increasing demand for the livestock products is of great urgency.

The biological mechanisms linking genetic variation with phenotype have been the major challenge for researchers. Understanding and capturing the genetic component of phenotypic variation could play an important role in productivity enhancement in the livestock species. The molecular genetics revolution in the 1980s and 1990s led to the emergence of a new scientific discipline, genomics, resulting from the convergence of genetics, molecular biology, and bioinformatics. The objective of genomics is systematic structural and functional analysis of complex genomes to understand what individual genes do and how they interact to control biological processes. The genomic tools have helped to know how to predict "sequence to consequence" and harness this genetic variation to facilitate stable changes in production, fertility, and health through selection. Advances in genomics have contributed significantly toward the quality and efficiency of livestock production such as commercial strains of chickens growing at implausible rates or pigs growing considerably faster, leaner, and utilizing much less feed and with increased litter size.

Encyclopedia of Biotechnology in Agriculture and Food DOI: 10.1081/E-EBAF-120043005

Table 1 Projected food consumption trends of various livestock products to the year 2020 in developing world.

	Projected growth of consumption (%/yr)	Total consumption (million metric tons)		Percent of total world consumption	Per capita consumption (kg)	
	1997–2020	1997	2020	2020	1997	2020
Beef	2.9	27	47	61	6	7
Pork	2.4	47	81	67	10	13
Poultry	3.9	29	49	64	7	8
Meat	3.0	111	188	65	25	30
Milk	2.9	194	391	57	43	62

Sources: From Delgado;[1] FAOSTAT statistical database. FAO,[2] http://faostat.fao.org/ default.aspx.; ftp://ftp.fao.org/docrep/nonfao/lead/x6155e/x6155e00.pdf.

Note: Consumption indicates direct use as food, measured as uncooked weight, bone in. Meat includes beef, pork, mutton, goat, and poultry. Milk represents cattle and buffalo milk and milk products in liquid milk equivalents. Metric tons and kilograms are three-year moving averages centered on the years shown.

Genomics can be grossly divided into two basic areas: 1) structural genomics; and 2) functional genomics. Structural genomics corresponds to characterization of the physical nature of whole genome and functional genomics is the understanding of the genes transcribed and translated into protein products, their interactions, and also the regulation of these processes.

STRUCTURAL GENOMICS

Structural genomics encompasses construction of genetic maps, physical maps, comparative maps, and ultimately, the determination of the complete DNA sequence of the genome of interest with a goal to understand the genome organization and locate DNA sequence variations, i.e.,

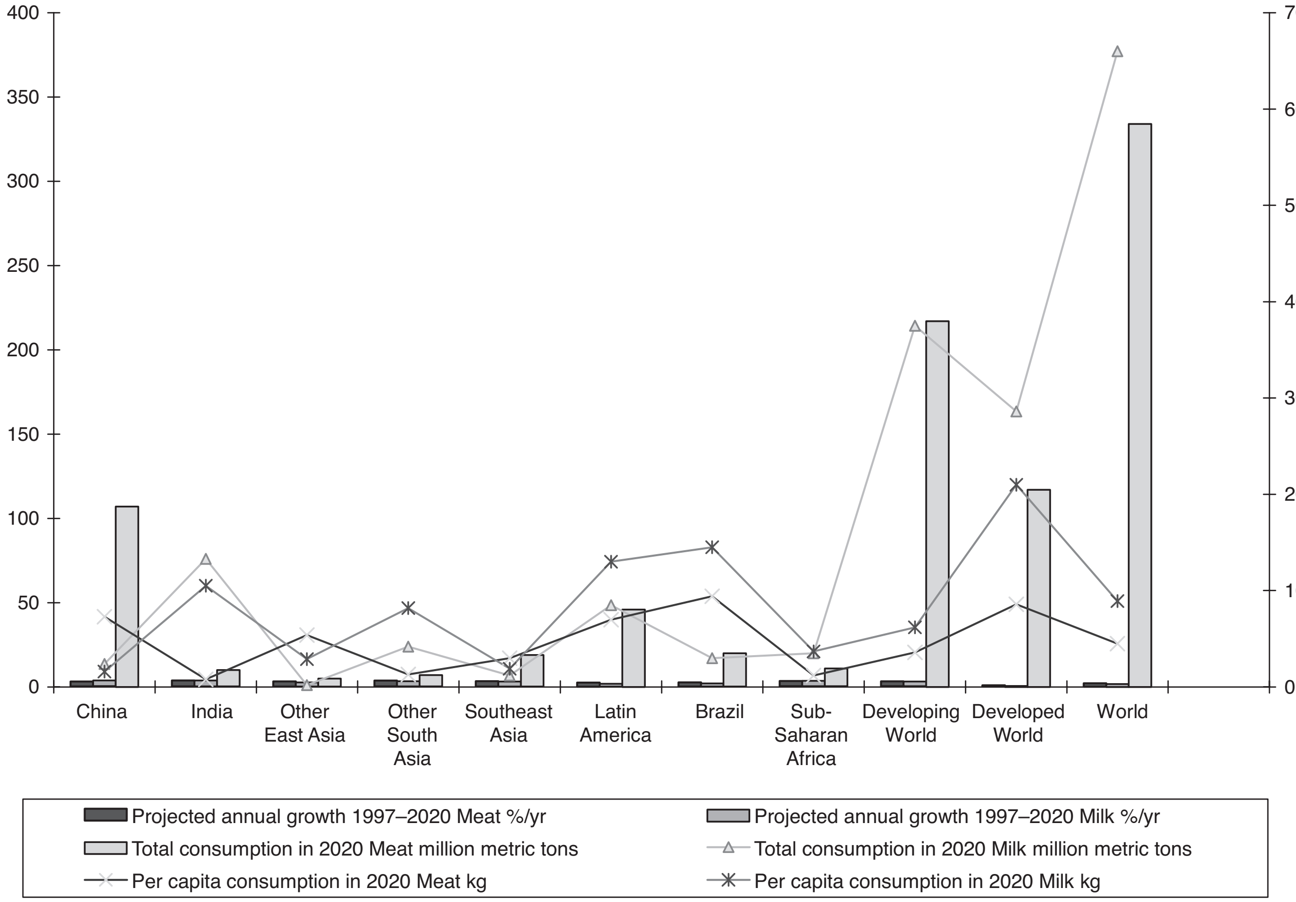

Fig. 1 Trend of demand vs. projected production of meat and milk. **Sources:** From Delgado.[1] FAO annual data 2002, total and per capita meat consumption for 1997 are annual average of 1996–1998 values. Projections are from the July 2002 version of IMPACT.

Table 2 Status of quantitative trait loci identified in different livestock species.

Species	QTLs	Traits
Pig	1831	316
Cattle	1123	101
Chicken	657	112
Sheep	53	28

Source: From http://www.animalgenome.org/QTLdb.

polymorphisms. Structural genomics started in 1980s with the genetic mapping to identify the locations on the chromosome that might contain the performance altering genes, which however, was not a very successful approach as the sequence of the DNA was not known. The development of new techniques enabled identification of genes that underlie the genetic variation of production traits in livestock species.

Although scientists have been searching for quantitative trait locus (QTL, a region that contains a gene [or locus] affecting a quantitative trait) in livestock for over 40 years, genome-wide QTL studies could not be conducted until genetic markers that spanned the entire genome were developed. For construction of high-density genetic maps, microsatellite markers (repetitive sequences) were the markers of choice because of their high polymorphism and abundant distribution throughout the genome. Microsatellite-based high-density genetic maps facilitated the fine mapping of hereditary traits of agricultural importance, characterization of meiosis, and provided a foundation for physical map construction. Resource populations required for construction of genetic maps were developed by crossing widely divergent breeds representing different alleles having large effects on QTLs. Worldwide resource populations are available for most of the livestock species and has been successfully used to identify numerous economically important trait loci (ETL) in a variety of livestock species (Table 2). The information related to livestock QTL is available in the animal quantitative trait locus database (AnimalQTLdb, http://www.animalgenome.org/QTLdb).

Over the years, QTL studies have contributed considerably to the development of more efficient selection procedures employing genetic markers, a strategy called marker-assisted selection (MAS). Presently several gene tests are being used in MAS programs to improve milk and meat quality, growth and reproduction in various livestock species (Table 3). QTL studies have improved the swine industry the most with several gene tests being used under MAS program for various production traits in over 60% of the pigs produced in United States.[4] However, mapping of QTL is not a very straightforward approach. It has been very difficult to search for a gene or mutation causing a QTL effect in an area surrounded by millions of unknown DNA sequences in the region. To locate these genes, the concept of comparative genomics was applied.

Comparative genomics utilizes the DNA sequence similarities between species. Although the arrangement of DNA sequences is not identical across species, large regions of the genome/functional elements have been conserved throughout evolution. Hence, it is possible to harness the information available in the gene-rich mammalian species and extrapolate the same in livestock.

Comparative mapping has been very effectively used to identify a number of genes in livestock.[5] The best example of the use of comparative genomics in livestock is the localization of chromosomal region containing the double muscling gene. Two research groups were able to localize the QTL effect to bovine chromosome 2 in the mid-1990s based on its location in the mouse genome. However, the specific gene was annotated in cattle by comparative mapping after the identification of "myostatin" gene in mice having a large impact on muscle development. The myostatin or GDF8 gene was mapped to a region of the human genome syntenic to that of bovine chromosome 2 and a single nucleotide switch from guanine to adenine at codon 313 in the gene that caused the double muscling effect was identified. Grobet et al.[6] were able to inactivate the GDF8 gene postnatally and demonstrated that these animals achieved the same level of muscle hypertrophy as animals with inactive myostatin genes. Such information is beneficial to the cattle industry as the percentage of lean in the carcass could be increased without the associated problems of dystocia because of the heavy muscled fetus. A few other genes that have been mapped in cattle through the "QTL search followed by comparative fine mapping" approaches include the thyroglobulin and calpastatin genes affecting the degree of marbling and meat tenderness; diacylglycerol acetyltransferase (DGAT) having an affect on fat deposition in milk and leptin, a protein important in energy metabolism.

Linkage maps, QTL searches, comparative mapping, and fine mapping were useful, but time-consuming and cost extensive. Most of the economically important traits in livestock are under the control of numerous genes simultaneously, and interact both with one another as well as the production environment. Searching these genes one by one and establishing the genotype–phenotype association was a gigantic task. Later, in the last half of 1990s, the efforts started for the whole genome sequencing of human and mouse using high-throughput sequencing (National Human Genome Research Institute, NHGRI) and whole genome shotgun (Celera genomics) approach. The animal scientists took advantage of infrastructure built by the NHGRI and efforts were initiated for sequencing the major livestock species.

The first drafts of the sequence of chicken and cattle genomes were completed in 2005 (http://www.genome.gov/12512874). In 2006, the sequencing of the horse and the pig genomes was also begun, with the first draft of the horse sequence completing in 2007, and the

Table 3 Commercial DNA tests available for different livestock species.

		Species		
Trait category	**Cattle—dairy**	**Cattle—Beef**	**Sheep**	**Pig**
Congenital defects	BLAD	CMS		RYR
	Citrulinaemia	Citrulinaemia		
	DUMPS	Congenital myasthenic syndrome		
	Freemartinism	Freemartinism		
	MSUD	MSUD		
	Mannosidosis	Mannosidosis		
	CVM			
Genetic disorder	α-Mannosidosis	α-Mannosidosis		
	β-Mannosidosis	β-Mannosidosis		
	Bovine hereditary zinc deficiency	Bovine hereditary zinc deficiency		
	Dwarfism	Dwarfism		
	Factor XI deficiency	Pompes disease (E7)		
	Factor IX deficiency	Pompes disease (E13)		
	α-Mannosidosis	Myophosphorylase deficiency		
	Hypotrichosis and oligodontia	Inherited congenital myoclonus		
	Deficiency of uridine			
	Monophosphate synthetase			
	Weaver syndrome	Protoporphyria		
	Platelet bleeding	Platelet bleeding		
	Albinism			
	Muscular hypertrophy	Muscular hypertrophy	Prp	F18
Disease	MC1R/MSHR	MC1R/MSHR		MC1R/MSHR
Appearance	Red coat color	Red coat color		CKIT
	Black coat color	Black coat color		
	TYR or Albinism	MGF or Roan		
Milk quality	κ-Casein			
	β-Lactoglobulin			
	FMO3			
Milk yield and composition	κ-Casein			
	GRH			
	DGAT			
Meat quality	TG			RYR
	CAST			RN/PRKAG3
	CAPN1			>15 PICmarq
	CAPN3			
	RN/PRKAG3			
	RYR			
	GH1			
Growth and composition		Myostatin	Callipyge	MC4R
				IGF-2
Reproduction			Booroola	
			Inverdale	
			Hanna	
Feed intake				MC4R

Source: From J. Anim. Sci.[3]

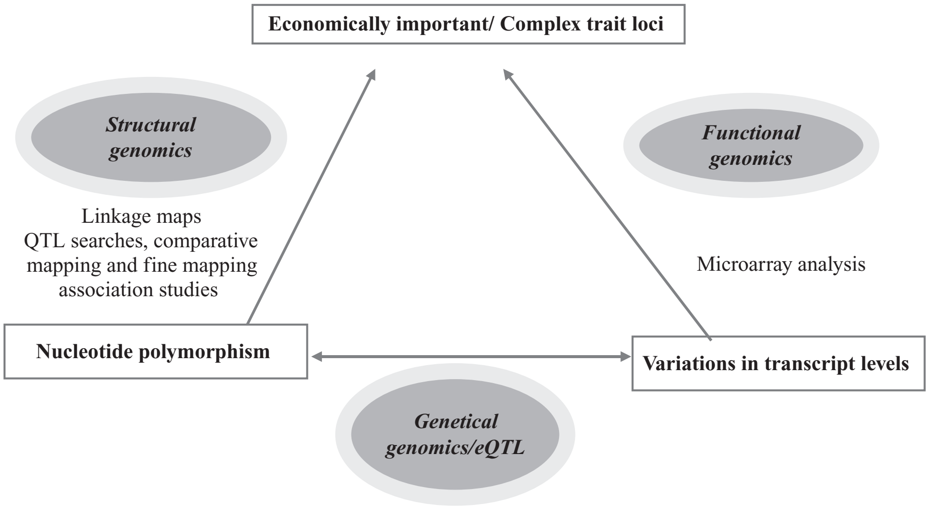

Fig. 2 Integrative approaches applied to decipher economically important traits.

pig sequence draft has also become available recently (http://www.ensembl.org/Sus_scrofa). Taking advantage of the availability of sequence draft, single nucleotide polymorphism (SNP) arrays have already been developed for chicken (Illumina^{TM} 18K iSelect chip), cattle (Bovine 50K Illumina^{TM} iSelect chip), pig (Illumina^{TM} iSelect pig DNA chip, 60K), and sheep (Illumina^{TM} OvineSNP50) and are under development for other livestock species. SNP chip provides a platform where hundreds or thousands of markers can be genotyped in a cost effective manner. SNP array-based association studies are being extended to traits like behavior, disease resistance, and structural and environmental soundness.[7]

With the availability of species-specific SNP chips, it is now possible to undertake whole genome scans[8] and genomic selection approaches can be accomplished to correlate phenotype and genotype across the whole genome simultaneously, rather than by one locus at a time. Thus, SNP-based platforms are available to predict the molecular genetic value of individual animals for specific traits, viz., marbling and tenderness in beef cattle. SNP chips also provide a higher resolution map of the genome that can be used to detect region of chromosomal abnormalities, e.g., aneuploidies, microdeletions, microduplications, and loss of heterozygosity (LOH). As a variety of diseases are linked to such chromosomal abnormalities, SNP chips have the power to identify such regions and provide insight about the diseases and further suggest targets for intervention.[9]

FUNCTIONAL GENOMICS

QTL mapping is a powerful method and a number of QTLs have been reported in various livestock species, but only a few of these have been localized at the gene level.[10] A gap still exists in the knowledge to localize QTL and then, to identify the underlying genes and their function which reduces the ability to harness the potentials of genomics. With the recent completion of the genome sequence of the major livestock species and availability of high-throughout technology, a functional genomics approach can now be used for the assignment of function to the identified genes and also for the organization and control of genetic pathways combining to determine the complex phenotype. The use of microarray technology for global profiling of gene expression is the primary method of functional genomics and has made it possible to compare expression levels for active genes under a variety of genetic and environmental conditions. Examples showing the power of this technology include identification of set of genes conferring resistance to Marek's disease in chicken and *Trypanosoma congolense* infection in cattle.

Another powerful application of microarray technology is to synergistically harness the powers of recombination and functional analyses in a combined approach known as "Genetical Genomics," or expression QTL (eQTL) mapping (Fig. 2). Such an approach has the potential to identify *cis*-acting and *trans*-acting genes in the region of the functional QTL and master regulators of quantitative trait variation as well, wherein polymorphisms at a single locus may regulate/control variation in gene expression of many other genes. Genetical genomics approach allows one to understand the groups of genes and governing variation in complex traits. Integrated information on phenotypic traits, pedigree structure, molecular markers, and gene expression can be used for estimating heritability of mRNA transcript abundances so as to infer the regulatory gene network and map eQTL. Such studies will help in answering the questions concerning genes involved in meat and milk production, meat and milk quality and composition, and response to production systems/husbandry stressors. Eventually, this knowledge will further aid in selection and management of livestock.

IMPLICATIONS OF GENOMICS

The most important utilization of the genomic data toward livestock production would be the use in selective breeding. Traditionally, the selection methods are based on the estimated breeding value (EBV) for traits of economic importance that are estimated from phenotypic records, genetic covariances among traits, and pedigree relationships in populations. In most cases, however, the actual location, identity, and functional role of the QTL remain unknown. In addition, efficiency of traditional selection practices is low when the traits are difficult to measure and have low heritability.

Solution to these problems is gene-assisted selection, which is easily applied to traits that are difficult to measure, and have low heritability and slow genetic change. With the availability of the high-throughput platforms (SNP array), it is possible to incorporate DNA information from markers into EBVs. Selection decisions based on genomic breeding values (GEBV) are calculated as the sum of effects of dense genetic markers or haplotypes across the entire genome and thus, all the QTLs contributing to variation in a trait are captured. The QTL effects are first measured on a large reference populations with phenotypic records and then, only marker information is required to calculate GEBV in subsequent generations. GEBV holds special importance in developing countries where structured resource populations are not available for most of the livestock species. GEBV approach has already been evaluated in United States, New Zealand, Australia, and the Netherlands and is expected to double the rate of genetic gain in the dairy industry.[11]

SUMMARY

The demand for livestock products is projected to grow significantly in the developing countries. Traditional breeding methods are not well equipped to meet this increasing demand of meat and dairy products. The integrated use of structural and functional genomics has the potential to speed up the livestock production progress through understanding the genotype–phenotype relationship and genotype × environment interaction of livestock genomes as a whole. Selection decisions based on GEBV are made possible with the advances in the whole genome sequencing and high-throughput SNP panels. This approach of GEBV to select animals with desired allelic combinations is cost effective and can even target non-measurable traits.

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