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Quantitative Trait Loci (QTL) Mapping and its Applications in Animal Traits

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Abstract

Many genes responsible for polygenic inheritance of particular characteristics are scattered around the genome. Their position is known as quantitative trait loci (QTL). It is the chromosome site at which a gene / group of genes affecting a quantitative trait is located. In case of disease susceptibility, it is useful to identify the individual genes to understand their normal function and to design accurate medical treatments. In case of animal and plant breeding it would be useful to identify young individuals with favourable alleles without waiting for their expression at maturity. Those with favourable genotype could be removed earlier from selective breeding programs, while potentially high quality types could be cloned immediately. Genome-wide association studies (GWAS) are becoming increasingly popular in genetic research, and they are an excellent complement to QTL mapping. Whereas, QTL contain many linked genes, which are challenging to separate. GWAS produce many unlinked individual genes or even nucleotides, but these studies are riddled with large expected numbers of false positives. Moreover, GWAS remain limited to organisms with genomic resources. Combination of these two techniques may provide the ultimate deliverable: individual genes or even nucleotides that contribute to the phenotype of interest.

Keywords: QTL, GWAS, Mapping, Designs, Animals

Genetic improvement is one of the most effective strategies available for increasing the performance of livestock. Since the genes are the blueprint not only for the structure, but also for the functioning of organism. Therefore, the analysis of the genomes of livestock can enable us to understand the genetic control of economically important traits in farm animals.

The economically important traits in dairy animals are affected by many genes as well as environment and their interactions. A Quantitative Trait Locus (QTL) is a region on a chromosome, detected by statistical analysis that harbours a gene or genes that influence the phenotypic expression of a complex, quantitative and economically important trait. Hence a QTL is defined as a polymorphic locus which contains alleles that differentially affect the expression of a continuously distributed phenotypic trait. Usually it is a marker described by statistical association to quantitative variation in the particular phenotypic trait that is thought to be cumulative action of alleles at multiple loci. More than one QTL for a particular trait can be present on a chromosome and in the entire genome. The genes segregating for a quantitative trait (QTL) cannot be individually identified in most of the cases. It is possible however, to localize those regions of the genome in which the relevant loci lie and to estimate how much of the total variation is accounted by QTL variation in each region. If QTLs are closely linked to a marker gene, then the different

marker genotypes in the segregating generation will also carry the QTL alleles that was linked to them in the original parental lines.

Necessity to Map QTL: The availability of highly polymorphic DNA markers on genetic maps in different livestock species and their association with phenotypes gave geneticists and breeders an effective tool for the QTL affecting traits of interest. Purpose of mapping QTL in livestock species is to identify genes affecting a quantitative trait and ultimately use existing variation in those genes to select superior individuals from a population.

A major objective of QTL studies is to find genes/ markers that can be implemented in breeding programs via Marker Assisted Selection (MAS). Once mapped, marker assisted selection for specific QTL can be more effective than mass selection on the traits of interest particularly for low heritability traits. In dairy animal, MAS could be used to pre-select young candidate bulls prior to progeny testing, thus increasing selection differentials, shortening generation interval and increasing genetic gain. Once a QTL is identified, it is necessary to identify families in the breeding population, which are segregating for that QTL. However, if a QTL has been fine mapped with respect to closely linked markers that are in linkage disequilibrium (LD) with the QTL, the associations between specific marker haplotypes and QTL alleles should be there across populations and need not be re-established for each individual family.

Identifying QTL has potential to significantly increase the rate of genetic improvement through implementation of marker-assisted selection (MacNeil and Grosz, 2002). For traits that are difficult or expensive to measure, are less heritable, occur late in life or are determined post-mortem, marker-assisted selection may substantially increase the rate of response relative to selection based on estimated breeding value alone (Davis and DeNise, 1998). Availability of highly polymorphic microsatellite DNA marker has made possible to assess linkge maps across whole genomes in many livestock species. These maps provide the basis for finding QTL in whole genome scans. Microsatellite DNA markers on genetic maps are used to identify inheritance patterns of linked segments of the genome in structured pedigree populations. Significant association of marker allele with the phenotype of interest suggest linkage of the markers to QTL.

Selection for such QTL can be undertaken throughout the population rather than only in specific families, thereby greatly simplifying the implementation of MAS. So identification of genes underlying QTL can provide the most accurate markers for MAS. Marker assisted introgression of specific mapped QTL can also be an effective means of upgrading native breeds while remaining adaptation to local conditions. QTL mapping will be an essential step in the cloning of QTL by application of the reverse genetic procedures.

Principles of QTL mapping

Trace chromosomal segments from parents to offspring and check if individuals that inherited alternative chromosomal segments differ with respect to the quantitative trait.

Information on an animal's genotype at a marker locus provides information on transmission of a chromosomal region from parents to offspring.

If QTL are located in the chromosomal region, then this information can be used to obtain a more accurate estimate of the breeding value because the inheritance of alleles at the chromosomal region can be traced more precisely than inheritance at an unmarked QTL.

In this case, the additive genetic value of an animal can be partitioned into additive genetic value at the marked chromosomal region and the sum of additive genetic effects at all other QTL affecting the trait.

Biases in Quantitative trait loci

Unless samples are large (>500), the effects of

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statistically significant QTL are substantially overestimated.

Closely linked QTL with effects in the same direction tend to give the appearance of a single QTL of large effect.

Resources structure for mapping QTL in dairy animals: The basic resources critical to mapping of QTL are appropriate pedigreed populations with production records and genomic DNA samples. Both partial and full genome scans for QTL have been conducted on a number of dairy cattle populations using grand - daughter designs. One such populations is the Dairy Bull DNA Repository (DBDR) maintained at the Laboratory of Immunogenetics, Department of Animal Sciences, University of Illinois at Urbana- Champaign, which is a collection of Holstein Friesians dairy bull semen and has been extensively used for QTL detection using the granddaughter design. Most of the DBDR sires were used in the 1980's and so this population may not be representative of the present population. A new population termed the Cooperative Dairy DNA Repository (CDDR) is being created for analysis of current generations

Detection of QTL: With the advent of genomic technology and research, detection of QTL has become the first step in the identification and further study of the genes that actually influence the expression of the trait being studied. In laboratory animals, the most efficient QTL detection designs involves crosses of inbred animals. The design is equivalent to one large family as the parental lines are completely homozygous. In most domestic animal species, however, no complete inbred line is available and QTL detection should be carried out within-family. Under these conditions, a key factor for QTL detection is the number of progeny per parent. In some species, e.g. cattle, female prolificacy is low and large dam families are very difficult to obtain. Consequently, only sire families efficiently contribute to QTL detection. In this context, two designs exist for detecting QTL in livestock species. These are daughter design and grand daughter design. In these designs, maternal meioses, i.e. half the total number of meiosis, are not used and this strongly affects their detection power. Consequently, these designs are typically 4 to 10 times larger than those involving inbred lines. For a daughter design, genotypic information is recorded for sires and their daughters, but with phenotypic observations made only on the daughters. For a grand daughter design, the grand sires and sires are genotyped, and phenotypic observations are made on the grand daughters. The power of QTL detection is more in a grand daughter design than daughter design as a result of highly accurate estimates of the breeding values of the sires.

Daughter Design

Principle: A parent heterozygous for both a marker locus and a linked QTL produces progeny that inherit different alleles for the marker. As the marker and QTL are linked, it is assumed that recombination do not occur between marker and QTL. So offspring receiving a particular marker allele from the parent will also tend to receive the linked QTL allele. Consequently, when progeny are grouped according to the marker allele received from a heterozygous parent, the presence of alternative alleles at the linked QTL will tend to generate a difference in mean value of the quantitative trait concerned between the two progeny groups. Conversely, a significant difference in mean quantitative value of progeny groups receiving alternative marker alleles from their common parent will be indicative of the presence of a linked QTL near the marker. In dairy cattle populations, large numbers of progeny can be obtained from a sire and accordingly sire-daughter families could be used to map QTL.

Model used: A hierarchical model can be applied in which daughter subgroups receiving the same marker allele from their sire are nested within sires. The analysis model will be:

$$Y_{ijk} = S_i + M_{ij} + e_{ijk}$$

Where,

Y_{ijk} = Trait value for daughter k of sire i that received the marker allele j

S_i = Effect of sire i

M_{ij} = Effect of marker allele j for sire i

e_{ijk} = is the random residual associated with each record.

The analysis tests the significance of the component of variance attributed to marker alleles. A quantitative effect associated with the marker alleles due to QTL linkage will show up a significant component of variance between daughter subgroups receiving alternative marker alleles from their sires. The problem with this approach is that it requires very large daughter groups and lot of genotyping to establish reliable links between markers and QTLs

Grand daughter design: In cattle populations, marker - QTL relationships are being detected, which are called granddaughter designs. These involve the use of bulls (grand sires), which are heterozygous for the marker gene. Hence, the marker can segregate among their sons such that some sons get a copy of the marker allele linked to the favourable QTL effect, and others get a copy of other marker allele linked to unfavourable QTL effect.

Principle: In this design a number of sons of a heterozygous sire would be screened for their genotype with respect to the genetic markers and grand daughters are evaluated for the quantitative traits. Therefore this type of analysis is termed as grand daughter design. The heterozygous parent in this design will be the grand sire. The advantage in this design is that it may be easier to collect blood or semen samples from sons of sires (for genotype screening) kept in AI centers, than from their daughters, scattered over many farms.

Model used: The model for the grand daughter design will be:

$$Y_{ijkl} = G_i + M_{ij} + SO_{ijk} + e_{ijkl}$$

Where,

Y_{ijkl} = Trait value of the granddaughter l of sire k (son of grandsire i) that received the marker allele j

G_i = Effect of grandsire i

M_{ij} = Effect of marker allele j for grandsire i

SO_{ijk} = Effect of son k (of grandsire i) with marker genotype j

e_{ijk} = is the random residual associated with each record.

In this model sons receiving the same marker allele from the" grand sire" are nested within grand sires. This is a three level hierarchical model, sons are nested within marker alleles, which in turn are nested within grand sires. As in the daughter design, this analysis test the significance of the component of variance attributed to marker alleles.

A significant marker–within sire effect (daughter design) or marker-within-grand sire effect (grand - daughter design) is then indicative of a segregating QTL linked to the marker. In both the models residuals are assumed to be distributed independently and identically normal. The daughter design requires between 5 and 20 sires with 200 to 2000 daughters each. This type of analysis might be feasible in situations, where the number of proven bulls used in any single year is low, herd size is large, and distances between herds are small. The granddaughter analysis might be more appropriate in situations where elite sires can have many progeny tested sons.

Types of QTL mapping approaches: The idea of marker-based QTL mapping is to utilize marker-QTL association created from linkage disequilibrium among loci by matings. These approaches are often used in QTL studies:

The single-marker analysis: This analysis examines the distribution of trait values separately for each marker locus. With the

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advent of linkage maps, QTL mapping using single marker analysis has been reported in the literature in which potential candidate gene markers may be mapped in the linkage group in outbred populations (Gelderman 1975; Weller 1986; Beckman and Soller 1988; Weller *et al.*, 1990; Le Roy and Elsen, 1995). Major drawbacks of this procedure (Knott *et al.*,1996) are: 1) When there is availability of multiple markers in the vicinity of the QTL, heterogeneity of information content among markers biases the estimation of QTL location toward the more informative rather than the closest marker. 2) There is a confounding between estimates of the QTL position and effects.

The interval mapping approach: It examines an association between each pair of adjacent markers and a QTL (Lee, 2002). The main advantage is that it offers both the effects of the QTL as well as the position. The disadvantage is that estimates from interval mapping are biased when multiple QTL are involved.

The multi-point mapping strategy: It involves the use of all the linked markers on a chromosome simultaneously. The main disadvantage is of over-estimation, when the number of explanatory variables is large. Lander and Botstein (1989) first proposed the multi-point approach called interval mapping. This approach has less sensitivity to violations of assumptions such as non-normality of distribution and provides more precise estimates of QTL position and effects than the single marker mapping in cross populations of inbred lines (Darvasi and Soller, 1993). The approach involves the analysis using a pair of multiple markers in a linkage group (Kim and Park, 2001).

Haley and Knott (1992) developed the least square regression method that did not require normality of residual terms and was found to be more efficient than the maximum likelihood approach to interval mapping. Knott and Haley (1992) and Haley *et al.* (1994) stated that the major disadvantage of the interval mapping method in out bred populations is that missing genotypes and different information contents among marker intervals due to variability in marker heterozygosity cause a bias in the estimated QTL location toward the more active marker interval. However, this heterogeneity between the marker intervals can be overcome by the simultaneous use of all markers in a linkage group (Knott and Haley, 1992; Knott *et al.* 1996; Knott and Haley, 2000). Another disadvantage is the bias of significance tests and estimates of QTL location and effect due to multiple and linked QTL on the chromosome (Martinez and Curnow, 1992). It must be stated that despite efficient applications in line-cross, half- or full-sib populations, these fixed QTL allele models cannot account for the complex data structures in commercial livestock populations in which the number of QTL alleles is unknown and the sires and dams are related across families (Kim and Park, 2001).

Furthermore, these models cannot provide breeding value estimates of each sire that are due to unlinked polygenic effects. Kadarmideen and Dekkers (2001) and De Koning *et al.*, 2001 described in detail the detection and mapping of multiple QTLs in halfsib populations: 1) To identify candidate gene regions, the chromosomes are analysed individually. 2) To choose the best candidate positions as cofactors and their effects are re-estimated jointly with multiple linear regression. 3) The phenotypic data are adjusted for the effects of cofactors and the linkage groups are re-analysed by interval mapping. If this reveals new or better candidate regions, the set of cofactors can be modified and the effects are-estimated.

The composite interval mapping method: It is a modified interval mapping procedure in which a few additional single markers for each analysis are incorporated (Zeng, 1993). The advantage is that resolution of the QTL locations is considerably improved by the introduction of a few additional well-chosen marker loci.

Multiple interval mapping uses multiple marker intervals simultaneously to fit multiple putative QTL directly in the model (Kao *et al.*, 1999). The advantage of this method is that epistasis for QTL can also be estimated. All these methods mentioned above are based on conditional probability of QTL genotype given the observed marker genotype and are used with various experimental designs for inbred lines (Lee, 2002). The identity-by-descent (IBD) mapping is often used in out bred populations. This method specifies the expected genetic covariance between arbitrary relatives as a function of the IBD relationships at a QTL and determines proximity based on the number of cases where marker alleles and QTL alleles have not recombined.

QTL in Animal Breeding

Dairy cattle DNA: information has been used to select against deleterious alleles such as Bovine Leukocyte Adhesion Deficiency, Complex vertebral malformation. Freyer *et al.* (2002) utilized a granddaughter design containing five half-sub families of German Holstein-Friesian for QTL analysis on chromosome 6 using micro-satellite markers. They detected significant and putative QTL at 49 cM for milk yield, at 70 cM for fat and protein yield and at 46 cM for protein content. Further QTL positions were suggested mostly for yield traits and protein content in the area of the casein gene cluster at 90-95 cM. The presence of two QTL on chromosome 6 was also indicated for milk yield (at about 47 and 91cM). This finding corresponded to earlier studies by Lien *et al.* (1995) who reported an association of QTL for milk and protein yield to the casein gene cluster (CSN) locus in chromosome 6 at about 95 cM.

Velmala *et al.* (1999) also obtained similar results in which significant QTL for fat and protein yield at about 70 cM which is close to the marker FBN13, were reported. Zhang *et al. (*1998) reported a QTL for milk yield at 40 cM while Georges *et al.* (1995) found a QTL for milk yield at about 60 cM. Similar reports on significant QTL for several traits at 95 cM have also been published by Velmala *et al.* (1999) and Ashwell and Van Tassel (1999). Freyer *et al.* (2002) stated that the casein cluster (CSN) located on chromosome 6 in particular, has been focused upon by researchers and significant positive effects of the CSN2A2 allele on milk yield have been reported (Bovenhuis *et al.,*1992; Bovenhuis and Weller, 1994, Ng-Kwai-Hang *et al.,* 1986, Ojala *et al.,* 1997, Freyer *et al.*, 1999).

Ashwell *et al.* (1997) studied associations of seven health and milk production traits with six microsatellite markers on bovine chromosome 23 using an elite Holstein population. They found QTL for protein yield and protein percentage in a single family. A QTL for protein yield had a LOD21 score of 1.821 and was located between BM1818 and BM1443, while the QTL for protein percentage had a LOD score of 1.554 and was located near marker BM1443. Elo *et al.* (1999) genotyped 469 bulls for six micro satellite loci in 12 families of Finnish Ayrshire cattle and reported that a quantitative trait locus for live weight mapped to bovine chromosome 23 located between markers BM1258 and BoLA DRBP1. These two reports seem to confirm earlier indications that the bovine lymphocyte antigen (BoLA) is associated with milk production traits (Simpson *et al.*, 1990), growth traits (Batra *et al.*, 1989; Stear *et al.*, 1989) and diseases such as mastitis, ketosis and infertility (Lunden *et al.*, 1990; Mejdell *et al.,* 1994; Dietz *et al.*, 1997). Bovine chromosome 14 has also been the subject of intense QTL study for dairy traits (Coppieters *et al.*,1998, Heyen *et al.*,1999, Looft *et al.*, 2001, Farnir *et al.,* 2002, Kim and Georges, 2002). Conor *et al.* (2006) selected eight genes from human chromosome 8 for mapping in cattle to improve breakpoint resolution and confirm gene order on the comparative map near the 40 cM region of the BTA27 linkage map where a QTL affecting dairy form had already been identified. The resulting map identified *ADRB3* as a positional candidate gene for the QTL contributing to the dairy form

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trait based on its estimated position between 40 and 45 cM on the linkage map. It is also a functional candidate gene due to its role in fat metabolism, and polymorphisms in the *ADRB3* gene associated with obesity and metabolic disease in humans, as well as, carcass fat in sheep.

The Stearoyl-CoA desaturase **(***SCD)* locus has been mapped on the bovine chromosome 26. Three single nucleotide polymorphisms (SNP) in complete linkage disequilibrium, which result in 2 haplotypes have been detected in the fifth exon (Taniguchi *et al.*, 2004). The third SNP causes the substitution of valine (allele V) with alanine (allele A) on the 293rd residue. Because valine is highly conserved across mammals, it is considered the ancestral amino acid in that position (Taniguchi *et al.,* 2004). The *SCD* polymorphism has been reported in Holstein Friesian, Jersey, Brown Swiss, and Japanese Black cattle breeds (Medrano *et al.*, 1999; Taniguchi *et al.*, 2004). Stearoyl-CoA desaturase (SCD) is a key enzyme in mammary lipid metabolism because it is able to add a double bond in the *cis* Δ9-position in a large spectrum of medium- and long-chain fatty acids. There are reports of polymorphism with 2 alleles (A and V) in the fifth exon of the *SCD* gene. Mele *et al.* (2007) investigated the effect of *SCD* genotype on individual milk fatty acid composition and on *cis*-9 unsaturated/saturated fatty acid ratios of 297 Holstein Italian Friesian cows. Relative frequencies of *SCD* genotypes were 27, 60, and 13% for AA, AV, and VV, respectively. Milk of AA cows had a greater content of *cis*-9 C18:1 and total monounsaturated fatty acids and a higher C14:1/C14 ratio than did milk of VV cows. The relative contribution of *SCD* genotype to variation of monounsaturated fatty acids, *cis*-9C18:1, and *cis*-9 C14:1 was 5, 4, and 7.7%, respectively. No significant differences were detected between *SCD* genotypes in the milk content of *cis*-9, *trans*-11 C18:2. Their results provide some indication of an association between *SCD* locus and the fatty acid profile in the Italian Holsteins, suggesting a possible role of this gene in the genetic variation of milk nutritional properties.

Marker-assisted selection could be used to decrease time and cost associated with selection for ovulation rate. Putative ovulation rate or twinning rate quantitative trait loci (QTL) have been identified on BTA5 (Kappes *et al.,* 2000; Lien *et al.,* 2000), BTA7 (Blattman *et al.* 1996; Lien *et al.*, 2000, Arias & Kirkpatrick 2004), BTA10 (Arias and Kirkpatrick 2004), BTA12 (Lien *et al.*, 2000), BTA19 (Arias and Kirkpatrick 2004) and BTA23 (Blattman *et al.*, 1996; Lien *et al.*, 2000). Approximately 40% of (half sib family 839802) and 26% (halfsib family 839803) of available progeny comprised the high and low pools combined.. Pooled typing revealed possible associations (nominal $P < 0.05$) between ovulation rate and marker genotype for 11 and 15 microsatellites in the paternal halfsib families 839802 and 839803, respectively. Subsequent interval mapping strengthened support for the presence of an ovulation rate QTL on BTA14 (chromosome-wise $P < 0.02$, Gonda *et al.*, 2004).

Based on a true dairy cattle population s, Berg et al, 2011 genotyped for 38 277 phased marker and concluded that QTL detection is feasible with Bayes C. They further recommended to use a large dataset for QTL detection and to focus on highly heritable traits and on the largest QTL. QTL statuses were inferred based on the distribution of the contrast between chromosomal segment effects. In original proposed models, either all markers were included in the model (Bayes A), or the proportion of markers included in the model was fixed at a certain value (Bayes B, Meuwissen *et al.* (2001), Gianola *et al.* (2009), Habier *et al.* (2011) proposed several modifications of the original models, including Bayes Cπ and Bayes C to overcome the statistical problems associated with these models. In Bayes Cπ, the proportion of markers included in the model is assigned a prior distribution and estimated during the analysis, while in Bayes C, the proportion is given a fixed value. In a simulation

by Sun *et al.* (2011), Bayes Cπ was successful in identifying large QTL, whereas, Bayes C has been used to identify QTL for various traits in beef cattle (Peter *et al.*, 2012, 2013), the horse (Schurink *et al.*, 2012) and pigs (Onteru *et al.*, 2011, Fan *et al.,* 2011). The performance of the Bayesian genomic selection models is known to be influenced by the genetic architecture of the trait and the number of records used to estimate the marker effects; the accuracy of predicted breeding values decreases with decreasing heritability (Calus *et al.*, 2007, Daetwyler *et al.*, 2010) and an increasing number of QTL (Daetwyler *et al,*. 2010 and Clark *et al.*, 2011). A large number of records is needed to obtain high accuracy (Goddard *et al.*, 2009).

Pig breeding: First test to be applied was for the Halothane-gene. Occurrence of pale, soft and exudative meat is associated with the recessive allele at halothane locus. Recessive allele reduces meat quality, but it improves lean meat. Jeon *et al.* (1999) generated an intercross between the European Wild Boar and Large White domestic pigs and used this pedigree to map quantitative trait loci1-4 (QTL). A QTL on pig chromosome 2p with a moderate effect on muscle mass was reorted (Anderson *et al.*, 1994, Knott *et al.*, 1998, Edifors lilga *et al.*, 1998, Andersson-Eklund *et al.*, 1998). The conserved synteny between this region and human chromosome 11p suggested *IGF2* as a candidate for the QTL. Jeon *et al.* (1999) isolated a porcine BAC *IGF2* clone (253G10) and used it for FISH mapping, resulting in a consistent signal on the distal tip of chromosome 2p (band 2p1.7). Direct BAC sequencing of the *IGF2* 3´ UTR revealed a microsatellite 800 bp downstream of the *IGF2* stop codon identical to a previously described microsatellite, *Swc9* (Alxender *et al.,* 1996). The *IGF2* microsatellite was found to be highly polymorphic, with three alleles among the two Wild Boar founders and another two among the eight Large White founders, and was fully informative in the intercross, as the breed and parent of origin could be determined for each allele in F2 animals.

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