Genetics of Quantitative Traits and Improvement of Dog Breeds

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Introduction

'Like begets like', one of the principal axioms of the acknowledged pioneer of animal breeding, Robert Bakewell (1725–1795) of Dishley Manor (Pawson, 1957), is the bedrock of quantitative genetics. Combined with Bakewell's second axiom, 'breed the best to the best', we see that the integration of quantitative genetics and animal improvement is guided by two very simple principles, whether we discuss livestock or the domestic dog. Breed improvement, or the process of genetic change, is a function of genetic variation, intensity of selection and the accuracy of identifying superior genotypes (Van Vleck, 1993). Of the three, animal breeders concentrate on the accuracy of identifying superior genotypes. The present chapter will examine the tools available to dog breeders that can enhance the accuracy of selection decisions. The number of papers that have examined quantitative genetics in the dog has been increasing over the past 20 years. However, the great majority of these investigations have done little more than estimate the heritability of a few traits in a handful of breeds. Understanding the quantitative traits of the dog is more

than estimating a few parameters (Kempthorne, 1997; Lynch and Walsh, 1998). Much more remains to be accomplished. In particular, we must examine how the explosion of knowledge in the canine genome can be used to breed better, healthier dogs.

Traits of Interest

Unlike breeders of livestock, dogs do not have production traits; objectively measured quantitative characters which breeders hope to increase through selection (Patterson, 2000). Nevertheless, there are traits which dog breeders hope to modify. The traits that dominate our interest can be broadly described under the headings of reproduction, conformation, temperament and disease. These characters are typically polygenic, where the variation we observe is a function of environmental contributions as well as the action of many individual loci distributed throughout the dog genome.

The statistic most commonly used to quantify genetic variation is heritability, the ratio of genetic variation to phenotypic variation (Falconer and Mackay, 1996). Most of the scientific literature in dog quantitative genetics is the publication of heritability estimates (see Willis, 1989, 1992). Yet, the job of animal improvement does not stop with the publication of this statistic, because heritability is a means to an end and not an end in itself. Heritability is used to predict the response to selection and as an adjunct to the prediction of genetic merit (Kennedy and Sorensen, 1988; Kempthorne, 1997). Moreover, the heritability of a character in one breed is no indication of the heritability of that character in a second or third breed (Bulmer, 1985). This caution aside, Willis (1992) presented a useful generalization of heritability values for a variety of traits in a cross-section of breeds.

Unfortunately, no large data sets of reproductive data in dogs have been presented that can lead to useful estimates of the heritability of reproductive traits. Willis (1989, 1992), drawing upon allied research in livestock, prudently supposes that the heritability of fertility, litter size, semen quality and early postnatal survival is low, with values that are likely to range between 0.10 and 0.20. The implication of these low values is that selection to improve reproductive performance is likely to be slow. Other than selection against reproductive disease states such as inherited cryptorchidism (Brandsch, 1964; Sittmann, 1976), or a variety of other inherited reproductive disorders (see Meyers-Wallen, 1993), breeders are more likely to concentrate their selection decisions on other inherited characters.

Although adequate data exists only sparingly, the heritability of body conformation traits suggests a moderate to high heritability, with values ranging between 0.35 and 0.65 across breeds. Table 17.1 presents the heritabilities, genetic and phenotypic correlations among hip, elbow, hock and shoulder measurements in a study of 3500 Labrador Retrievers collected by the Institute for Genetic Disease Control (unpublished data). Such results demonstrate that, not only are structural traits heritable, but that they are typically positively

Table 17.1. Estimates of heritability (diagonal), phenotypic (above diagonal) and genetic (below diagonal) correlations for joint measurements in Labrador Retrievers.

Trait	Hips	Elbows	Hocks	Shoulders
Hips	0.65	0.22	0.06	0.07
Elbows	0.55	0.48	0.06	0.08
Hocks	0.21	0.00	0.18	0.10
Shoulders	0.41	0.43	0.12	0.15

genetically correlated to one another. Early studies in German Shepherd dogs from the Swedish Army suggest a heritability for 60-day weight of approximately 0.4 (Reuterwall and Ryman, 1973; Hedhammar *et al.*, 1979). Other stature traits in German Shepherd dogs suggest that measures of body size are moderate to high in heritability, with values of 0.81 for chest width or 0.54 for height at the withers (Verryn and Geerthsen, 1987). The interpretation of these high values is that a large percentage of the observed variation in body conformation is genetic variation, suggesting that selection could change body size in only a few generations of directional selection. However, dog breeders are interested in stabilizing selection (see Hartl, 1988) when thinking of conformation, hoping to eliminate dogs at the extremes of size or structure (Willis, 1989; Craige, 1997).

Behaviour traits, among the most important characters of interest to dog breeders, are also the most difficult to evaluate genetically (Willis, 1989). Clearly, behaviour patterns are inherited, most visibly illustrated by the range of breed differences in temperament, nervousness and any of a variety of behavioural characteristics (see, for example, Scott and Fuller, 1965; Burns and Fraser, 1966; Hart and Hart, 1985; Willis, 1989). But behaviour is also highly dependent upon acquired and environmental influences, so that the interaction of heredity and the environment can never be far from one's mind. Add to this the subjective nature in evaluating the phenotype of behaviour traits, and one can readily see the dilemma for the quantitative geneticist who hopes to separate nature from nurture.

Depending upon the character to be studied, and the breed to be investigated, the heritability (h) of behavioural traits can vary from low to high, from 0.10 to 0.60. Probably the most reliable genetic work on behaviour has been done through breeding organizations with an emphasis on service performance. At the Royal Guide Dogs for the Blind Association of Australia, Goddard and Beilharz (1982, 1983) were able to estimate the heritability of a variety of behavioural traits in Labrador Retrievers: nervousness ($h = 0.58$), suspicion ($h = 0.10$), nose distraction ($h = 0.0$) and successful graduation from the training programme ($h = 0.44$). Working with German Shepherd dogs bred by the Division of Bio-Sensor Research of the US Army, Mackenzie *et al.* (1985) estimated the heritability of temperament (as measured by the dog's ability to chase and attack a decoy) as 0.51. In more recent work at the Swedish Dog Training Centre, Wilsson and Sundgren (1997) found a range of heritability

estimates in German Shepherd dogs and Labrador Retrievers from a low of 0.05 for prey drive in Retrievers to a high of 0.37 for affability (i.e. friendliness) in German Shepherds.

The reason for citing these few reports is not to present a comprehensive review of the genetics of behaviour (that can be found in Chapter 13). The intent of this brief outline is to demonstrate that behaviour can be modified by selection. Yet, as the titles given for these behavioural traits suggest, we also see the difficulty in drawing universal conclusions about the inheritance of behaviour traits. For example, how does one quantify 'affability' (a trait evaluated by Wilsson and Sundgren, 1997) in a repeatable manner? While most of us can distinguish a friendly dog from an unfriendly one, how can this be quantified reliably and consistently. This remains one of the important challenges for dog breeders in the coming years, the effort to better quantify temperament traits for use in selection programmes.

Finally, breed organizations hope to reduce the incidence of disease through breeding. The American Kennel Club has established the Canine Health Foundation (AKC-CHF) with this purpose in mind, surveying breed clubs on the diseases they hope to eliminate through selection and breeding (Wilkie, 1999). At the top of the list are the diseases of hip dysplasia and epilepsy (Wilkie, 1999). The heritability of hip dysplasia has been variously estimated in the range of 0.26 (Mackenzie *et al.*, 1985) to 0.35 (Leighton, 1997) in German Shepherd dogs. Although investigators now universally agree that hip dysplasia is a polygenic trait (Willis, 1989; Todhunter *et al.*, 1999), the environmental effect of food consumption also plays a role in the prevalence of this disease (Kealy *et al.*, 1992, 1997). As for epilepsy, Famula *et al.* (1997) recently estimated the heritability of this disease in Belgian Tervuren at 0.71. Further investigation suggests that a single locus with a large effect on epilepsy is segregating in this population at a frequency of 0.14 (Famula and Oberbauer, 2000a). Kathmann *et al.* (1999) conclude that epilepsy in the Bernese Mountain Dog is polygenic, yet provide no estimate of genetic variation.

Of course there are a great many other health disorders of dogs that have a polygenic component, ranging from inherited cardiac arrhythmias (Moise, 1999), the vertebral disease spondylosis deformans in boxers (with a heritability of 0.4; Langeland and Lingaas, 1995), calcification of intervertebral discs in the Dachshund (with a heritability of 0.22; Stigen and Christensen, 1993), primary angle-closure glaucoma in Samoyeds (with a heritability of 0.58; Ekesten and Torrang, 1995) or histiocytosis in Bernese Mountain Dogs (with a heritability of 0.30; Padgett *et al.*, 1995). Chapter 9 presents a more complete discussion of the genetics of disease in dogs.

In the context of breed improvement, the emphasis on disease as a component of selection decisions is increasing. A recent examination of the effects of selection for improved hips in German Shepherd dogs of the Finnish Kennel Club (Leppanen *et al.*, 2000) showed no improvement over the years 1985 to 1997. This analysis stands in contrast to the reduction of hip dysplasia in German Shepherd dogs and Labrador Retrievers observed in a closed colony trained as guide dogs for the blind (Leighton, 1997). Table 17.2

Table 17.2. Percentage normal hearing, unilaterally deaf and bilaterally deaf Dalmatians by year of hearing test (brainstem auditory-evoked response) at the University of California, Veterinary Medicine Teaching Hospital, from 1984 to 1998

	Percentage		
Year of test	Normal hearing	Unilaterally deaf	Bilaterally deaf
1984	70	30	0
1985	64	27	9
1986	75	20	5
1987	74	17	9
1988	65	24	9
1989	67	25	8
1990	79	14	7
1991	76	15	9
1992	74	19	7
1993	71	18	11
1994	80	16	4
1995	86	10	4
1996	74	19	7
1997	64	27	9
1998	82	9	9

demonstrates a similar absence of observable genetic improvement in the reduction of deafness in Dalmatians from 1984 to 1998 (unpublished data). Apparently, although breeders may be interested in reducing the incidence of disease through breeding, they may lack the resolve to turn their interest into action, a point also suggested by Leppanen *et al.* (2000).

This summary of traits, though by no means complete, illustrates that breeders do not suffer from a lack of selection objectives. Whether behaviour, conformation or disease, breeders have sufficient raw material to manifest genetic change. The future will show whether breeders have the resolve to establish the genetic change that the parameters listed above suggest can materialize.

Genetic Improvement in Quantitative Traits

Interestingly, the use of statistical decision aids is a new and exciting topic in dog breeding (Canine Health Foundation), although the techniques and tools available to breeders are not new, having been used by livestock breeders for generations (Henderson, 1977, 1984, 1988; Searle *et al.*, 1992; Mrode, 1996). Yet, dogs are not livestock, and the problems and interests of dog breeders are quite different from those that interest agriculturally oriented animal breeders. In essence, dog breeders hope to create dogs of a uniform standard of performance across several traits (Frankling, 1974), avoiding the extremes of phenotype that are typically the goal of livestock breeders (Patterson, 2000).

As evidence of this growing interest to apply statistical tools to breed improvement, the American Kennel Club is developing a database of health information (Canine Health Foundation) and other private businesses (e.g. Institute for Genetic Disease Control) and breed clubs are considering the same. Assuming such data can and will be assembled, what use will such information provide for dog breeders? It is unlikely that individual breeders, those with only one or two dogs (the majority of the dog owning population), will be able to take advantage of these computerized databases and the associated statistical decision aids such data can provide (Leppanen *et al.*, 2000; Patterson, 2000). However, large breeding organizations such as Canine Companions for Independence (Santa Rosa, California) or Guiding Eyes for the Blind (Patterson, New York) can, and no doubt will benefit from the use of statistical tools. Armed with objective, quantifiable traits, pedigree information and statistical advice, these organizations will be able to select better animals efficiently and effectively (Famula and Oberbauer, 1998), in a manner that will mirror that of livestock geneticists (e.g. Ollivier, 1998).

Quantitative methods for animal improvement

Most dog breeding is based on individual selection, using observations from the animals in question and deciding which is best on a subjective scale (Hutt, 1979; Willis, 1989; Robinson, 1990; Patterson, 2000). Many breeders attempt to incorporate family information and knowledge of the performance of relatives as well, but do so on 'intuition' (Robinson, 1990; Craige, 1997). Ideally this incorporation is done through formal statistical procedures for weighting pedigree information (Van Vleck, 1993) or other mating strategies outlined in texts of animal breeding (e.g. Bourdon, 2000). However, much of dog breeding is done on subjective opinion and a sense of what constitutes an ideal dog (Craige, 1997). The weakness of such a strategy is the accuracy of identifying superior genotypes, one of the three components of genetic progress.

Of course, genetic progress is still possible without elaborate statistical techniques. Figure 17.1 presents a plot of average breeding values computed via the mixed model techniques discussed by Henderson (1984) for the joint measurements discussed in Table 17.1 for the population of Labrador Retrievers collected by the Institute for Genetic Disease (unpublished data). This process, plotting estimated breeding values against year of birth, is typically how livestock geneticists evaluate genetic trends, or the response to selection (e.g. Nizmani and Berger, 1996). Although the analysis of this data was done with mixed model methods, the selection decisions were not based on these calculations. Breeders could only make use of the phenotypes of individuals and their relatives with only 'intuition' of superiority as a guide. Nevertheless, breeders were able to show a dramatic change in hip and elbow measurements between 1991 and 1998, with virtually no change in hock and shoulder measurements. So change is possible, only likely to be slower than that possible with more advanced statistical technology.

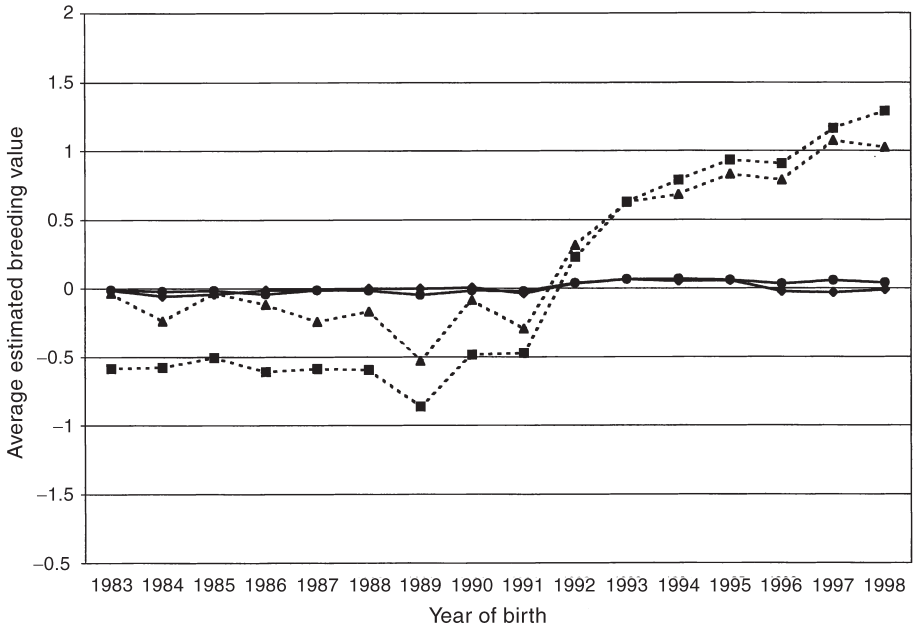

Fig. 17.1. Average estimated breeding values for joint measurements on hips (■), elbows (▲), hocks (♦) and shoulders (●) in Labrador Retrievers by year of birth.

As databases accumulate objective data, we should anticipate the application of mixed linear model techniques to dog improvement (suggested by Leppanen and Saloniemi, 1999; Leppanen *et al.*, 2000). The advantage of a mixed model approach is the broad applicability to a variety of genetic models (e.g. maternal effects, repeated measures) and the simultaneous ability to correct for non-genetic factors (Henderson, 1984). These techniques have been extended to evaluate and rank animals for traits that are categorical rather than continuous (Gianola and Foulley, 1983; Harville and Mee, 1984), a form of data quite typical for disease (e.g. deafness in Dalmatians by Famula *et al.*, 1996) or behavioural traits (e.g. hunting behaviours evaluated by Schmutz and Schmutz, 1998). Mixed model techniques are also useful in analysing several traits simultaneously (Henderson, 1984, 1988). Yet, as Patterson (2000) and Leppanen *et al.* (2000) suggest, with the exception of large, institutional breeders of service dogs, most breeders are unlikely to use statistical decision aids and mixed models. How then, can breeders improve the accuracy of selection decisions without turning to computers, databases and statistical algorithms?

Breed Improvement and Genomics

The past 10 years has brought an explosion of genetic information including genome maps (Mellersh *et al.*, 1997, 2000; Langston *et al.*, 1999), DNA markers (Rothuizen *et al.*, 1999; van de Sluis *et al.*, 1999) and a host of new acronyms in

molecular biology (Lewin, 1999). The future will see the integration of the pedigree based selection tools of mixed linear models with the expanding canine genetic map through marker-assisted selection (Hospital and Charcosset, 1997; Spelman and Bovenhuis, 1998). Many dog breeders can already benefit from the direct use of DNA information (e.g. the von Willebrand's disease mutation, Venta *et al.* (2000) see Chapter 16) for simply inherited Mendelian traits. The integration of map information into selection decisions for quantitative traits is more problematic.

Currently there are no concrete examples of the identification of quantitative trait loci (QTL) and the application of this information to dog breeding and improvement. Before this process can begin, researchers have several obstacles to overcome. The first step is to establish that the trait of interest (often a polygenic disease trait) is inherited, along with an evaluation of the impact the environment may have on expression of the trait. With inheritance firmly established, investigators must next evaluate the role that single genes play in the expression of the trait. Armed with this basic information, investigators can take the final step to identify the specific genes that govern expression of the quantitative trait. Though no example illustrating all three phases of such work can be given for dogs at present, our own work in reducing the prevalence of epilepsy in the Belgian Tervuren can serve as a model for the direction of quantitative genetics research in dogs.

Establishment of inheritance

As discussed earlier, estimation of heritability is not an end in itself (Lynch and Walsh, 1998). Knowledge of genetic variation is required to evaluate the potential success of breeding programmes (de Andrade *et al.*, 1999), as well as to serve as an adjunct to the prediction of breeding values (Kennedy and Sorensen, 1988). Not to be ignored, the process of estimating heritability (Searle *et al.*, 1992) also compels investigators to examine the environmental influences on quantitative traits. An example of where investigators are still sorting out fixed non-genetic contributions to genetic disease is in the influence of gender on hearing loss in Dalmatians (Wood and Lakhani, 1997, 1998).

Regardless of the problem, the methodology for estimating heritability and genetic correlations is well understood and software is widely available (Van Vleck, 1993; Lynch and Walsh, 1998). The advantage of mixed model methods is their ability to incorporate all known relationships among animals, to accommodate inbreeding and fixed non-genetic effects, to evaluate potential environmental covariances and to do all this in multiple trait settings (Kennedy and Sorensen, 1988; Kennedy *et al.*, 1992). In addition, these strategies of parameter estimation can be applied to discrete phenotypes and threshold models (Famula *et al.*, 1996, 1997).

Complex segregation analysis and major genes

Finding those loci (i.e. QTL) that are known to contribute to quantitative traits of interest could lead to efficient, workable selection aids (Xie and Xu, 1998). Genes large enough to detect, and thus large enough to facilitate significant genetic change when the subject of a selection decision, are referred to as major genes (Falconer and Mackay, 1996; Lynch and Walsh, 1998). Though no formal definition is necessary, a major gene is usually defined as a locus where the difference between homozygotes exceeds one phenotypic standard deviation (Morton and MacLean, 1974). Methods to uncover major genes extend from the detection of a departure from a normal distribution of phenotypes (Hammond and James, 1970), to tests based on family variances (Fain, 1978), pedigree analysis (Karlin *et al.*, 1979; Famula, 1986) and mixture models (Elston, 1984; Hoeschele, 1988). However, such methods have not been used on data from dogs.

Complex segregation analysis (CSA), developed for work in human genetics (Elston and Stewart, 1971; Morton and MacLean, 1974), is the ideal method for the detection of major genes in dogs, although also the most computationally difficult. The intent of this statistical tool is to search for the hidden patterns of Mendelian inheritance in a polygenic trait. For complex quantitative traits (e.g. behaviour) or polygenic disease traits (e.g. hip dysplasia, epilepsy), we can not directly observe the Mendelian segregation of individual loci. Complex segregation analysis is the integration of Mendelian transmission genetics, allele frequency and penetrance with the patterns of covariance among relatives expected in polygenic models of inheritance (Bonney, 1986; Bonney *et al.*, 1989).

A detailed discussion of CSA can be found in a variety of sources (e.g. Lynch and Walsh, 1998; Sham, 1998). Jarvik (1998) has recently reviewed the use and limitations of complex segregation analysis, asserting that prudence dictates the use of CSA prior to a molecular search for QTL. Although CSA has seen limited use thus far in dog genetics, Famula *et al.* (2000a) and Famula *et al.* (2000b) are two recent applications of this technique to major gene detection in dogs. The purpose in both investigations has been to provide sufficient statistical evidence for QTL prior to proceeding with more expensive and time-consuming linkage studies.

Elston *et al.* (1975) outline criteria that must be satisfied before acceptance of the major gene model. The principal concern in the interpretation of the results of CSA is the risk of false positives (Demenais and Bonney, 1989; Jarvik, 1998). Skewness or kurtosis in the distribution of phenotypes can be misinterpreted as evidence of a major locus (MacLean *et al.*, 1975), as can other departures from normality (Go *et al.*, 1978; Eaves, 1984; Morton, 1984; Tiret *et al.*, 1993). Population sampling is also an issue in CSA. Many studies of disease are structured around the discovery of diseased animals, called probands. This ascertainment bias, the bias of how animals and their relatives

are selected for study, must be accommodated to ensure appropriate interpretation of CSA and avoid the risk of a false positive declaration of major gene inheritance (Elston and Sobel, 1979; Lalouel and Morton, 1981; Greenberg, 1986; Vieland and Hodge, 1995).

Although the statistical power of this method for dichotomous traits can be disappointing (Greenberg *et al.*, 1998), quantitative and polychotomous traits can benefit from dissection with these tools. Investigators are urged to apply these techniques to problems in dog genetics prior to the search for QTL via linkage analysis (Jarvik, 1998) through a variety of commercially available software packages (e.g. SAGE, 1997).

Complex linkage analysis

If we assume that dog breeders are unlikely to apply the statistical methods traditionally employed in other species (Leppanen *et al.*, 2000; Patterson, 2000), then the long-term hope for improvement will have to rely upon the identification of specific loci as an adjunct to making selection decisions. Assuming complex segregation analysis suggests a major gene is segregating, our attention then turns to locating this gene amongst the thousands present in the genome of the dog.

One strategy of locating QTL is based on the knowledge of candidate genes. Investigators have already identified important biochemical pathways and the genes that control their expression (e.g. Veldhoen *et al.*, 1999). It remains a relatively simple statistical process to correlate a dog's candidate genotype to a phenotype of interest. The statistics are simple (e.g. analysis of variance) and the results easy to interpret (Kennedy *et al.*, 1992). Several AKC-CHF supported investigators (Wilkie, 1999) are using this approach to finding QTL associated with epilepsy and canine cancer.

The limitation to this process is candidate genes. We can only investigate loci that have been previously identified, are polymorphic and which we suspect are involved in the expression of a phenotype. For many of the disease and behavioural traits that interest dog breeders we have, as yet, no knowledge of where to begin this search. In epilepsy, for example, there are hundreds of loci that are responsible for a properly functioning nervous system. Yet, beyond a handful of possible candidates borrowed from the human genetic map (Greenberg *et al.*, 2000), dozens more surely remain unknown.

A more powerful, though more complicated, strategy is to search for loci of which we are not already aware. In this approach we use anonymous sections of DNA, commonly small repeated sequences (e.g. microsatellites). These non-coding, highly polymorphic sections of each dog chromosome are easily identified and of known map location (Mellersh *et al.*, 2000). Although microsatellites do not translate into important physiological information, they

are physically located near potential QTL. To make use of this information, samples of tissue (e.g. blood, buccal swab) are taken from dogs within a breed, the DNA extracted and genotyped at each of potentially hundreds of marker locations across the genome. The hope is to link a particular marker to a trait of interest.

Strategies of linkage analysis for complex traits vary in their degree of statistical complexity. A recent review of the assumptions of several methods (Elston, 1998) outlines the applicability of these techniques to various forms of pedigree data (Lander and Schork, 1994; Lander and Kruglyak, 1995; Kruglyak *et al.*, 1996; Morton, 1998). As part of his review of methodology, Ott (1999) includes a discussion of the software available for analysing pedigree and phenotypic data. Chase *et al.* (1999) discuss methods traditionally used in plant genetics, where inbred lines form the basic unit of investigation, and their application to breeds of dog of small population size such as the Portuguese Water Dog. The rationale behind each of these strategies is that the variation observed between the phenotypes of siblings can be related to the probability of identity by descent for the QTL influencing the trait in question (Liu, 1998).

As with complex segregation analysis, these methods have not yet seen wide use in dogs. In our continuing investigation of epilepsy in the Belgian Tervuren, we have made use of sib pair analysis (SAGE, 1997) to identify several promising markers associated with a putative QTL for epilepsy (unpublished data). Having screened 88 tetra-, tri- and di-nucleotide microsatellite markers, we have found 11 markers with a significant association to seizures. Of these, two markers fall to the same chromosome assignment (unpublished data). However, debate continues on the appropriate criterion for the declaration of a 'significant' result (Lander and Kruglyak, 1995; Witte *et al.*, 1996; Morton, 1998). As one might expect, violations of model assumptions can decrease the power of linkage detection (Elston, 1998; Jarvik, 1998) and lead to erroneous conclusions. As the literature on QTL in dogs expands in the coming years, this concern may dissipate, but the first efforts in this area are likely to be fraught with as many errors as useful discoveries.

Summary

Naturally, this brief discussion only introduces the basic concepts for the future of quantitative genetics and breeding in dogs. The key to this discussion has been increasing the accuracy of making selection decisions. This search for increased accuracy begins with the collection of reliable phenotypic data and pedigrees. The future will increasingly make use of marker information and the identification of QTL influencing traits of importance. What remains is for dog breeders to maintain the resolve necessary to turn research results into wise breeding decisions.

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