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Review

Bovine genomics update: making a cow jump over the moon

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Summary

Recent research in bovine genetics has focused on characterization of the biological differences underlying phenotypic variation for qualitative and quantitative traits of economic value in existing cattle populations. The much-anticipated benefits of DNA-based tools to routinely guide selection decisions for more efficient genetic gain and widened profit margins have not been fully met since the origin of this premise over two decades ago. However, the impending release of a high-quality draft genome sequence in 2005 should mark a turning point in these efforts. The following discussion summarizes how the bovine genetics research community has positioned itself to fully utilize a genome sequence resource and frames how genome sequence information can not only be applied to better implement marker-assisted selection, but also address rising consumer concerns relative to animal well-being and food safety.

1. Introduction

Selection for desirable phenotypes has been practised in cattle since domestication approximately 7500–10 000 years ago. More than 1 billion cattle populate the world, and nearly all these animals were derived from *Bos taurus* and *Bos indicus* cattle subtypes that diverged approximately 100 000 years ago prior to their separate events of domestication (Loftus *et al.*, 1994). Today, at least 264 breeds have been established to produce meat, milk and draft animals in a broad range of management systems under differing environmental conditions (see Table 1).

For the past two decades, the application-based goal that has driven research in bovine genetics has been the premise that selection of animals based on DNA marker information will account for substantial variation inherent in quantitative genetic approaches of selection. The economic value of this research stems from the potential of marker-assisted selection (MAS) to shorten generation intervals and reduce the cost of progeny testing by more accurately distinguishing animals with desired allele combinations for well-defined selection objectives. The promise of this potential, especially with regard to capturing the value of lowly heritable traits and widening profit margins, continues to be anticipated by producers. Therefore, one purpose of this discussion is to assess accomplishments in bovine genomics relative to MAS implementation in the dairy and beef cattle industries. Although the role of MAS in the production scheme is still in its infancy, past efforts to construct genetic resources for identifying genes of large effect and quantitative trait loci (QTL) of interest have been considerable; genomic locations for 28 monogenic traits and more than 200 potential QTL (suggestive and genome-wide significance) have been identified (Table 1).

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2. Linkage maps

Clearly, linkage maps of the bovine genome were the most critical resource needed to map QTL and generate the type of genetic information for development of the MAS-based cattle breeding programmes initially proposed by Beckmann & Soller (1983). The first reference linkage maps were developed using microsatellite markers, and the resolution and coverage of these maps was adequate to select markers for QTL analysis in most populations on a genome-wide basis (Barendse *et al.*, 1994; Bishop *et al.*, 1994). Subsequent medium-density versions of these initial linkage maps were produced (Barendse *et al.*, 1997; Kappes *et al.*, 1997) along with two lower-density male-specific linkage maps (Georges *et al.*, 1995;

Table 1. *URL resources for bovine genetics and genomics*

	Web URL address
Phenotypes	
Cattle breeds	http://www.ansi.okstate.edu/breeds/cattle/
Dairy traits[a]	http://www-interbull.slu.se/national_ges_info2/framesida-ges.htm
Definitions of conformation traits[a]	http://www-interbull.slu.se/conform/framesida-conf.htm
Definitions of udder health[a]	http://www-interbull.slu.se/udder/framesida-udder.htm
Map resources	
USDA, MARC linkage map	http://www.marc.usda.gov/
Dairy QTL map	http://www.vetsci.usyd.edu.au/reprogen/QTL_Map
COMRAD RH map	http://www.projects.roslin.ac.uk/comrad/mapsmarkers.html
TX/IL RH map	http://cagst.animal.uiuc.edu/ComparativeGenomics.html
BAC libraries and map	http://www.bcgsc.ca/lab/mapping/bovine
Bovine Genome project	http://www.ncbi.nlm.nih.gov/genome/guide/cow/ http://www.usda.gov/news/releases/2003/12/0420.htm
Causative variation and marker tools	
Single gene traits and disorders	http://www.angis.org.au/Databases/BIRX/omia/mdmd.html#_CATTLE
Igenity L	http://us.igenity.com/index.asp
TenderGENE, DoubleBLACK, ParentMATCH	http://www.geneseek.com/index.sp
GeneStar Marbling, Tenderness 2, Black & Sire Track	http://www.bovigensolutions.com/
Quantum, Optimum, epidermolysis bullosa	http://www.boviquest.com/Index.asp
National Beef Cattle Evaluation Consortium	http://www.nbcec.org/nbcec/

[a] Based on National Genetic Evaluations and phenotypic traits defined by country.

Ma *et al*., 1996). Combined, these maps have provided all the necessary microsatellite marker information needed to scan the genome for segregating QTL in all population types. Only the USDA linkage map has continued to improve marker interval resolution by adding gene-associated single nucleotide polymorphism (SNP) markers (Stone *et al*., 2002) and increasing microsatellite marker density through a joint effort by the USDA, Meat Animal Research Center (MARC) and the Shirakawa Insitute of Japan (Gary Bennett and Yoshikazu Sugimoto, respectively, personal communication). The current USDA linkage map of approximately 3200 centimorgans (cM) positions 3898 microsatellite markers, 921 SNP markers, and 64 other marker types across the 29 bovine autosomes and X and Y chromosomes (Gary Bennett, personal communication).

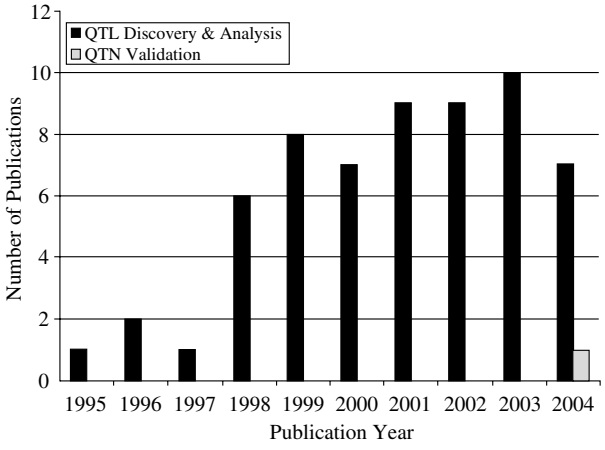

Fig. 1. QTL detection and analyses in cattle.

3. QTL detection

Since the first reported genome-wide QTL analysis by Georges *et al*. (1995), the quantity and breadth of QTL mapping reports have steadily increased, and this trend has continued into 2004 (Fig. 1). Cattle QTL results are generated from two different categories of phenotypic data: that acquired from national genetic evaluations of commercial populations and that recorded by researchers from experimental populations.

QTL detected in commercial populations have typically corresponded to phenotypes recorded for dairy production, conformation and health traits (Table 1). Because of its origin, QTL analysis methods for this type of phenotypic data were formulated to leverage the large half-sib families generated by the extensive use of artificial insemination for progeny testing dairy bulls. Weller and colleagues (1990) proposed the use of the granddaughter and daughter designs to utilize this existing population structure to detect QTL. QTL analyses have been done using this methodology for Holstein grandsire and sire families in Canada (Plante *et al*., 2001), France and Germany (Bennewitz *et al*., 2003), Israel (Mosig *et al*., 2001), Holland and New Zealand (Spelman *et al*., 2000) and the United States (Ashwell *et al*., 2004). Other dairy

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breeds with large half-sib pedigrees in Finland (Viitala *et al*., 2003), France (Boichard *et al*., 2003), Norway (Olsen *et al*., 2002) and the United Kingdom (Wiener *et al*., 2000), have also been analysed for dairy and health-related QTL.

A summary and comparison of QTL results which were generated from these dairy populations and published before May 2003 (45 of 55 publications), was recently published by Khatkar *et al*. (2004). In this study a draft QTL map for dairy production was produced (see Table 1 for URL). This map provides an illustration of how QTL with pleiotropic effects across milk production traits may be segregating on chromosomes (chr) 3, 6, 9, 14 and 20 in several dairy populations. Putative quantitative trait nucleotides (QTN) for QTL on chr 14 and 20 have been identified as SNPs in the coding regions of *diacyglycerol acyltransferase 1* (*DGAT1*; Grisart *et al*., 2002) and *growth hormone receptor* (*GHR*; Blott *et al*., 2003), respectively. Recent analyses also support the presence of multiple QTL affecting milk production traits on chr 6 and 14 (Freyer *et al*., 2003; Bennewitz *et al*., 2004, respectively). Since the summary of QTL by Khatkar and colleagues, another five publications describing QTL detection and map refinement have been published (Ashwell *et al*., 2004; Hiendleder *et al*., 2003; Liu *et al*., 2004; Schulman *et al*., 2004; Van Tassell *et al*., 2004). Interestingly, the report by Hiendleder and colleagues (2003) was the first to describe the locations of novel QTL for nervous/aggressive or docile behaviour during milking. Study of traits related to behaviour will become increasingly important to understand for the purpose of responding to consumer concerns over animal well-being in intensive production systems.

QTL reports from experimental populations have occurred at a much lower frequency. This may be due in part to the high costs of creating, maintaining and phenotyping populations at a research facility. However, the different experimental populations have provided an opportunity to detect QTL for growth, carcass, meat quality, ovulation rate and parasite indicator traits. These latter three traits are either lowly heritable or too impractical or expensive to collect in commercial populations.

The majority of the growth and carcass QTL results were generated using beef cattle populations developed at the USDA, MARC (for results summary see Smith *et al*., 2003). Other QTL for carcass traits and growth were reported for a Brahman × Angus backcross/F2 and Line 1 Hereford backcross populations (Kim *et al*., 2003; MacNeil & Grosz, 2002, respectively). Together, over 100 QTL of genome-wide and suggestive significance have been detected for these types of trait. Comparison of all these results suggests common QTL of significance are located on chr 2 and 5 affecting fat deposition and on chr 6 affecting birth weight. Putative QTN were found at two locations in the coding region of *mu-calpain* (*CAPN*) for QTL affecting tenderness on chr 29 and in the 5′-region of *thyroglobulin* (*TG*) for QTL affecting marbling on chr 14 (Page *et al*., 2002; Barendse, 1999, respectively).

The majority of ovulation rate QTL results were generated using the twinning population developed at the USDA, MARC (Arias & Kirkpatrick, 2004; Blattman *et al*., 1996; Kappes *et al*., 2000; Kirkpatrick *et al*., 2000). QTL for ovulation rate were also detected in a commercial Norwegian dairy population using twinning phenotypes (Lien *et al*., 2000). Comparison of results between these two populations suggests common QTL affecting ovulation rate are segregating on chr 5 and 23.

QTL corresponding to phenotypic indicators of gastrointestinal parasite infection have been reported for an Angus population selected for immunological differences in response to natural infection by *Ostertagia ostertagi* (Gasbarre *et al*., 2002). The preliminary results of this study found QTL for fecal egg counts and immune response on chr 3, 5 and 6. These locations were synonymous with genomic locations of parasite indicator QTL found in sheep (Beh *et al*., 2002).

Studies with other experimental populations developed for QTL mapping are in progress to detect either novel QTL or production and fitness QTL in more phenotypically diverse crosses (i.e. beef × dairy crosses). Some of these populations include: (1) a Holstein × Gir F2 population in Brazil to identify QTL for ecto- and endoparasite resistance, (2) Charolois × Holstein populations in Germany and UK to identify QTL for production from a beef-dairy cross, (3) a Wagyu × Limousin population in USDA, Miles City, MT to find carcass and growth trait QTL, and (4) an F2 population based on Angus × Brahman and Angus × Romosinuano in USDA, Brookesville, FL to detect QTL affecting reproduction, heat tolerance and disease resistance.

4. Genomic tools and draft genome

It was apparent from studies on the role of myostatin in double-muscling syndrome (Grobet *et al*., 1997; McPherron *et al*., 1997; Smith *et al*., 1997) that without a draft sequence of the cattle genome, progression from mapping traits to identification of the causative genetic variation underlying a trait would rely on comparative genomic tools. The tools existing at that time were gene-poor linkage maps, somatic cell hybrid panels and cytogenetic maps. These resources did not have the resolution or coverage to build precise comparative maps between the cattle and human chromosomes for the purpose of identifying

positional and functional candidate genes underlying QTL. Subsequent efforts were initiated to generate bovine expressed sequence tags (EST) and radiation hybrid (RH) maps to better exploit the sequence and map resources developed from the human and mouse genomes.

As of April 2004, more than 415 000 *Bos taurus* and *Bos indicus* EST accessions were in the dbEST collection in GenBank. The majority of these EST (69%) were sequenced from normalized cDNA libraries that were made by pooling mRNA from tissues of physiological importance for dairy and meat production (Smith *et al*., 2001; Sonstegard *et al*., 2002). A significant number of EST (>200 000) have also been generated in the private sector through efforts by AgResearch in New Zealand and a bovine EST project in Brazil.

Some of the public EST information aided development of gene-associated markers for RH mapping. These markers along with previously mapped microsatellite markers were used to generate two different whole genome RH maps (TX\IL & COMRAD) that better define the conserved synteny of genes between the human and bovine genomes (Band *et al*., 2000; Williams *et al*., 2002, respectively). These maps continue to grow in marker density defining the positions of more than 1000 bovine markers with human sequence connections (See Table 1 for URLs).

In 2001, the International Bovine BAC Map Consortium (IBBMC) was formed to generate a comparatively anchored whole-genome physical map for cattle. The DNA fingerprints were generated by the laboratory of Dr Marco Marra at the Genome Sciences Center (GSC) in Vancouver, Canada during 2003. The BAC contig assembly was done using the DNA fingerprints of 294 561 BAC clones from CHORI-240 (male Hereford), RPCI-42 (male Holstein) and TAMBT (male Angus) BAC libraries (Table 1). BAC-end sequence was also generated from more than 192 000 clones of the CHORI-240 library to help anchor the BAC contig assemblies to the human genome. Finally, an effort is in place to integrate the bovine linkage maps with the physical maps (RH and BAC maps) to create a web-based tool that should better facilitate positional cloning and QTL discovery (Warren Snelling, personal communication).

In the past year more than US$50 million funding was obtained from a number of public and private partners for a cattle genome sequencing project that will be done mainly by The Human Genome Sequencing Center at the Baylor College of Medicine in Houston, Texas with help from the GSC (Table 1). The project plans to provide a ~7× coverage of the genome by combining ~4–5× of whole-genome shotgun sequencing and ~1× clone coverage using a BAC skim of clones in the minimal tiling path of CHORI-240 BAC contig map (Steve Kappes, personal communication). The whole genome shotgun sequence is being generated from a daughter (son–mother mating) of the Hereford bull used to make the CHORI-240 library. These sequences along with the BAC-end sequences from the CHORI-240 library make up the main body of sequence information, and the reduced genetic variability between the two sources of sequence should facilitate initial assembly. An additional ~1× combined coverage of whole genome shotgun will be generated from six different breeds (Holstein, Jersey, Angus, Limousin, Norwegian Red, Brahman) to discover SNP for validation and use in QTL and other studies. One aspect of the bovine genome project not yet fully addressed is annotation and curation. However, annotation of the genome should be facilitated greatly by existing bovine EST and new full-length cDNA that will be generated by the GSC. The rate of QTN discovery from current QTL information should improve rapidly upon completion and annotation of the bovine genome draft sequence, even though these types of investigations will remain a challenging aspect of bovine genomics research.

5. Marker selection tools

What molecular genetic information was made available to the cattle industry to guide animal selection decisions prior to the onset of bovine genome sequencing effort? Construction of the genetic maps for cattle has generated a number of informative markers based on either microsatellites or SNP, and probably the simplest commercial application of this information is towards parentage identification and animal traceability. Although a number of parentage tests are commercially available, the value of testing to increase statistical accuracy of genetic indices does not currently exceed the cost of the available parentage tests. Reduction in parentage test costs may occur with advances in genotyping technology and increases in volume that will arise concomitantly with increased testing for bovine spongiform encephalopathy (BSE) and possible identification programmes. A panel of informative markers is a high-priority resource, and the development of this resource will be greatly facilitated by information from the genome sequencing effort.

Linkage and biochemical analysis together with comparative genomic information from other mammals has helped identify causal mutations for 28 different qualitative traits and genetic disorders that affect development or health (Nicholas, 2003). DNA marker tests have been developed for some of these disorders (e.g. bovine leukocyte adhesion deficiency (BLAD), deficiency of uridine monophosphate

synthase (DUMPS) and complex vertebral malformation (CVM) and the dairy industry has implemented testing of sires for those disorders known to be segregating in the population. However, the impact of these DNA tests relative to long-term genetic improvement is minimal, because these diagnostic tests lose utility as deleterious alleles are removed from the commercial populations. Diagnostic tests associated with major milk proteins have also been widely used, because these polymorphisms have been associated with differences in production as well as manufacturing properties of the milk (e.g. Bovenhuis *et al*., 1992). In contrast, some diagnostic markers denote major effects that initially appear attractive for selection but upon further investigation deleterious effects associated with a locus make selection impractical. For example, the desirable effects of reduced myostatin activity on meat composition and tenderness have been documented (Casas *et al*., 1998), yet US beef producers have not widely used this diagnostic marker to quickly improve carcass value traits. The main reasons for this are: (1) animals homozygous for inactive myostatin alleles are not amenable to extensive beef production systems due to calving difficulties, (2) homozygous animals must be purchased or raised to maintain a germplasm source for introgression of inactive myostatin alleles into a heterozygous animal production scheme, (3) animals carriers of double-muscling syndrome were traditionally considered undesirable, and (4) diagnostic testing is not 100% reliable unless all the multiple forms of inactive myostatin are interrogated by the testing regimen.

Marker tests that hold relatively more promise of having a long-lasting impact on selection are those based on putative QTN described earlier in this review. The test for QTN in *DGAT1* (marketed as Quantum) has been elegantly proven by biochemical analysis to affect the synthesis of triglycerides (Grisart *et al*., 2004), thus explaining the observed phenotypic variation in fat deposition caused by the two different functional alleles segregating in cattle populations (Grisart *et al*., 2002; Thaller *et al*., 2003). The tests for *GHR* (Optimum), *CAPN* (TenderGENE & GeneStar Tenderness 2) and *TG* (GeneStar Marbling) are commercially available, but currently lack biochemical evidence to support an irrefutable claim as QTN. However, the latter two tests, along with SNP tests for marbling based on the corresponding candidate gene of *leptin receptor* (Igenity) and for tenderness based on *calpastatin* (GeneStar Tenderness 1), are being evaluated by the National Beef Cattle Evaluation Consortium for value in MAS on a commercial scale (Table 1). These validations provide valuable external confirmation to industry users that should build the trust of the users in genomics technology.

6. Conclusions

A potential explosion in the discovery of QTN is imminent with the tools now available for extended studies of existing QTL. The recently constructed BAC map together with the future genome draft sequence will be the central resources for facilitating QTN discovery. As more of the genetic variation for a specific trait is explained by QTN, researchers will begin to understand pleiotropic and epistatic gene action through changes in phenotypes that result from designed selection programmes and by changes in gene expression patterns identified by functional genomic studies of animals with a known genotype for a specific trait.

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