

# So many doggone traits: mapping genetics of multiple phenotypes in the domestic dog

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Received July 2, 2012; Revised and Accepted August 1, 2012

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**The worldwide dog population is fragmented into >350 domestic breeds. Breeds share a common ancestor, the gray wolf. The intense artificial selection imposed by humans to develop breeds with particular behaviors and phenotypic traits has occurred primarily in the last 200–300 years. As a result, the number of genes controlling the major differences in body size, leg length, head shape, etc. that define each dog is small, and genetically tractable. This is in comparison to many human complex traits where small amounts of variance are controlled by literally hundreds of genes. We have been interested in disentangling the genetic mechanisms controlling breed-defining morphological traits in the domestic dog. The structure of the dog population, comprised large numbers of pure breeding populations, makes this task surprisingly doable. In this review, we summarize recent work on the genetics of body size, leg length and skull shape, while setting the stage for tackling other traits. It is our expectation that these results will contribute to a better understanding of mammalian developmental processes overall.**

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## INTRODUCTION

Most common dog breeds were developed recently, within the last 200–300 years in Europe and were optimized for both appearance and behavior (1,2). As a result, domestic dog breeds today display a dazzling array of variations in terms of leg length, skull shape, coat color, bone width, body size, etc. However, the number of genes that are likely to control each trait is small, compared with the large numbers assigned to many human phenotypes (3,4). Why is this? The observation likely reflects several aspects of canine population structure. Fanciers have historically placed dogs under strong selection to create breeds with specific phenotypes. In addition, many dog breeds are descended from small numbers of founders and, additionally, many underwent bottlenecks early in their development. As a result, the number of genes controlling major traits that have slipped through the bottleneck is limited (5,6). So, rather than having a large number of genes of small effect, as is observed in humans, a small number of genes of large effect predominate in dogs. Many such loci are marked by the presence of selective sweeps, or regions of reduced heterozygosity, indicating loci that breeders have been selecting for the formation of particular breed-defining traits (7).

We have been interested in finding the genes that control fixed morphological traits in the domestic dog and then determining the importance of those genes in humans. In the United States, today, there are 167 dog breeds recognized by the American Kennel Club (AKC) and worldwide, over 350 breeds are recognized. In this review, we discuss current findings, highlighting the advances in canine genomics that have contributed to our growing understanding of mammalian morphologic genetics.

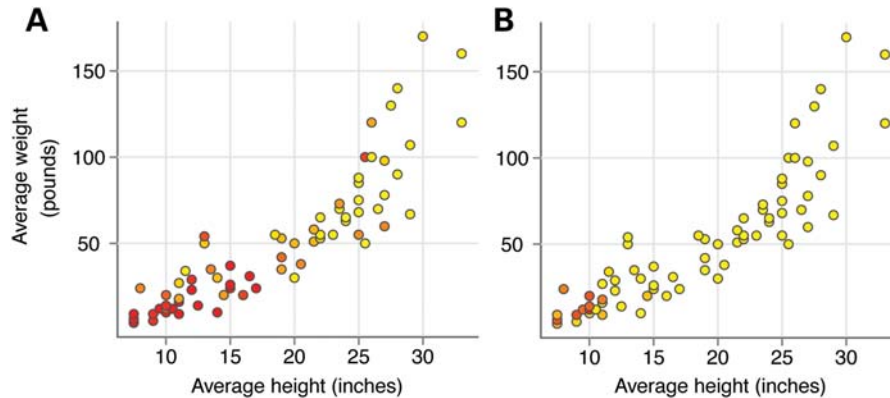
## ORIGINS OF THE DOMESTIC DOG

The dog is the only large carnivore that has been domesticated (8), and several studies show that the wolf is the direct ancestor of today's dog (9–11). However, the timing and geographical region where key domestication events took place are controversial. Archeological data suggest that dogs first appeared 15 000 up to 100 000 years ago in multiple locations, including Europe, the Middle East and East Siberia (10,12–15). Studies of the canine nuclear genome support this statement, suggesting that South West Asia and/or Europe were principle regions of domestication (16). However, separate studies analyzing mitochondrial and the Y-chromosome

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**Figure 2.** Correlation of the allele frequency and size at *IGF1* and *IGF1R* loci. The average height and weight of breeds from the CanMap dataset are plotted (3). Each circle represents one breed. The ancestral allele frequency is represented as a gradient from red (low) to yellow (high). SNPs depicted include CFA15:44,226,659 (A) and CFA3:43,756,620 (B). These SNPs are highly associated with canine body size at *IGF1* and *IGF1R* loci, respectively (3,31).

## CANINE GENOMICS AND IMPLICATIONS FOR ASSOCIATION STUDIES

In 2005, a female boxer dog was sequenced to 7.5 $\times$  and several other breeds were sequenced to a lesser extent (11). Based on the analysis of these data, the authors proposed that ancestral dogs started out with short linkage disequilibrium (LD) blocks, as would be expected from their more ancient history. The development of breeds introduced tight and breed-specific bottlenecks, with modern breeds retaining only a small percentage of the original haplotype pool. Surprisingly, the tight bottlenecks did not result in massive random fixation of individual haplotypes within specific breeds. In fact, <15% of the small ancestral haplotypes identified proved monomorphic within any single breed (11). There was also significant sharing of large haplotypes across breeds, with 60% of 100 kb haplotypes observed in multiple breeds, albeit at varying distributions (11,24).

This information provided a blueprint for how to set up canine genome-wide association studies (GWAS) (25). There is sufficient homogeneity within breeds that a large number of dogs are not required for any single GWAS (11). It is important, however, to develop maximally unrelated populations among both the case and control populations to improve power. Since LD in dogs extends long distances, sometimes up to megabases (Mb), only tens of thousands of SNPs would be needed to complete a GWAS in dogs, compared with the hundreds of thousands required for comparable human studies (11,24).

Today, a successful canine study, seeking to disentangle a 1–2 gene trait, uses 100–200 cases and controls, each, for the initial GWAS and  $\sim$ 50 000 SNPs. A variety of related breeds are then used to reduce the region of interest to <0.5 Mb. Fine mapping or next generation sequencing is then used to find the mutation. The dog system can, therefore, be used to circumvent many of the problems faced by human geneticists who have limited numbers of adequately sized families for linkage, small datasets for association studies and who frequently face the problem of phenocopy. Regarding the latter, since all dogs of a breed share the same genetic background, there is far less variation in the presentation of disease phenotypes in dogs than in humans (26).

## THE CANMAP STUDY

In 2008, we initiated a dataset that would allow us to map multiple breed-defining traits simultaneously. The study, termed CanMap, had at its heart a population of 915 dogs from 80 domestic breeds as well as 83 wild canids (3). Each breed is represented by  $\sim$ 12 highly unrelated individuals. Each dog was genotyped with a 127 000 SNP chip, and the data analyzed for 57 morphological traits, allowing us to identify 51 regions of the dog genome associated with phenotypic variation. This includes traits as varied as ear position to tail curl, leg length/width ratios to skull measurements (3). As predicted (27,28), a small number of loci ( $\leq$ 3) appear to underlie most morphological features (3). We explore several of these below.

## BODY SIZE

One of the most interesting things to come out of the CanMap project was further elucidation of the study of body size in dogs. A microsatellite linkage study of Portuguese Water Dogs (PWD) (27) and a multi-breed SNP study (28) had previously reported that about six QTLs are important in regulating canine body size, with the most predominant on canine chromosome 15 (CFA15).

Building on that work, Sutter *et al.* fine-mapped the 15 Mb region on CFA15 (29) by first reducing the region using data from very large and small PWD. Then, analyzing 14 small dog breeds, he found evidence for a selective sweep that corresponded precisely with the insulin-like growth factor 1 (*IGF1*) gene (Fig. 2A). He analyzed dogs of all sizes from over 80 breeds, ultimately demonstrating a 20 SNP haplotype spanning part of *IGF1*. While several haplotypes were theoretically present, the ‘B’ haplotype was found on the majority of chromosomes from small dogs, suggesting that the contribution that *IGF1* makes to small dogs uses alleles that have been in existence since early in breed development.

However, finding the associated mutation has proven difficult. A  $\sim$ 10 kb interval spanning intron 2 was most strongly associated with size variation. Both a short interspersed SINEC\_Cf element and a SNP that were in strong LD were reasonable candidates. Gray *et al.* extended the *IGF1* studies



**Figure 3.** Skull shape variation in the dog. Above are shown extreme examples of brachycephalic breeds (on top, from left to right: Pug, Japanese Chin, Brussels Griffon, French Bulldog, Neapolitan Mastiff) and dolichocephalic breeds (on bottom, from left to right: German Shepherd Dog, Bull Terrier, Saluki, Ibizan Hound, Collie) (images: Mary Bloom, AKC).

by considering these two polymorphisms using gray wolves (30). Both of these markers were part of the ‘B’ haplotype, and the alleles were fixed in the nearly all the small breeds tested. However, in wolves the ‘derived’ or canine allele was rarely present. Indeed, it was found only in Middle Eastern wolves, suggesting that the dog variant arose, perhaps, coincident with dog domestication, in the Middle East. However, neither the SINE nor the SNP appear to be trait-associated, and the variant remains to be found.

Recently, work on the other loci has matured (Rimbault *et al.*, personal communication). We have been especially interested in loci that control extremes of size, i.e. very large and very small dogs. Toward that end, Hoopes *et al.* has shown that the IGF1 receptor (*IGF1R*) is strongly associated with very small skeletal size in dogs (31) (Fig. 2B). We again made use of the CanMap dataset and found a strong signal on CFA3 ( $P = 1.9 \times 10^{-70}$ ) when comparing tiny dogs with the rest. Fine mapping revealed a non-synonymous SNP at CFA3:44 706 389 that changed a highly conserved amino acid (R204H) in the *IGF1R* gene. This particular mutation is likely functional, as it is predicted to block formation of multiple hydrogen bonds within the cysteine-rich domain of the receptor’s ligand-binding extracellular subunit. Further evidence from SIFT (32) and Polyphen-2 (33) indicate that the R204H substitution is ‘not tolerated’ and ‘probably damaging’.

In addition to *IGF1* and its receptor, many other genes remain to be investigated. While it is unlikely that dogs will require 180 or so genes that have been reported in human GWAS studies of height (34–38), several papers (3,4,27,28) highlight common loci, including good candidates like *HMGA2* (38) and the growth hormone receptor, both of which have been implicated in studies of human height. Our challenge is to find the underlying variants, determine how they account for the continuum of body size in dogs and then use that data to try and help organize the human GWAS findings.

## LEG LENGTH

Chondrodysplastic breeds have disproportionately short, curved limbs and heavy bones (39) and include the Basset

Hound, Corgi, Pekingese and Dachshunds among others. Using AKC standards, a multi-breed GWAS compared 95 dogs from eight chondrodysplastic breeds with a control group of 64 non-chondrodysplastic breeds (40), revealing a locus on CFA18. Sequencing showed that all short-legged breeds have a 5 kb insertion containing a conserved retrogene of the fibroblast growth factor 4 (*FGF4*) gene. The retrogene includes a complete coding sequence as well as the 3’ untranslated region and a polyadenylated tail, but is lacking the 5’ regulatory sequences of the original canine *FGF4* gene. The retrogene is expressed in the articular cartilage of the long bones from chondrodysplastic dogs. We proposed that this insertion could result in the increased levels of FGF4 protein, leading to premature closure of growth plates in the long bones of carrier breeds. The *fgf4* retrogene was absent from all wolves tested, suggesting that this duplication event probably occurred after domestication but before radiation of early dogs into modern breeds. Therefore, not only does this study suggest a novel type of mutation for mammals, but it also provides a new candidate gene for unaccounted cases of human dwarfism.

## SKULL SHAPE

One of the most interesting breed fixed differences observed between breeds is in skull shape (Fig. 3). The literature describes two approaches for finding genes associated with differences in skull shape that characterize the various breeds. One, involving cloning candidates genes associated with diseases such as Treacher Collins syndrome, has been fruitful (41), but is limiting because it only evaluates one gene at a time and relies entirely on known information (42).

Using a GWAS approach, Schoenebeck *et al.* collected skull phenotypes from 533 dogs representing 120 breeds and 4 wolf subspecies sampled from all over the United States and Europe (42). Fifty-one stereotyped landmarks were recorded using a microscribe digitizer, which allowed them to later perform principal component analyses and determine which sets of measurements were likely to be coordinately regulated. The data showed that four PCs controlled over 75% of the variance in the canine skull, including changes in rostrum length and angle, palate and zygomatic arch

width, and depth of the neurocranium. These are essentially the cranioskeletal features that describe the continuum between dolichocephalic (hounds) and brachycephalic breeds (i.e. Bulldogs) (Fig. 3).

One locus had been explored previously. Bannasch *et al.* mapped the locus on CFA1 to an interval of ~300 kb (43). However, no gene or mutations were ever identified, although several are plausible and presumably studies are continuing.

Schoenebeck chose to focus on CFA32, as it was highly associated with PC1, displayed showed strong evidence of selection, and it had not been previously examined (42). The initial locus was 190 kb and spanned two genes, one of which was bone morphogenesis protein 3 (*BMP3*), an excellent candidate. Analysis of additional SNPs contributed from the sequence of 11 breeds other than the reference Boxer reduced the interval to 85 kb and 48 critical variants. Only one of those 48 was compelling in terms of its conservation, association with the phenotype and likely functional significance: a phenylalanine to leucine change at amino acid 452 (F452L).

The argument was strengthened by making zebrafish morpholinos which, when injected, reduced the expression of the nascent *BMP3* transcript in the zebrafish embryo. We then assessed the head phenotype of the fish at various times post fertilization. This loss of function experiments demonstrated a clear role of *BMP3* in craniofacial development with loss of jaw structures and frontal bossing apparent in both severely and mildly affected embryos. Thus, these brachycephalic-like zebrafish demonstrate the importance of *BMP3* expression in skull formation, particularly at about 48 h post fertilization.

Interestingly, several cases have been reported in the literature of children with microdeletions at 4q21, and the deletion always includes at least part of the *BMP3* gene (44). In each case, the deletion is associated with craniofacial abnormalities that are reminiscent of those seen in our zebrafish experiments. This argues for the value of studying naturally occurring breed phenotypes as a way of further understanding rare human syndromes. It also suggests that *BMP3* dysfunction could form the basis of cephalic conditions in humans whose genetic cause remains, to this day, unknown.

## SUMMARY

The domestic dog is an entirely unique experiment in human history. Never before, or since, have humans had the chance to determine the physical and behavioral attributes of such an important member of the animal kingdom. As a result, dogs serve not only as our closest companion, but they aid us as hunters, guide dogs, herders, drafters, etc.

In this review, we have considered how genomics has influenced the types of experiments that are now possible in model organisms. We now have in hand the tools to understand the genetic basis of that variation in a unique way. In doing so we are learning about new roles of old genes, roles of genes we knew nothing about and new ways to think about how variation occurs.

In the world of science, it is common to love what we do and take our work home with us. But it is rare that we let it crawl in bed with us, feed it off our plate and with expectant

eyes ask it ‘what kind of a day did you have?’. It is our considered good luck to be working in a time where genomics and genetics make it possible to do experiments that 20 years ago were unimaginable. It is our absolute privilege to be doing them with our best friend.

## ACKNOWLEDGEMENTS

We thank Ostrander lab colleagues for reading this manuscript and their helpful comments.

*Conflict of Interest statement.* None declared.

## FUNDING

E.A.O. and M.R. are funded by the Intramural Program of the National Human Genome Research Institute (NHGRI) at NIH.

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