ASSOCIATION STUDIES

Dog genes mapped at a SNP

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A SNP genotyping platform that has been developed for use in dogs proves that efficient genome-wide association mapping can be carried out in this organism. The array — which contains ~27,000 SNPs — has been used in a two-step protocol to map the variants that underlie two Mendelian traits.

Several disorders that affect humans also afflict their best friend, and so human health stands to benefit from improvements in gene mapping in dogs. The strategy underlying the new approach was suggested by the canine genetic structure: the two historical population bottlenecks are associated with linkage disequilibrium (LD) of different length — a shorter one that results from the domestication event and a longer one that corresponds to the subsequent creation of breeds. The mapping protocol relies on the long LD within breeds to roughly locate the locus that is associated with a trait, and then exploits the short LD across breeds to fine map the mutation.

Elinor Karlsson and colleagues developed and validated the SNP array, and then used it to map two visible Mendelian traits: the major white spotting (*S*) locus in boxers and the presence of a dorsal hair ridge in Rhodesian ridgebacks. It took an average of only 20 dogs (~10 affected and ~10 controls) to get to within 1 Mb of each trait locus. The authors went on to fine map the *S* locus — which affects the pigmentation of the skin and coat — to a 100-kb region that contained the 5′ end of the pigmentation gene *MITF* (microphthalmia-associated transcription factor); sequencing *MITF* in the spotted and solid coat phenotypes revealed three candidate regulatory mutations that underlie the phenotype.

In a second paper, Nicolette Salmon Hillbertz and colleagues exploited the short LD across dog breeds to fine map the locus for the second trait, the hair ridge. This dominant trait is caused by a duplication that includes three fibroblast growth factor genes. The involvement of developmental genes could explain the high incidence of a neural tube defect in ridged dogs.

Association mapping of simple phenotypes in dogs is therefore both feasible and can be done unambiguously with only a few individuals. The authors predict that it could take as few as 200 dogs to fine map genes that convey a three- to fivefold increased disease risk, raising the hope that the approach can be extended to map complex traits.

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ORIGINAL RESEARCH PAPERS
Karlsson, E. K. *et al.* Efficient mapping of Mendelian traits in dogs through genome-wide association. *Nature Genet.* 30 September 2007 (doi:10.1038/ng.2007.10) |
Salmon Hillbertz, N. H. C. *et al.* Duplication of *FGF3*, *FGF4*, *FGF19* and *ORAOV1* causes hair ridge and predisposition to dermoid sinus in Ridgeback dogs. *Nature Genet.* 30 September 2007 (doi:10.1038/ng.2007.4)