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Personal View

Analysis of the canine genome and canine health: A commentary

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The widespread consensus among biologists is that, with a few exceptions, inbreeding leads to a loss of biological fitness. Animals in an inbred lineage are less likely to survive and less likely to reproduce than animals in more outbred lineages. This has been demonstrated many times in well-studied, naturally outbreeding species. Inbreeding can result in reduced fertility both in litter size and sperm viability, developmental disruption, lower birth rate, higher infant mortality, shorter life span, increased expression of inherited disorders, reduction of immune system function and cancer (Charlesworth and Willis, 2009).

Many of the effects of inbreeding have been found in isolated populations of wolves, the wild ancestors of domestic dogs, with detrimental effects (Laikre and Ryman, 1991; Smyth et al., 2006). Severe inbreeding depression has been documented in Scandinavian wolves that had passed through an extreme bottleneck (Liberg et al., 2005). During their first winter after birth the number of surviving pups per litter was strongly and inversely correlated with the level of inbreeding in the pups. There have been few comparable studies in dogs. Rehfeld (1970) showed a correlation between neonatal death and level of inbreeding in pups from a highly inbred Beagle colony, whilst studies of Foxhounds (Wildt et al., 1982) and of Irish wolfhounds (Urfer, 2009) showed the greater the degree of inbreeding the smaller the litter size. A range of diseases including autoimmune conditions, neoplasia and osteochondrosis show significant associations with coefficient of inbreeding measured on seven generation pedigrees in the Bouvier Belge des Flandres dog (Ubbink et al., 1992).[1]

The genetic repertoire of dogs resulted from what is believed to be a relatively small number of ancient domestication events from wolves to establish modern dogs (Vilà et al., 1997; Savolainen et al., 2000; Vonholdt et al., 2010; Ardalan et al., 2011; Ding et al., 2012; Wayne and von Holdt, 2012) together with some further genetic introgression from local wolf populations into specific lineages (Verginelli et al., 2005; Malmström et al., 2008; Boyko et al., 2009; Klütsch et al., 2011); see, however, the critical comment by Larson et al. (2012). The genetic diversity available to dogs was further partitioned during the formation of breeds. Deleterious alleles ('disease genes') were unwittingly captured within breeds due to the genetic makeup of the breed founders. In addition, some disease alleles were positively selected during breed formation by their link to animal conformation, skin type or pelage or desired behaviour. An example is the artificial selection for reduced muzzle length to enable bite locking or simply to enhance appearance, associated with the presence of brachycephalic obstructive airway syndrome in English bulldogs and a number of companion breeds. Disease alleles may also have accumulated to high frequency in lineages indirectly by 'hitchhiking' through linkage with selected loci or potentially through effects of inbreeding.

Domestic dogs should be no exception to the rule that breeders should avoid close inbreeding as much as possible (APGAW, 2009; Bateson, 2010; Rooney and Sargan, 2009). Despite considerable agreement on the issues, and after Wade's own careful review of

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[1] See: Canine Inherited Disorders Database http://ic.upei.ca/cidd/, Accessed 05 February 2012.

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the molecular data (Wade, 2011), Nicholas and Wade (2011) suggested in this journal that '... *direct estimates of the extent of canine genetic diversity indicate that dog breeds retain a very high proportion of genetic diversity. In other words, in terms of the extent of genetic diversity, dogs are far, far closer to humans than to inbred lines*.' In this article we consider alternate constructions of the available molecular data, and ask whether breeders can afford to relax on the issue of genetic diversity in pedigree dog breeds.

Genetic diversity estimates in dog breeds

Molecular approaches to genetic diversity offer a very precise way to decide how inbred dogs are, but even molecular approaches are capable of different interpretations. Wade (2011) found that '*Even after the formation of breeds, restrictive breeding practices in breed registries and geographical isolation, breeds have retained (on average) 87% of available domestic canine genetic diversity*.' This impressive number is based on measuring single nucleotide polymorphism (SNP) heterozygosity obtained from individuals within breeds and expressed as a percentage of the SNP heterozygosity from a large number of individuals from many different breeds, using SNP arrays. Three assumptions are made:

(1) That SNPs used in the analyses are representative of all SNPs in the dog genome. The SNPs used in these array based analyses were selected by position, but also as showing polymorphism in a small number of breeds in which they were originally discovered. They are likely to come from regions of the genome in which diversity has been maintained in these breeds, and may not be representative of regions placed under purifying selection in multiple dog breeds. Hence it is possible that some areas of the genome have lost a higher proportion of original variation than the arrays reveal.
(2) That estimates of total genetic diversity based on individuals drawn from many different but largely Western and purebred breeds represent the whole of domestic dog genetic diversity including that of feral and mixed breed dogs. If total diversity is underestimated, then the proportion of diversity already lost within current breeds will also be underestimated.
(3) That the average heterozygosity measured in a limited sample of (usually) unrelated individuals is representative of heterozygosity in all individual dogs within a purebred breed. Line breeding and popular sire effects may mean that some individuals within breeds have much reduced heterozygosity.

As noted by Wade (2011), complete loss of SNP alleles within breeds is up to 30% compared with the entire population, even when this is defined using arrays as above (Karlsson et al., 2007). A different method, comparing full sequence information in a small region of a single chromosome, led Gray et al. (2009) to estimate that loss of nucleotide diversity with breed formation averaged 35%. Whilst heterozygosity is a good measure of short term capacity to respond to selection, loss of allelic diversity restricts the likelihood of being able to respond to selection over the long term (Allendorf, 1986) and in particular reduces retention of useful alleles to reverse long term directional selection.

One genomic structure associated with loss of allelic diversity is the presence of long runs of homozygosity (Kirin et al., 2010). In the human data these long runs correlate highly with coefficients of inbreeding obtained from pedigrees stretching back many generations (McQuillan et al., 2008). Long regions of homozygosity have already been detected in dogs, although these may be the results of selective sweeps around desirable alleles, as well as of the contributions of breed founder and popular sire effects and line breeding to consanguinity (Karlsson et al., 2007; Sutter et al., 2007; Boyko et al., 2010; Vaysse et al., 2011). Small effective population sizes such as those found in pedigree breeds in the UK (Calboli et al., 2008) and probably elsewhere, will reduce recombination around loci experiencing selection and increase the presence and length of these tracts.

Whatever the cause, Karlsson et al. (2007) showed that for seven breeds, 25% of the genome on average was found in homozygous tracts above 100 kb in length, whilst Boyko and co-workers (2010) showed that for 10 individuals from each of 59 American Kennel Club (AKC) recognised breeds, between an average of 7.5% of the genome (in the Jack Russell) and an average of 51% (in the Boxer) existed in homozygous tracts >1 Megabase in length, considered likely to be autozygous. (It is notable that Jack Russell terriers are not a pedigree breed in the UK and show substantial variation.) In agreement with Karlsson et al. (2007), and as might be predicted from the reduced numbers of long haplotypes seen by Vonholdt et al. (2010), Boyko et al. (2010) found that average individuals from most breeds examined had 25–30% of their genomes in these long homozygous tracts.

Implications of loss of heterozygosity and of the presence of homozygous tracts

Many monogenic recessive diseases are considered relatively rare but quoted allele frequencies based on DNA testing either of samples collected deliberately as representative of the whole population have varied from a few per cent to over 50% (see, for example, Jobling et al., 2003; Lee et al., 2007; Davis et al., 2008; Mellersh et al., 2009; Karmi et al., 2010; Gentilini et al., 2011; Gould et al., 2011; Minor et al., 2011; Mizukami et al., 2011; Gavazza et al., 2012; Vidgren et al., 2012). If monogenic recessive disease alleles are present in the population at a frequency of 10% (giving a disease frequency of 1% in an outbred population), then in a population with 13% loss of heterozygosity the frequency of disease will increase to less than 2.2%. However, many such recessive diseases are reported for each canine breed. In the database 'Inherited Diseases in Dogs'[2] 1552 disease types are associated with 273 breeds, (Sargan, 2004). This database relies on the peer reviewed literature and so is necessarily incomplete, with more numerous and better surveyed breeds suffering much larger numbers of diseases.

Assuming there are six independently segregating inherited monogenic diseases per breed, with the same (10%) allele frequency for each disease allele, 5.85% of an outbred population would suffer one or more of these diseases. But with 13% loss of heterozygosity, the disease proportion will more than double to 12.34% – a substantial additional welfare burden for individual affected animals as well as presenting emotional, ethical and potentially financial responsibilities for owners of affected dogs. As can be seen from Fig. 1, for breeds with higher than average levels of homozygosity this problem is more severe, and even disease allele frequencies of 0.1 for six alleles could imply that inbreeding is causing an additional 15% or more of individuals of these breeds to suffer reduced genetic health, based only on monogenic recessive disorders.

In some common breeds, much rarer disease alleles are circulating, but for larger numbers of different monogenic diseases. Some common breeds have 15 or more such disorders reported. Excess morbidity is not negligible when these larger numbers of alleles are involved even at low disease alleles frequencies: for example, $P = 0.02$ (giving disease frequency 1 in 2500 for each allele, or less than 0.6% of individuals suffering morbidity in total across all these diseases in the outbred population), will give 7–10 fold higher frequency of morbidity at levels of inbreeding seen in most pedigree breeds.

[2] See: www.vet.cam.ac.uk/idid/, Accessed 13 August 2012.

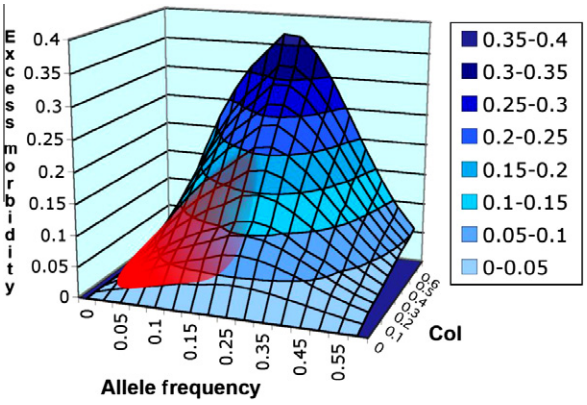

Fig. 1. Excess morbidity associated with inbreeding at different disease allele frequencies, The surface presented here represents the extra morbidity summing all diseases as a fraction of all live births, (vertical, *Y* axis) when autosomal recessive disease alleles, with frequencies equal for each disease, (represented on the *X*-axis) at six independently segregating loci interact with genomes showing varying coefficients of inbreeding (*Z* axis). The majority of dog breeds and diseases are probably represented in the area overlaid in red, although allele frequencies are higher in some disease and breed combinations and levels of inbreeding (or at least of homozygosity) are higher in some breeds (see text). The graph shows the difference between the proportion of animals with one or more homozygous disease loci in a totally outbred population and in one with a given coefficient of inbreeding. This was calculated as $(1-p^2)^6-(1-[pf+(1-f)p^2])^6$ where p is the frequency of each disease allele and f is the probability of two alleles at a locus showing identity by descent (the coefficient of inbreeding; Wright, 1922). Increasing excess morbidity bands are represented by darkening shades of blue on this graph.

The very presence of homozygous tracts might suggest that they are not highly detrimental to the health of most of the dogs that carry them. However, even if they do not contain monogenic recessive lethals or other monogenic disease alleles, they do contain alleles that may be involved in more complex diseases such as those associated with exaggerated conformation, and reduce the diversity available to cope with environmental challenges. If homozygous regions are shared by all individuals of a breed, then clearly back selection against an undesired characteristic, or even against an adventitiously fixed gene will only be possible through outcrossing. A good example of this problem is the fixation of an allele of the SLC2A9 gene causing hyperuricosuria in Dalmatian dogs (Bannasch et al., 2008), where outcrossing to German pointer dogs, followed by backcrossing has provided the diversity needed to select against the defect.

The health of a dog may also be adversely affected by inbreeding if the genes used in generating an immune response become homozygous. As noted by Wade (2011), breeds or species can survive within a limited habitat with reduced MHC polymorphism (Angles et al., 2005; Castro-Prieto et al., 2011). But the ability of an individual to cope with pathogens in one habitat is no guarantee that the same individual will be able to survive in another habitat where the pathogens are different (Maki, 2010; Wilbe et al., 2009). Further, Angles et al. (2005) state that '*inbreeding can have profound effects on the immune system, predisposing to increased immunodeficiency, autoimmune disease and cancer*.' Direct evidence for heterozygote advantage at the MHC and significant associations between MHC and production, disease and fertility traits have been noted in cattle (Codner et al., 2012).

In considering both recessive monogenic disease traits, MHC polymorphism, and polygenic disease associated with conformation, to equate breed survival with individual health provides an incomplete picture. Any breeding practice that increases genetic diversity in the MHC up to a given optimum is likely to increase the proportion of healthy individuals and hence to improve the overall health of a breed.

Conclusions

Inbreeding can have the effect of purging (removing from the gene pool) a proportion of alleles with seriously damaging effects, with obvious fitness and health benefits. But in the process of inbreeding, other alleles with less serious effects can become homozygous and can be retained in the population. Outcrossing to introduce fresh blood can mitigate such effects by introducing greater variability into the gene pool, but outcrossing does carry the possibility that the benefits of purging are undone by introducing new deleterious recessives. While inbreeding is generally seen as being undesirable, the debate has become more nuanced in recent years. By no means all inherited diseases are carried by single pairs of genes. Many inherited diseases arise from the interaction of the products of several genes. If one or more of these genes contributing to the inherited disease are eliminated by genetic drift or by skilful breeding, it is possible, although still hypothetical, that the disease may no longer be seen in the offspring. Leroy (2011) took the view that purging has been relatively unimportant in dogs. The ratio of non-synonymous to synonymous polymorphisms, d(N)/d(S), is about 50% greater for SNPs found in dogs than SNPs in wolves suggesting a relaxation of centralizing selection at many loci (Cruz et al., 2008).

We have examined the evidence about genetic diversity in dog breeds and its relationship to disease because breeders could be tempted into complacency by suggestions that inbreeding is slight or does not matter concerning their own current practices, and denial about the health problems in the dogs they breed. Any thoughtful breeder of dogs should worry about the potentially adverse effects of inbreeding, but breeders are typically faced with a dilemma. They are aware of the effect of closed breeding in excluding or even purging undesirable alleles, and in fixing desirable qualities, so that in considering matings of closely related animals, this desire for 'purity' often wins over any fears about inbreeding too much. The conflict between preserving desirable characteristics and avoiding the potentially unfavourable outcomes that may accompany inbreeding is real.

Notwithstanding the dilemma, the concern about the effects of inbreeding should be taken seriously. We note that the effective population sizes of six out of ten popular UK breeds (surveyed by Calboli et al., 2008), already fall below the 'short term minimum' rule of thumb of Ne = 50 suggested by Franklin (1980) as necessary to ensure against inbreeding depression. Aside from the arguable danger to whole breeds, genetic diseases can lead to suffering and distress in affected animals. It is the responsibility of scientists and dog breeders alike to encourage breeding choices directed at reducing the burden of genetic disease on individual animals – a duty that in our view overrides that of preserving the rather nebulous notion of breed purity. Tools such as the UK Kennel Club's Mate Select website, 2012[3] are helpful in empowering breeders with knowledge to make mating decisions although based on pedigree information of varying completeness. It is to be hoped that in future rapid molecular techniques may further inform these decisions. In the meantime it is important that scientists consider the issue of inbreeding from the point of view of individual as well as whole breed consequences, and therefore every effort is made to encourage the retention of genetic diversity within breeds.

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[3] See: www.the-kennel-club.org.uk/services/public/mateselect/Default.aspx, Accessed 17 August 2012.

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