What Holds the Future of Quantitative Genetics? - A Review**

Chaeyoung Lee*
Laboratory of Statistical Genetics, Institute of Environment and Life Science, Hallym University
Chuncheon, Kangwon-do 200-702, Korea

ABSTRACT: Genetic markers engendered by genome projects drew enormous interest in quantitative genetics, but knowledge on genetic architecture of complex traits is limited. Complexities in genetics will not allow us to easily clarify relationship between genotypes and phenotypes for quantitative traits. Quantitative genetics guides an important way in facing such challenges. It is our exciting task to find genes that affect complex traits. In this paper, landmark research and future prospects are discussed on genetic parameter estimation and quantitative trait locus (QTL) mapping as major subjects of interest. (Asian-Aust. J. Anim. Sci. 2002. Vol 15, No. 2 : 303-308)

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INTRODUCTION

Today, the basic structure and biological properties of DNA have become well known by numerous scientific efforts. The DNA sequence with only four kinds of bases and its duplication property have allowed geneticists to detect particular DNA sequences to be purified or immortalized. DNA itself has shown only modest evidence of possessing any intrinsic catalytic activities, but its importance lies on the interaction of a DNA with another DNA, other molecule, or proteins. Many experimental efforts from clinical diagnoses to gene identification were made to understand the function of genes. Although the prospect that many functions will be discovered by experimental tests (for example, use of knock out animals) in the future is plausible, the functions of genes responsible for many phenotypes are not straightforward. The complexities of genetics in human and animals are often staggering, especially for quantitative traits. These complexities arise from the fact that each factor contributes, at most, to a modest amount in explaining the phenotypic variance for the trait. Multiple genetic and environmental factors may interact with each other in unpredictable ways. The expression of such trait may not be anticipated from knowledge of each factor considered alone, no matter how thoroughly the factors may have been separately understood. Thus, the entire effect is not likely to be the same as the sum of effects for its components. Rational quantitative approaches are in need to understand such complex genetics.

The genetic architecture of a complex trait consists of all the genetic and environmental factors that affect the trait, along with the magnitude of their individual effects and interaction effects among the factors. It is critical to recognize that the genetic architecture represents more of a characteristic of a trait in a particular population rather than a fundamental biological property of the trait. Quantitative genetics may guide an important way in understanding the genetic nature of populations. Genetic variation is assumed for many genetic phenomena such as inbreeding, selection, and genetic drift. Quantified genetic variation serves a variety of purposes in related disciplines. For example, genetic variance within a population is used for selection in animal breeding, and genetic variance among populations helps us capture traces of evolution. Recently, genetic variance components in mixed model methodology have been a great concern to animal geneticists. More recently, quantitative trait locus (QTL) analysis became a hot issue with genome projects, and the mixed model approach will be of great use in developing methods for QTL analysis. This paper addresses some landmark research and future prospect in quantitative genetics.

A HISTORICAL VIEW

A landmark study of quantifying Darwinian natural selection was established by Ronald Fisher, and was published as ‘The Genetic Theory of Natural Selection’ (Fisher, 1930). His major contribution was also to introduce to various genetic theories such as progressive selection and inbreeding and to develop the corresponding statistics such as selection intensity and inbreeding coefficient. Fisher is called the father of Modern Statistics and Fisherian Genetics considerably influenced current quantitative genetics. Along with Fisher, Sewall Wright contributed to developing theories of inbreeding, genetic drift, and finite population size. Haldane showed us a mathematical theory of selection at a single locus. One of the successors for the theoretical Genetics was Motoo Kimura who studied the neutrality theory, linkage, population structure and quantitative traits and published an invaluable textbook on population genetics with his fellow, James Crow (Crow and

Meanwhile, selection model for estimating individual genetic merits has been a great concern to animal geneticists. Since least square analysis of Jay Lush had been widely used for such a purpose, a landmark research was found in the development of the mixed model by Charles Henderson in 1950s. Such models include random effects, and the genetic merits are assumed as these random effects. In the last half of the twentieth century, a considerable amount of efforts were devoted to develop methods for estimating genetic variance and genetic effects with the mixed models by Henderson and his students and fellows. Nowadays a standard analytical method is to use the animal model (Quaas and Pollak, 1980) with the restricted maximum likelihood (REML) estimates of variance components (Patterson and Thompson, 1971). Furthermore, the use of the mixed model has gained its popularity in various fields now.

Although there has been a rapid proliferation of methods for variance component estimation and QTL mapping, some scholars who lack understanding of technically demanding methods had claimed the decline of quantitative genetics and have avoided to deal with it as a successful research field. To such an unfortunate claim, I would like to cite Michael Lynch and Bruce Walsh (1998) as a response:

“… the reality is that as a tool for the analysis of complex characters, quantitative genetics is as alive as it has ever been. … quantitative genetics is still fully capable of accommodating characters with small numbers of loci, nonadditive effects, non-Mendelian inheritance, … the current machinery of quantitative genetics stands waiting to incorporate the fine genetic details of complex traits being elucidated by molecular and developmental biologists. …”

Lynch and Walsh (1998)

GENETIC PARAMETER ESTIMATION

Genetic parameters are stressed not only for characteristics of populations but also for estimation of individual genetic merits. This is because the variance component estimates are important to obtain accurate predictors and estimators when data are analyzed using a mixed model. Variance component estimation is straightforward for balanced data but not for unbalanced data. Lack of orthogonality among factors in unbalanced data led to a variety of methods for variance component estimation (Lee, 2000a). For unbalanced data, Henderson (1953) developed four different sets of quadratic forms from Fisher’s (1925) ANOVA table which summarizes a partitioning of observed variability. A merit of these ANOVA-based methods is unbiasedness of the estimates, but the estimates are not necessarily nonnegative, which is a fatal property for researchers to avoid them. Other methods to estimate variance components are minimum variance quadratic unbiased estimation (MIVQUE) and minimum norm quadratic unbiased estimation (MINQUE) with desirable properties of unbiasedness and minimum variance. The MIVQUE is to minimize an unknown variance and to assume normality. The MINQUE is to minimize a known Euclidean norm. The MINQUE does not require the normality assumption and reduces to MIVQUE under normality. Despite of the desirable properties, their empirically biased variance component estimates and large mean square errors also made researchers to avoid them (Van Tassell et al., 1995). Next, maximum likelihood (ML) of Hartley and Rao (1967) was introduced to variance component estimation. The ML estimator has attractive features of large sample properties. The estimators are asymptotically unbiased, and the asymptotic dispersion matrix of the estimators is available. The dispersion matrix is in fact the inverse of Fisher’s information matrix. Furthermore, the dispersion matrix asymptotically achieves the Cramer-Rao lower bound for the dispersion matrix of unbiased estimators. That is, the estimators have the property of asymptotic efficiency (Casella and Berger, 1990). In order to account for the loss in degrees of freedom on estimating fixed effects, restricted maximum likelihood (REML) of Patterson and Thompson (1971) was also introduced to variance component estimation. Although REML estimators have almost the same statistical properties as ML regardless of merit or demerit, researchers prefer REML to ML only because ML does not take account of the degrees of freedom involved in estimating fixed effects while REML overcomes the problem. REML estimates must be in the parameter space, and this leads to the estimates biased. However, the REML estimators are likely to have the property of unbiasedness when considering that, for balanced data, the solutions to REML equations are equivalent to those from ANOVA (Searle et al., 1992). Simulation studies showed that input values of the variance components were obtained by REML regardless of selection (Jensen and Mao, 1991; Lee and Pollak, 1997a; Schenkel and Schaeffer, 1998). Today, REML estimation is most widely used method in animal breeding. Development of computing algorithms for REML estimation of variance components have been a nontrivial task and a great concern because the highly nonlinear likelihood functions are not allowed solutions in closed form for variance components. Various maximization methods are available, and these methods are typically divided into the three types: 1) methods using first and second derivatives of the likelihood, 2) methods using only
first derivative, and 3) methods using no derivative. The final category is called derivative free REML (DFREML, Smith and Graser, 1986) and is a choice for researchers.

Meanwhile, best linear unbiased predictors (BLUP) of individual genetic merits exist under the assumption of known variance components. In reality, the variance components estimated by methods addressed above are used, so they are not any more BLUP. Bayesian inference overcomes the problem on non-BLUP of genetic merits when using REML variance component estimates. Furthermore, Bayesian approach always gives exact posterior densities of variance components while REML estimates have unknown distributions for small data sets (Gianola and Fernando, 1986). Bayesian approach became feasible through Markov Chain Monte Carlo (MCMC) methods with increasingly powerful computers. The Gibbs sampler as an MCMC is a method of numerical integration that iteratively generates samples from the full conditional densities of all the unknowns. Full conditional posterior densities have been derived for the application of Gibbs sampling by Wang et al. (1993) for a sire model, by Lee and Pollak (2001) for a sire-maternal grandsire model, by Van Tassell et al. (1995) for an animal model, by Jensen et al. (1994) for a maternal effect model, by Van Tassell and Van Vleck (1996) for a multivariate model, by Sorenson et al. (1995) for a threshold model, and by Thaller and Hoeschele (1996a) for a linkage analysis. Intensive computing from Gibbs sampling became feasible through availability of powerful computers. Considering dramatic development of computing facilities, MCMC will be widely used wherever difficulties like multi-dimensional integrals make it unable to obtain likelihood and posterior density in closed forms.

Furthermore, advances in variance component estimation with complicated models such as generalized linear mixed models (GLMM) enabled animal breeders to analyze non-normal data. The GLMM is to combine mixed models with Nelder and Wedderburn’s (1972) generalized linear model (GLM) where observations have the distributions of exponential families, and systematic effects are monotonically linked to the mean. The likelihood produced with the GLMM is hardly obtained in closed form due to high dimensional integrals. In order to avoid the problem, researchers suggested various methods such as penalized quasi-likelihood (Breslow and Clayton, 1993), simulation-based method (McCulloch, 1994), Laplace approximation (Tempelman and Gianola, 1993), Gibbs sampling (Sorenson et al., 1995), and maximum adjusted profile hierarchical likelihood estimation (Lee, 2000b). Advances in the efficiency of computing algorithms made the increasingly complex models possible. More complicated models are expected to explain complex biology with advanced statistics and efficient computing algorithms. In order to explain heterogeneity of variance components by different environments, log-linear structural model of San Cristobal et al. (1993) would be more flexible and complicated. Flexible Models with random effects having non-normal distributions are also expected. An example is a Poisson-Gamma hierarchical model by Lee and Lee (1998). The model assumes a Poisson distribution for residuals and a Gamma distribution, as a conjugate family of the Poisson distribution, for random effects. This hierarchical model might overcome the lack of consistency and invariance shown from the joint maximization of the likelihood in GLMM. Furthermore, in order to explain complex genetics, a lot of attention will be given on more complex analytical models such as multistage hierarchical models and the corresponding optimal computational algorithms.

QUANTITATIVE TRAIT LOCI MAPPING

Determining the number of genes involved with quantitative traits and their effects on the traits had been a difficult task before intensive efforts were given on genome project that sequenced genomes. Recently, many genetic markers have become available, and there has been a rapid proliferation of methods for identifying, locating, and characterizing quantitative trait loci (QTLs) linked to the genetic markers.

The idea of the marker–based QTL mapping is to utilize marker-QTL association created from linkage disequilibrium among loci by matings. The single marker analysis examines the distribution of trait values separately for each marker locus. The additive and dominance effects are, however, confounded with the amount of recombination. The interval mapping examines an association between each pair of adjacent markers and a QTL (Lander and Botstein, 1989), and offers the position and the effects of QTLs. However, the estimates from the interval mapping are biased when multiple QTLs are involved. The multipoint mapping uses all the linked markers on a chromosome simultaneously. An overfitting problem is created from the multipoint mapping when the number of regressor variables is large. The composite interval mapping is a modified interval mapping by incorporating a few additional single markers for each analysis (Zeng, 1993). Usually, the resolution of QTL locations is considerably improved by introducing a few additional well-chosen marker loci. The multiple interval mapping uses multiple marker intervals simultaneously to fit multiple putative QTLs directly in the model (Kao, 1999). Epistasis for QTLs can be also estimated by this method. The methods addressed above are based on conditional probability of QTL genotype given the observed marker genotype, and are used with various experimental designs for inbred lines.
On the other hand, the identity-by-descent (IBD) mapping is often used for the outbred population which is more popular in human and animals. This method is to specify the expected genetic covariance between arbitrary relatives as a function of the IBD relationships at a QTL and to determine proximity based on the number of cases where marker alleles and QTL alleles have not recombined.

More recently, developing methods for QTL mapping in multiple crosses or populations has drawn various research endeavors from quantitative geneticists (George et al., 2000; Walling et al., 2000; Zou et al., 2001). QTL designs combining information from multiple crosses or populations are more powerful than those involving a single cross (Lynch and Walsh, 1998). Current methods for complex pedigrees are not completely satisfactory (George et al., 2000). The difficulties arise from unknown marker genotypes and unknown marker phases, especially for data with multiple generations. Another great concern is to analyze QTL as random effects by introducing mixed model methodology (Xu and Yi, 2000). This again demonstrates the importance of estimating genetic parameters in the mixed model framework.

More new methods with abundant markers are expected in order to examine the nature of complex traits. In near future, the number of markers will be dramatically increased by numerous efforts to produce quality maps of single nucleotide polymorphisms (SNPs). Computing algorithms should be efficiently developed for intensive computing, not only because it deals with complex traits, but also because the sample size is expected to be tremendously large.

More complicated experimental designs and analytical models are required to understand genetic architecture as more candidate loci are revealed. Increasing interests in genotypes at candidate loci push to identify and quantify epistasis with other loci and interaction with environmental factors. Genetic variance unexplained at the candidate loci should be explained by correlation among relatives and be quantified as a residual genetic variance component or as a polygenic variance component. It is quite feasible, in the future, that genetic merit of individual for some complex traits of interest is predicted from its known genotypes at particular candidate loci and from its relatives’ phenotypes by pedigree.

**FUTURE CONSIDERATION**

The keys that hold the future of quantitative genetics are largely on developing more legitimate methods for genetic parameter estimation, especially for QTL analysis as discussed above. In this section, I would like to address three important questions to be considered for future genetic parameter estimation. **Could it be that genetic effects are too complex for us to find an explanation with current methods?** This question goes beyond the typical question of asking whether a specific method has sufficient power for a specific data set. Two examples are presented here.

The first example is about complex interaction between genetic and environmental effects. It is not the matter of measuring the size of the interaction, but the matter of biological explanation. Sire-by-year interaction variance explained 3% of phenotypic variance when a maternal genetic model was used for analyzing Simmental cattle data (Lee and Pollak, 1997a). Such interaction is rather too complex to be biologically explained. Another study by Lee and Pollak (1997b) showed that possible bias on that interaction variance estimate could be from the sire misidentification.

The second example is the debate on direct-maternal genetic correlation in beef cattle. This debate goes beyond the fact that direct-maternal genetic correlation estimates vary by data sets. The more relevant question to pursue is whether negative genetic correlation estimates are artifacts or not. Many researchers found negative genetic correlation between direct and maternal effects in real data. However, it was suspected that the estimates might not be obtained directly from real genetic antagonism, but indirectly from other factors such as sire-by-year interaction (Lee and Pollak, 1997b) and selective reporting (Mallinckrodt et al., 1995). On the other hand, there was an attempt to explain the genetic antagonism with a physiological theory (Lee and Pollak, 2001).

**How realistic are the systematically explained environmental effects included in an analytical model?** Genetic architecture explains genetic and environmental effects. Theoretically speaking, it is possible to define the genetic factors in terms of Mendelian segregation and the location along a genetic map. On the other hand, the environmental factors are hardly partitioned into separate factors whose individual effects and interactions can be sorted out. Although their ambiguous parts are explained as residuals from the model, there is always the possibility of failure to notice some significant environmental effects and their complex interactions with other environmental effects or genetic effects.

**How do we handle the possibility of a false positive or false negative QTL detection?** The false positive or negative QTL detection may be due to an insufficient statistical power or an unreasonable significance threshold, and may be revealed by replicated studies. This problem becomes more serious when a large number of marker loci are examined. Technically, they are so called Type I and Type II errors, and the question also goes beyond the matter of reducing those errors. A QTL detected by one group but not by other groups should not be ignored because of different genetic structure of populations. Suppose a simple case
where a trait is significantly influenced by the interaction of two recessive alleles at different loci. In a certain population, one allele is extremely rare and the other extremely common. The trait appears to be influenced by the rare allele in the population because its presence guarantees a large probability of having the two alleles while the probability is small given the presence of the common allele. Suppose another population where their allele frequencies are reversed. Then the other allele would appear to be influencing the trait. The QTL should be located differently between the two populations, and the different results are both correct. The fact is, however, that both recessive alleles in either population influence equally to the trait. The different QTL locations were caused by different gene and genotype frequencies in the two populations. Of course, mutation may also generate new QTL in a particular population. Genetic architecture is, in fact, a moving target that changes depending on genetic and environmental variances of a certain population.

CLOSING REMARKS

Widely publicized genome projects brought about a great deal of interest from the general public as well as from the scientific community. However, the knowledge on relationships between genotypes and phenotypes for quantitative traits has been extremely limited, and will not be clarified in a foreseeable time frame. This is because of complexities in genetics. Further difficulties arise from the fact that typical human and animal families are naturally quite limited, and most of them are considerably heterogeneous. We need to recognize that genetic mechanisms fundamentally distinguish complex traits from simple traits and that statistics explain the uncertainty in genetic mechanisms as well as in population genetic properties.

Advances in statistical methods is essential for analyzing experimental crosses and pedigrees to detect segregating QTLs associated with molecular markers based on quite dense linkage maps produced by genome projects. The future of understanding quantitative traits is quite promising. It is our exciting challenge to find genes that affect virtually any trait of interest, and quantitative genetics will play an unprecedentedly important role in understanding the inheritance of quantitative traits.

It is a time to reflect on development of new methods in Asia, which has lagged far behind the efforts outside of the continent. Most Asian countries are sufficiently naive about complex traits. Animal geneticists in Asian countries have paid less attention in exploring and adopting methods developed in other areas. Every effort should be made to encourage the development of new methods. It is also important to emphasize that no single method for complex genetics can be universally adopted and the universal use of single method in every study leads to limited, biased, or wrong findings. Our knowledge on genetic architecture will be more extensive only by developing various methods.

REFERENCES


