Current Status of Quantitative Trait Locus Mapping in Livestock Species - Review -

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ABSTRACT : In the last decade, rapid developments in molecular biotechnology and of genomic tools have enabled the creation of dense linkage maps across whole genomes of human, plant and animals. Successful development and implementation of interval mapping methodologies have allowed detection of the quantitative trait loci (QTL) responsible for economically important traits in experimental and commercial livestock populations. The candidate gene approach can be used in any general population with the availability of a large resource of candidate genes from the human or rodent genomes using comparative maps, and the validated candidate genes can be directly applied to commercial breeds. For the QTL detected from primary genome scans, two incipient fine mapping approaches are applied by generating new recombinants over several generations or utilizing historical recombinants with identity-by-descent (IBD) and linkage disequilibrium (LD) mapping. The high resolution definition of QTL position from fine mapping will allow the more efficient implementation of breeding programs such as marker-assisted selection (MAS) or marker-assisted introgression (MAI), and will provide a route toward cloning the QTL. *(Asian-Aust. J. Anim. Sci. 2001. Vol. 14, No. 4 : 587-596)*

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INTRODUCTION

Recent rapid developments in molecular biotechnology and of genomic tools in domestic animals (as well as plants and human) have enabled changes in animal breeding paradigms. Sire selection can be based on the evaluation of major genes with the aid of genetic markers as well as polygenic breeding values estimated using infinite allele models. Most economically important traits in livestock species are polygenic and multifactorial. Phenotypic variation in these traits is influenced by the effect of many genes along with interactions with environmental factors. Individual chromosomal locations where the genes responsible for variation in the trait reside are called quantitative trait loci (QTL). Current selection schemes (i.e., progeny testing) are based on time and resource consuming processes. This is because some traits (carcass quality, milk production and longevity) are sex limited, expensive or difficult to measure in live animals, and many agricultural livestock species have relatively long generation intervals.

In the last decade, the application of highly polymorphic and ubiquitous molecular markers such as microsatellites has expedited the creation of dense linkage maps across whole genomes in most livestock species. In pig and cattle, for example, approximately 1 or 2 cM marker interval maps are currently available totaling around 2000 markers (Haley, 1999). These maps would provide a basis for finding QTL in whole genome scans and performing fine mapping, marker-assisted selection (MAS) and marker-assisted introgression (MAI). Markers on the genetic maps are used to identify inheritance patterns of linked segments of the genome in structured pedigreed populations. Significant asso- ciations of marker alleles with the phenotypes of interest suggest linkage of the markers to a QTL. Selection based on detected QTL for growth at different ages may uncouple the positive genetic correlations between the growth traits and change the shape of the growth curve. Also, MAS will allow the preselection of young candidate sires prior to progeny testing, thus increasing selection differentials in the new generation of bulls (MacKinnon and Georges, 1998).

Knott and Haley (1992a) summarized the importance of QTL mapping of quantitative traits of economic interest. First, it provides fundamental knowledge of individual gene actions and interactions, allowing the construction of more realistic models of phenotypic variation, response to selection and evolutionary processes. Second, marker information can be used directly to improve breeding value estimation and MAS and MAI may be an effective means of introgressing a few genes of value from one breed or line to another or of improving selection responses within a breed. Third, the mapping of a QTL provides a route for the eventual cloning of the locus.

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In this paper interval mapping models, their methods and candidate gene approach are described and discussed. These approaches have been successfully applied and are commonly practiced in livestock species such as swine, beef and dairy cattle. Prospects for application of QTL fine mapping are also evaluated.

SINGLE MARKER AND INTERVAL MAPPING

Single marker mapping

The search for QTL through the use of genetic markers in plant and animal species is not new. Associations between seed coat pattern and pigmentation with the seed size in the bean, *Phaseolus vulgaris* reported by Sax (1923) showed the initial implications of linkage between major genes and quantitative traits. Extensive efforts to find associations between the blood groups and quantitative traits of economic importance in livestock species were made in the 1950s and 1960s. One typical example was the significant effects of the B blood group system on milk fat percentage in Danish dairy cattle (Neimann-Sørensen and Robertson, 1961). However, lack of an adequate experiment size, statistical methods or marker polymorphism resulted in inconsistent findings between similar studies. Starting in the late 1980s, associations due to variation in expressed genes with production traits were investigated. Examples include the effects of κ-casein or β-lactoglobulin genotypes on milk protein content (Ng-Kwai-Hang and Grosclaude, 1992) and effects of BoLA and blood group systems on growth and carcass traits in cattle (Beever et al., 1990).

With the advent of linkage maps, considerable attention has been paid to the topic of QTL mapping via the use of single marker analyses in which potential candidate gene (expressed gene of interest) markers may be mapped *a priori* in the linkage group in outbred populations (Geldermann, 1975; Weller, 1986; Beckman and Soller, 1988; Weller et al., 1990; Le Roy and Elsen, 1995). Knott et al. (1996) summarized the drawbacks of these methods as being: 1) heterogeneity of information content among markers biases the estimate of QTL location toward the more informative rather than the closest marker when multiple markers in the vicinity of the QTL are available, and 2) there is a confounding between estimates of QTL position and effects.

Interval mapping under fixed models

A multipoint approach referred to as interval mapping was proposed by Lander and Botstein (1989). The approach involves analysis using a pair, or multiple markers in a linkage group and has been found to provide greater power, more precise estimates of QTL position and effect, and has less sensitivity to violations of assumptions, such as non-normality of the distribution than the use of single marker mapping in cross populations of inbred lines (Knott and Haley, 1992a; Darvasi and Soller, 1993). A simple least squares regression method was developed by Haley and Knott (1992) which does not require normality of residual terms and is much more efficient to implement than the maximum likelihood approach to interval mapping. Modified least squares approaches have been applied in experimental line-cross or halfsib models in domestic animals (Haley et al., 1994; Knott et al., 1996). The line-cross model is generally applied in a cross experiment population of two divergent lines or breeds and the halfsib model is used within a commercial breed.

The first studies reporting the discovery of QTL from whole genome scans in livestock species were published by Andersson et al. (1994) and Georges et al. (1995) in an experimental cross of pig breeds under the line-cross model and a commercial population of dairy cattle under the halfsib model, respectively. In Andersson et al. (1994) where genetically divergent breeds of European wild boar and Large White sows domesticated by long term selection were crossed, alternate breed QTL alleles were assumed to be fixed within each breed, while markers were segregating within breeds (Haley et al., 1994). This assumption may be suitable for traits with dissimilar characteristics between the two breeds, and the line-cross model of Haley et al. (1994) has been applied in experimental pig populations (Andersson-Eklund et al., 1998; Knott et al., 1998; de Koning et al., 1999; Walling et al., 2000). Even though the QTL alleles are not fixed, this approach still has power for QTL detection if QTL allele frequencies were skewed between the two breeds (Alfonso and Haley, 1998). The greatest disadvantage of this line-cross model occurs in the case when there are multiple QTL alleles in the alternate breeds, since the model cannot detect QTL unless the average effects of the alleles differ significantly between the breeds (de Koning et al., 1999; Kim, 1999). Also, it is questionable whether the QTL detected from the line cross model segregate within commercial elite populations (Georges and Andersson, 1996). However, QTL for which the allelic effect of the donor breed is favorable, such as the Meishan QTL alleles for litter size, can be utilized for MAI into the recipient or commercial breeds (Visscher et al., 1998).

The halfsib model of Georges et al. (1995) was based on allele substitution effects at the putative heterozygous QTL of sires and the analysis was performed separately for each family with a maximum likelihood method. Knott et al. (1996) presented a simple, fast and efficient least-squares multiple

regression method for large half-sib populations. In the halfsib model QTL effects are estimated within paternal halfsib families by contrasting the trait scores of the progeny that inherited alternate paternal haplotypes. This approach was applied to QTL mapping in dairy cattle (Spelman et al., 1996; Uimari et al., 1996; Zhang et al., 1998), and was extended to a full-sib model with large full-sib families such as in poultry (van Kaam et al., 1998). One advantage of the half- or full-sib designs is that the QTL detected in a commercial population can be directly selected within the commercial population by MAS. However, larger experiments are required to compensate for the reduced heterozygosity or information content of markers compared to breed or line cross populations (Georges, 1998a).

There are some disadvantages to the described interval mapping methods. In outbred populations, missing genotypes and different information contents among marker intervals due to variability in marker heterozygosity cause a bias in the estimate of QTL location toward the more informative interval (Knott and Haley, 1992b; Haley et al., 1994). However, the heterogeneity between the marker intervals can be overcome by the simultaneous use of all markers in a linkage group (Haley et al., 1994; Georges et al., 1995; Knott et al., 1996). Another disadvantage is the bias of significance tests and estimates of QTL location and effect due to multiple and linked QTL on the chromosome (Haley and Knott, 1992; Knott and Haley, 1992a; Martinez and Curnow, 1992).

Despite the 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 sires or dams are related across families. Further, these models cannot provide breeding value estimates of each sire that are due to unlinked polygenic effects.

Interval mapping under random or mixed models

A variance component approach under a random model was proposed by Grignola et al. (1996a) where all of the relationship information between sires or families was included to model covariances at individual marked QTL and to assign random effects to the QTL alleles within the parents of a family. This approach was based on a mixed linear model to estimate the variance due to the QTL alleles, polygene effects and residuals using approximate restricted maximum likelihood, and was applied in experimental or commercial populations (Zhang et al., 1998; Kim, 1999). This model can be fitted to any general complex pedigree and is robust to the number of QTL alleles and normality assumptions, and provides accurate estimates of QTL location and effects when family size is large (Grignola et al., 1996b). However, detection of QTL with a dominance mode of gene action, which is a main goal for application in livestock crossbred populations, is not possible in the model. Thus de Koning et al. (1999) and Kim (1999) recommended simultaneous use of both line-cross and random (or half-sib) models for QTL detection in outbred line-cross populations, because they are complementary for examining the underlying assumptions concerning different modes of gene action and skewness of QTL allele frequencies. However, use of both models does not provide evidence of fixation of QTL alleles within breeds, which is essential for subsequent MAS or MAI strategies.

Pérez-Enciso and Varona (2000) presented a mixed linear model approach where both mean differences between parental breeds (or lines) and variation within breeds could be identified in outbred line cross populations. Their simulation results showed that this model provided high power, unbiased estimates of QTL parameters for linked QTL when analyzed with 'segment mapping' that adjusted for effects of linked QTL, and allowed the ability to test for heterogeneity of variances between the two parental breeds. The practical application of this model to experimental data remains to be accomplished in consideration of the likelihood of incomplete and heterogeneous markers, and the need to determine statistical test thresholds.

Other interval mapping approaches

Bayesian approaches have attractive properties for QTL mapping. Bayesian analyses extract additional information from phenotypes, incorporate complex pedigree relationships and provide inferences based on the joint posterior distribution of many other parameters such as QTL genotypes and their effects, number, map position and allele frequencies (Hoeschele et al., 1997). This approach also has the potential to be robust to bias due to selection commonly occurring in dynamic livestock populations. However, the Bayesian analyses are very demanding in terms of computing requirements particularly for a whole genome scan for multiple traits, and require operator expertise in regard to ensuring the proper mixing and convergence of the sampler (Hoeschele et al., 1997).

Kruglyak and Lander (1995) presented a non-parametric method, which fits traits with non-normal distribution, and Coppieters et al. (1998) adapted the approach to an outbred half-sib design for QTL analyses of milk production traits in dairy cattle. Simulation results of Coppieters et al. (1998) showed that the approach had more power under conditions of non-normality. However, the multiple regression approach of Knott et al. (1996) was robust to various failures of the normality assumptions.

Some traits follow non-Mendelian modes of gene

action. Roberson et al. (1986) and Thallman et al. (1992) found progeny with larger birth weight from Brahman or *Bos indicus* sires than from *Bos taurus* sires. Cockett et al. (1996) reported polar overdominance effects of the *callipyge* locus on ovine muscular hypertrophy. Paternal imprinting effects of the IGF2 locus on porcine muscularity traits were detected using candidate genes harbored in homologous human and murine regions (Jeon et al., 1999; Nezer et al., 1999). Systematic searches for QTL detected with paternal or maternal line of origin effects on body composition and growth traits were conducted in pig and beef cattle cross populations by de Koning et al. (2000) and Imumorin (2000), respectively. Identification of imprinted QTL and their utilization in MAS will allow the design of more efficient breeding schemes and also more efficient terminal cross production programs.

ADVANCED INTERVAL MAPPING

Multiple-QTL mapping

Jansen (1993) and Zeng (1994) introduced methods of multiple-QTL mapping for the analysis of crosses between inbred lines. In Zeng's approach, which is denoted "composite interval mapping", fitting markers flanking the test interval improves precision and yields unbiased estimates in the case of multiple linked QTL, while fitting unlinked markers with significant associations on phenotype increases power. This model can be applied to experimental outbred cross populations where it is possible to trace the origin of QTL alleles to the parental breeds (Kim, 1999). However, due to the loss of genotypes at uninformative flanking markers, blocking the effects of linked QTL may not be possible. When using raw marker genotypes in any general outbred population, selection of unlinked markers should be performed within each family due to different sets of parents being heterozygous for different markers and QTL (Hoeschele et al., 1997).

Multiple-trait mapping

Multiple trait analyses, which take into account correlations that exist among traits, improve power and precision of parameter estimation, and allow testing for various biological features such as pleiotropy, QTL x environment interaction and pleiotropy versus close linkage. Maximum likelihood procedures have been developed for performing these tests in crosses between inbred lines (Jiang and Zeng, 1995), sib-pairs (Eaves et al., 1996) and half-sib families (Ronin et al., 1995), but requires intensive computing and the empirical determination of critical values for each hypothesis test. Knott and Haley (2000) presented a simple least-squares multi-trait QTL mapping approach in outbred line-cross populations. Permutation and parametric bootstrapping approaches can be implemented with their approach to determine empirical thresholds for testing pleiotropy and close linkage versus pleiotropy, respectively.

Joint mapping

Power for QTL detection depends mainly on experiment size and QTL effect. The current status of livestock QTL experiments may not allow the conclusive detection of QTL of moderate size of effect. Joint analyses, which combine independent QTL experiments into one overall search, may provide strong statistical evidence for QTL with modest effect or which segregate in only a subset of families (Lander and Kruglyak, 1995). There are two forms of joint analysis; meta-analysis and data pooling. The former (based on published results) is useful when the raw data from some experiments are not publicly available, and which may be generalized to include different circumstances of comparison (different set of markers, statistical models, type of phenotype measures (Allison and Heo, 1998). However, the meta-analysis cannot provide a precise location or confidence interval for a QTL due to the varying experimental conditions, and the selection of only published results leads to the selection of statistically significant samples, which introduces a source of bias to the test.

A joint analysis with data pooling provides more information such as evidence for interactions of QTL effects with breeds or populations, but also allows the confirmation of QTL that are detected with limited statistical supports in some populations. Walling et al. (2000) reported the first joint analysis of this form in livestock species. In their study, growth and fat trait QTL on porcine chromosome 4 were investigated by pooling data from six different QTL research groups, and the advantages of the joint analysis were validated. However, it was pointed out that caution should be taken in interpreting significant results, because in some cases false positive results might be due to different environmental conditions and variation in measured traits.

CANDIDATE GENE APPROACH

QTL detection by linkage mapping requires large pedigree structures of several generations and hundreds of markers to saturate the entire genome, which is costly and time consuming. Further, finding QTL from primary genome scans does not provide the actual identity of the causal genes or even precise estimates of the regions harboring these genes, due to the low mapping resolution in common livestock QTL populations. It is also problematical to commercially exploit QTL detected from line cross populations using

exotic breeds, since the desirable QTL alleles are usually found within the domesticated breed and there is usually no evidence of variation in QTL alleles within the domesticated breed (Georges and Andersson, 1996). To overcome these limitations, a candidate gene approach has been practiced where genes with known biological functions relating to the traits of interest are selected, and associations between polymorphisms at, or near, the gene with the traits are tested (Rothschild et al., 1996; Rothschild and Soller, 1997; Rothschild et al., 2000).

The candidate gene approach is based on close linkage and linkage disequilibrium (LD) between loci of the tested candidate gene mutations and the causal mutations. Contrary to single marker mapping or interval mapping, the approach does not necessarily require linkage maps and thus can be applied without estimation of the candidate gene position. This approach can also be applied to any type of population, and the verified gene markers can be directly used in MAS schemes. Because the LD exists at the population level, detection power is as high as in F_2 inbred lines, which is not the case in linkage mapping approaches, where information comes only from the sub-populations in which QTL alleles are segregating. One considerable drawback is that searching for QTL is confined, *a priori*, to the physiological categories of candidate genes. Haley (1999) summarized other potential problems associated with candidate gene analyses. Briefly, the problems include false positives due to application of nominal or insufficiently stringent statistical thresholds to a single experiment, population stratification and extensive LD in dynamic livestock populations where forces exist such as selection, small numbers of founders and hybridization.

Selecting candidate genes can be based on the location of QTL detected in primary genome scans. Generally, comparative maps are used to identify homologous chromosomal regions in other information-rich species (usually human or mouse). Because significantly more is known about gene location, structure and function in human and mouse, plausible candidate genes can usually be found in the region of interest. This approach is called positional comparative candidate gene analysis. After integrating candidate genes into the linkage map, a second-stage genome scan yields genome wide significance threshold levels, along with positional information of the candidate genes relative to the QTL (Casas et al., 1998; Taylor et al., 1998; Gerbens et al., 2000). Spurious LD between candidate genes and causal mutations due to population stratification/ admixture can be eliminated by association analyses performed within families in which the marker alleles are segregating (Ewens and Spielman, 1995).

There have been inconsistencies in candidate gene effects across different lines or populations, as in the case of Meishan allelic effects of the estrogen receptor gene on litter size in pigs (Rothschild et al., 1996; Short et al., 1997). This could be explained as an interaction of the candidate gene with the background genetics of the tested breeds, or by a low repeatability of the association test for genes of moderate or small effect (Long and Langley, 1999). However, when polymorphism of the candidate gene is associated with mutations at linked loci causing phenotypic variation, the variability of candidate gene effects is due to LD (Haley, 1999). Farnir et al. (2000) found extensive LD among most syntenic microsatellite markers and even between some non-syntenic markers in a Dutch dairy population. To achieve more reliable results, some advanced statistical approaches, such as the transmission disequilibrium test (TDT) that considers both linkage and association can be employed (Spielman et al., 1993; Allison 1997). Haplotype testing by using all polymorphisms across candidate gene sequences will also yield increased power and specificity (Rothschild and Soller, 1997).

As more genes and/or expressed sequence tags (ESTs) became available from the completion of the human transcript map and results are accumulated from genomic research on experimental animals or livestock species, excellent resources for candidate gene selection will be developed. Also, high-resolution comparative maps between livestock and human or mouse will allow the refinement of regions harboring QTL for positional candidate gene approaches (Womack et al., 1997). However, the number of candidate genes will increase as more genes are identified. If there are 20-30 genes in one centimorgan in a mammalian genome, there are 100-150 genes within a 5 cM region refined from fine mapping (Haley, 1999). In conclusion, candidate gene approaches require many independent validation analyses to verify a candidate gene as the QTL affecting traits of interest.

QTL FINE-MAPPING

The detection of QTL with reasonable magnitude of effect using interval mapping methods has been successful in experimental and outbred livestock populations (Georges, 1998a; Haley, 1999). However, the precision of QTL mapping is much lower than for monogenic traits, because phenotypes are not only characterized by the QTL, but are also influenced by other segregating QTL with environmental interaction. Confidence intervals for the estimated QTL position have been shown to be within 20 to 30 cM. This range is too large to efficiently implement technologies such as MAS, MAI, positional cloning or positional

candidate gene identification. Thus, the development and implementation of fine-mapping methods is essential to provide a route toward eventually cloning QTL. However, the successful application of fine-mapping of QTL in livestock species using the methodologies proposed by Darvasi (1998) is unlikely, primarily because of the difficulties in experimental designs, animal maintenance, economic cost and time.

Fine mapping requires dense maps

The first objective for fine mapping is to construct dense maps of ordered markers within chromosomal regions harboring genes of interest. Chromosome flow sorting or chromosome-band microdissection methods have been used to develop region-specific genetic markers (Georges and Andersson, 1996), and radiation hybrid panels can be used to order these markers along with expressed sequence tags (ESTs) without the need for polymorphism within the ESTs (Womack et al., 1997). The new human genome map (following the second-generation map using microsatellite markers) is under construction using single-nucleotide polymorphisms (SNPs) and chip-based microarrays (Wang et al., 1998). While microsatellite marker maps of domestic animals provide average intermarker distances of 1 or 2 cM (1 or 2×10^6 DNA base pairs), a SNP map could provide 1000 times greater marker density, even up to an average intermarker distance of 300 base pairs (Haley, 1999). However, such dense maps across whole genomes will not be available in livestock species in the near term. Thus fine-mapping strategies must continue to be developed for specific regions where QTL have been localized from a primary genome scan.

Fine mapping by generating new recombinants

The resolution of chromosomal intervals harboring QTL depends on the number of recombination events in the specified chromosomal region; the more recombinants, the higher the mapping accuracy. Two methods have been proposed for increasing the number of recombination events, 1) increasing the size of the sample within the primary genome scan, and 2) accumulating meioses over a number of generations (Haley, 1999). In the former case, a QTL confidence interval could be narrowed to as little as 8 cM for a QTL explaining 11% of the phenotypic variation in an F_2 population of 1000 animals with a 10 cM marker-spaced map (Knott and Haley, 1992a). Darvasi and Soller (1995) presented the latter strategy referred to as advanced intercross lines (AIL). By randomly and sequentially intercrossing each generation that originated from a cross between two inbred or line-cross outbred lines, the confidence interval for a QTL location can be reduced up to fivefold after eight generations, with the same amount of phenotyping and genotyping in F_2 or BC populations. This approach also allows the high-resolution mapping of QTL in different chromosomal regions for a number of traits measured in the original cross population, and characterization of the QTL (as a single major gene or several closely linked genes). However, the maintenance of reasonable sample size across several intercross generations limits its application to low-cost experimental populations with short generation intervals, such as poultry (Haley, 1999).

Marklund et al. (1999) used this approach for fine-mapping QTL for fatness and growth on chromosome 4 in a cross of wild boar and Large White pigs. Two F_2 sows with alternate breed-specific segments at the target region were backcrossed to a recipient Large White sire. One of the two sows carried a smaller heterozygous segment around the putative fatness QTL due to a previous recombination event. Two resulting BC_1 sires, which were shown to have inherited intact, non-recombinant chromosomes spanning the QTL region, were selected for further breeding. Eighty-five progeny of the two selected sires were pooled into two groups according to QTL genotypes (heterozygous or homozygous) determined from flanking marker haplotypes. Significance levels and marker positions with the highest test values indicated the presence of the QTL for fatness traits to be distal to the recombination break point.

Applicability of this design to the experimental pig populations was due to a relatively small sample size in the backcross generations and control of background genetic homogeneity. Using modern reproductive techniques, this approach could also be applied in cattle and other species with low prolificacy.

Identity-by-descent (IBD) and linkage disquilibrium (LD) fine mapping

Riquet et al. (1999) proposed a new fine-mapping approach for QTL responsible for milk production traits in the Holstein-Friesian dairy cattle population and utilized the strategy with 29 paternal half-sib families totaling 1158 sons. This approach is based on the utilization of historical recombinants and identity-by-descent (IBD) mapping using LD as opposed to generating new recombination events by intercrossing individuals of each generation. Its application is suitable in young isolated populations with a relatively small number of founders.

In LD and IBD mapping, it is assumed that one locus with a mutant allele and the flanking region on an ancestral chromosome is shared by many descendents, because the closely linked segments cosegregate in subsequent generations. Thus the mutant allele shared in descendents (in IBD state) at the disease locus and alleles at neighboring loci are non-randomly associated (LD). The degree of LD

existing in a region depends on the number of generations separating the most recent individuals from the founders. The larger the number of generations, the more recombinants and the smaller will be the IBD segments among affected individuals. In young populations, however, there are fewer recombination events resulting in LD between distant markers. If the number of founders or the effective population size is small, there is a greater chance that the mutant allele comprises a large proportion of the variation in the trait or disease in descendent populations. This population structure may be well fitted to livestock breeds. For instance, in the American Holstein-Friesian cow population with more than 10 million animals, the effective population size is estimated to be approximately 100, due to intensive selection of a few elite sires with systematic use of artificial insemination (Georges and Andersson, 1996).

The IBD mapping approach can be applied to most inherited livestock diseases, because the diseases have a greater tendency to be genetically homogeneous within a given breed. Charlier et al. (1996) found that 12 individuals affected with *syndactyly* shared a common carrier ancestor seven to nine generations distant in a Holstein-Friesian pedigree. If a mutant allele is homogeneous across populations or breeds due to migration and selection, which have been commonly practiced in livestock, the causal mutation could be mapped with higher resolution by interbreed IBD mapping. Dunner et al. (1997) fine-mapped the *mh* locus responsible for double muscling on the centromeric end of chromosome 2 by combining samples of the Belgian Blue and the Spanish Austuriana cattle breeds. The *mh* loci of each breed were mapped virtually to the identical position and the size of the IBD segment flanking the locus could be predicted in proportion to the number of breeds in the analysis and number of generations to coalescence.

Riquet et al. (1999) successfully applied the IBD approach to QTL fine-mapping and found that all seven selected sires segregating a QTL of large effect on the centromeric end of chromosome 14 had a common haplotype for five linked markers flanking the QTL. The IBD haplotype segment size reduced the estimated size of the interval harboring the QTL to 5 cM. Further, the chromosomal position with the highest likelihood value from multi-point LD tests was within this IBD segment in the pooled group of progeny with the QTL allele of large effect.

Because the successful use of LD mapping depends on the genetic structure of the population, its application to livestock breeds appears to be promising. As most domestic livestock populations are young and dynamic, there should be large regions of LD, as discovered by Farnir et al. (2000), where LD was found to exist over extended chromosomal interval in the Holstein-Friesian population. Identification of large regions of LD in livestock populations does not require highly dense maps as in human, where the inter-marker distance should be within 3 kb to effectively implement LD mapping (Kruglyak, 1999). However, the resolution for fine-mapping will be reduced in proportion to increases in LD. The simultaneous use of several linked markers for the construction of haplotypes for LD mapping will eliminate false positive associations of the trait-causative allele with a marker allele due to identity-by-state of the marker allele (Georges, 1998b).

Even if fine mapping successfully localizes a QTL to a relatively small region, the cloning, isolation and identification of the QTL remains a daunting task, due to the number of genes and mutations residing within the interval, and the potential lack of complete penetrance between the causal allele mutation and phenotypic variation.

IMPLICATIONS

Development and application of quantitative trait loci (QTL) fine-mapping methodologies for economically important traits of livestock species are at an early stage (Riquet et al., 1999; Meuwissen and Goddard, 2000; Thaller and Hoeschele, 2000), while the use of whole genome scans using relatively coarse maps and candidate gene analyses are routinely practiced. The high resolution of QTL localization that is feasible with current QTL fine mapping methods will pave the way for more efficient implementations of schemes such as marker-assisted selection and marker assisted introgression. However, size of the regions harboring QTL achieved by the fine mapping methods will remain sufficiently large to deter QTL cloning which is the ultimate goal of QTL mapping.

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