

Finding Genes for Complex Disease Traits: How a Single Parent Club Makes All the Difference!

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As a result of differential selection for phenotype traits, dog breeds are, by definition, closed breeding pools. Because registration to a particular breed requires that one's parents were also registered members of the same breed, genetic diversity can always decrease, but not increase. Small numbers of founders, population bottlenecks, and popular sire effects have thus conspired to make the domestic dog an ideal resource for mapping genes associated with both simple and complex traits, and for understanding the dynamics of population evolution. We have evaluated this in several ways.

First, using data from 5 unrelated dogs of each of 85 breeds, we demonstrated previously that breed barriers result in strong genetic isolation, with breed membership accounting for ~30% of total genetic variation among dogs. In addition, genetic cluster analysis based on microsatellite data groups modern breeds into four populations reflecting similarities in morphology, behavior and geographic origin. We now expand on that analysis by including data from 40 additional breeds to more precisely describe the historical relationship between founding populations.

In addition to the above, we have evaluated the extent of linkage disequilibrium (LD) in five well-selected breeds of unique ancestry. We found that LD in dogs is 20-100 times more extensive than in human populations and varies by as much as 10-fold between breeds. This suggested that a correspondingly smaller number of markers would be required for association studies in dogs than humans. We also evaluated haplotypes and found that dog breeds, in general, are characterized by low haplotype diversity and high haplotype sharing. Thus, we predict that a single SNP map of 3,000-30,000 SNPs will be useful for mapping traits of interest in most breeds. Overall these findings set the stage for mapping genes associated with disease susceptibility by our lab and others.

Lastly, we and others have increasingly turned our attention to the identification of loci associated with morphologic variation with collaborators Gordon Lark and Kevin Chase, and the localization of disease genes. Particular areas of disease interest are loci for histiocytic diseases in the Bernese Mountain Dog and Flat-Coated Retriever, hip dysplasia in the Portuguese Water Dog, and other cancers in the Golden Retriever. Mapping

and positional cloning of the underlying genes as well as identification of relevant variants is underway using SNP-based haplotype approaches.