Inherited defects in pedigree dogs. Part 2: Disorders that are not related to breed standards

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\section*{Introduction}

Inherited disorders in domestic dogs have long been reported in the veterinary literature, and include metabolic defects, neurological and sensory disorders, immune system abnormalities, blood disorders and congenital physical deformities (\textit{Darwin}, 1868; \textit{Hodgman}, 1963). Pedigree dogs have been bred to conform to published aesthetic (but not health-based) standards using closed stud books, selective breeding and the repeated use of popular sires. Such breeding practices could have increased the expression of inherited defects and thus compromised the health and welfare of many breeds (\textit{Cruz et al.}, 2008; \textit{Galibert and Andre}, 2006; \textit{Ubbink et al.}, 1998). In this second part of a two-part review we aimed to examine inherited defects which show no link to conformation by assessing their number, prevalence and severity. Part 1 addressed conformation-based inherited defects (\textit{Asher et al.}, 2009).

Within the pedigree-dog population are many individual breed populations and distinct genetic subgroups have developed and been maintained through selective breeding to produce bloodlines which consistently produce offspring with particular characteristics (\textit{Bjornefeldt et al.}, 2008). The UK Kennel Club (KC) was established in 1873 in response to the growing popularity of exhibiting dogs in organised shows. At that time a stud book was produced as a register of dogs considered to be good breeding stock.\textsuperscript{1} From this original small pool of breeding dogs, many new breeds have been created. In addition, working strains (that have been bred for specific purposes, often in particular geographic locations) have been ‘recognised’ by the Kennel Club (KC) and have had a population accepted into the closed studbook system. The Jack Russell and the Border collie are fairly recent inclusions into the KC under this system (for example the Border collie was not recognised by The Kennel Club until 1976).\textsuperscript{2}

Concerns have been raised regarding the level of inbreeding and health effects within canine pedigree breed groups. The inheritance of genetic diseases can be controlled by a single gene (monogenic conditions) or several genes (polygenic conditions). There are four forms of single gene inheritance: (1) autosomal recessive; (2) autosomal dominant; (3) X-linked recessive, and (4) X-linked dominant. For a dog to present with clinical signs of an autosomal recessive disease, two copies of the recessive allele must usually be present at a particular gene locus on a non-sex chromosome. Autosomal dominant diseases or traits will present clinically when only a single copy of the gene is present on a given chromosome (\textit{Irving et al.}, 2006; \textit{Robinson}, 1990). Polygenic inheritance refers to transmission of those conditions or traits whose clinical expression is controlled by several genes and, often, additional environmental influences. The reduced heterozygosity of a highly inbred population can contribute to the frequency of occurrence of inherited disease in the population as the likelihood of inheriting two
recessive gene alleles (therefore the expression of recessively transmitted disorders or traits) is also increased (Cruz et al., 2008; Meyers-Wallen, 2003).

In the creation of a breed, an important issue is the ‘fixing’ of desirable features within the breed so that an exclusive group of dogs will breed true to type, reliably displaying the features preferred by the breeder. Once a breed is established, fixed features are maintained by selective breeding of registered animals. Selection can be made simply on the basis of the phenotypes of individual prospective parents or with additional reference to the familial traits of potential parents’ relatives (Robinson, 1990). In many breeds the former approach has led to the relative overuse of popular sires (sometimes called the ‘common sire effect’). Certain popular (usually champion) stud dogs are used extensively and to the exclusion of other registered stud males, so effectively reducing the number of sires represented in the closed studbook of a particular breed (Björnerfeldt et al., 2008; Calboi et al., 2008).

The effect of ‘fixing’ and the use of popular sires on modern breed gene pools has raised concern (Cruz et al., 2008). However a recent genetic study by Calboi et al. (2008) using KC pedigree information on the top nine most popular breeds concluded that the extent of inbreeding over the last 6–7 generations was 4.4%.

This suggested that for the breeds in this study, ‘fixing’ and the use of common sires have not had a dramatic effect on heterogeneity. The average rate of increase in inbreeding was 0.66% per generation (Calboi et al., 2008).

In this review, we identify and enumerate non-conformation-linked inherited canine disorders and associations with certain breeds. The overall impact of these inherited diseases on the canine population is affected by several factors: (1) population sizes within breeds; (2) the number of inherited diseases in the population; (3) within-breed disease prevalence; and (4) the severity of the disease for the affected individual. Our aim was to assess the scale of impact of each of these diseases on the UK pedigree-dog population by considering disease prevalence, breed popularity and the comparative severity of the disease, using the Generic Illness Severity Index for Dogs (GISID) (Asker et al., 2009). Due to the scale of pedigree-dog breeding as a whole, our review focusses solely on the top 50 most popular pedigree breeds according to UK KC registrations 2007.

Materials and methods

The list of top 50 KC registered breeds in the UK for 2007 was compiled from KC registration statistics for 2007.6 In addition, data from KC registrations from 1998 to 2007 permitted recent UK pedigree-dog population dynamics to be estimated. Breed-disorder combinations were identified through a systematic search of peer-reviewed scientific literature, conference proceedings and veterinary textbooks. Those breed-disorder combinations meeting the criteria for ‘inherited disorders not directly linked to breed standards’ outlined below were included in the final list of disorders.

Literature search

Resources used for this review included scientific literature, conference proceedings, published literature on dog breeding, policy documents and veterinary textbooks. Initially, three online databases of inherited disorders in dogs (List of Inherited Disorders in Animals, LIDA4; Canine Inherited Disorders Database, CIDD5; and Inherited Diseases in Dogs, IDID6) were searched to produce a comprehensive list of all reportedly inherited disorders documented in the top 50 most popular breeds. Also consulted were breed club websites for the top 50 breeds, and international Kennel Club websites (for a complete list, see electronic Supplementary material). Using this comprehensive list of disorders, we conducted a systematic search of the scientific and veterinary literature, using online bibliographic databases such as PubMed, Web of Knowledge and Google Scholar, employing each of the following search criteria in separate, consecutive searches.

1 http://www.thekennelclub.org.uk/item/1623.
2 http://www.ncbi.nlm.nih.gov/Omim/omimfaq.html#mim_number_symbols

Inclusion of a disease in the final list of inherited disorders not directly linked to conformation was restricted to those diseases with a proven or justifiably suspected hereditary basis as reported in peer-reviewed scientific literature. There is considerable variation in the quality of evidence presented in the peer-reviewed literature for hereditary bases to disorders in pedigree dogs. This variation reflects differences in study size (ranging from single case reports to national population scale studies), study design (cohort, case-control, cross-sectional), and scientific angle and approach (epidemiological studies to molecular-level investigations). To reflect the variation seen in the strength of published evidence for the hereditary basis of disorders in one or more breeds, a scoring system, the Strength of Evidence for Hereditary Basis scale (SEHB), was developed.

The SEHB scale is a 6-level grading system from 0 (supposed inherited basis but lacking substantial evidence) to 5 (single-locus inheritance confirmed by DNA evidence), which was designed to compare the quality of available evidence for a hereditary nature across various breed-disorder combinations (Fig. 1).

1 An important precedent to the SEHB was proposed in the first edition of McKusick’s Mendelian Inheritance in Man (McKusick, 1966). McKusick introduced a two-tiered categorisation: disorders whose single-locus inheritance was ‘quite certain’ and those where sufficient evidence of single-locus inheritance was lacking. In the present online version, this has evolved into a multi-tiered system.7 Our SEHB system was applied to the peer-reviewed literature available for each breed-disorder combination identified in the literature review. Individual case studies reporting a condition of possible inherited basis in a single purebred dog were excluded.

Condition classification

Disorders were classified as conformation-related (C) if the disorder was reported to be resulting directly from selection for a conformational trait; conformation-inherited link (CD) if the disorder was reported to be an inherited disorder exacerbated by a conformational trait; or non-conformational (D) if the disorder was an inherited disease that showed no link with conformation in the literature reviewed. Conditions were also categorised according to the body system primarily clinically affected, again with reference to published literature.

Severity score

A disease severity scoring system, the Generic Illness Severity Index for Dogs (GISID), was used to compare the impact of different disorders on dog health and welfare. GISID scores were derived from information available in the scientific and veterinary literature. Details of development and features of the GISID are given by Asker et al. (2009). When assigning GISID scores to a disorder, it was assumed that the most appropriate care and treatment would be provided, and for each condition a score range was given to reflect the impact range with which the disorder can manifest.

Statistical analysis

Disorders were totalled for breeds and body systems. For each breed, we summed the severity scores of disorders to which the breed was predisposed (cumulative GISID score, cGISID) and summed the number of breeds reported affected by each disorder. Individual disorders were ranked according to their GISID severity score, and ratios of GISID scores to number of reported D disorders were calculated for each breed. Non-parametric Spearman’s correlations (adjusted for multiple testing using the Bonferroni correction) were used to explore associations between number of disorders per breed and popularity (number KC registrations, Level of available evidence for hereditary nature
2007); increase in popularity (change in KC registrations 1998–2007); breed height (median of range specified in UK KC Breed standards, 2007); and breed weight (median of range specified in UK KC Breed standards, 2008, or where these details were missing from breed standards, from Grandjean, 2003). Kruskal–Wallis tests (adjusted for multiple testing using the Bonferroni correction) were used to compare numbers of disorders in breeds with different head shapes (brachycephalic, mesocephalic, and dolichocephalic).

Results

In the top 50 breeds, a total of 396 disorders were identified from the literature with 312 of these being categorised as D disorders. Breed-specific prevalence estimates were reported for 21 of all identified D disorders. Of the D breed-disorder combinations, 80 had available data on mode of inheritance in the reviewed literature. The majority display autosomal recessive transmission (71%; 57 breed-disorder combinations), followed by autosomal dominant (11%; 9 combinations), X-linked (10%; 8 combinations) and polygenic (4%; 3 combinations). The final 4% (3 combinations) had either incomplete proven information on mode of transmission (for example, stating only autosomal) or were disease complexes where multiple modes of transmission are involved according to different aspects of clinical manifestation (Fig. 3).

Of the 50 most popular pedigree dogs in the UK, German shepherd dogs were predisposed to the greatest number of D disorders (58 different disorders), followed by the Golden retriever (50), Boxer (45), Labrador retriever (44) and English Springer spaniel (42). Dogue de Bordeaux had the fewest reported number of these disorders (3) (Table 1).

The four D disorders affecting the greatest number of breeds were hypothyroidism (reported in 43/50 breeds considered), hereditary adult-onset cataract (38 breeds), progressive retinal atrophy (35 breeds), and Von Willebrand’s disease (26 breeds) (see Table 2 for D disorders affecting more than 10 breeds in the top 50). Severity scores for these conditions were: 4–13, 2–12, 7–11, 0–12, respectively, demonstrating a wide range of possible severity from low to high within each of these D disorders.

The primary body systems affected by each of the D diseases were distributed as follows: Nervous-sensory (82 disorders); integument (58); cardiovascular (49); urogenital (33); gastrointestinal (30); musculoskeletal (23); immune (19); endocrine (13), and respiratory (5). A comprehensive table of the disorders related to the top 50 breeds, including breed specific information on mode of inheritance, GISID and SEHB scorings, and source material listings can be seen in the electronic Supplementary material.

Strength of evidence

Based on peer-reviewed scientific literature, it was possible to score strength of evidence for heritability (SEHB) greater than or equal to one to 192 of the 312 D disorders identified. The level of evidence for the inherited nature of a given condition frequently varied between breeds. The total number of individual D breed-disorder combinations listed was 1420 and 470 of these combinations were assigned an SEHB score. Fig. 2 shows the distribution of assigned SEHB scores from 1 to 5 based on the 470 D breed-disorder combinations listed; of those with an SEHB score ≥1, the modal score was 2, with a range of 1–5.

Comparative disease severity

The most severe disorders were renal agenesis (1 breed affected; GISID 12–16), and bilateral renal hypoplasia (2 breeds affected; GISID 12–16). Of the 10 most severe disorders, none affected more than nine breeds (see Table 3 for disorders with a maximum GISID score of 15 or over). Of those D disorders affecting 10 or more breeds from the top 50, several were of particular note due to their moderate to severe GISID scores. These included retinal detachment/dysplasia (25 breeds affected; GISID range 10–14), portosystemic shunt (12 breeds affected; GISID range 7–14), hypoadrenocorticism/Addison’s disease (11 breeds affected; GISID range 9–13), hypothyroidism (43 breeds affected; GISID range 4–13) and patent ductus arteriosus (11 breeds affected; GISID range 0–14).

German shepherd dogs had the greatest cumulative GISID score for associated D disorders (303–685), followed by the Pug (223–548), Bull mastiff (218–516), Rhodesian ridgeback (226–516) and Shetland sheepdog (218–489). The Dalmatian (6–21) and Whippet (18–60) had the smallest cumulative scores (Table 1).
Predictive factors of D disorders

The number of D disorders to which a breed was reportedly predisposed (in total and by some systems affected) was found to correlate negatively with the percentage increase in registrations over the past decade (Table 4). A negative correlation between the percentage increase in registrations was found when the disorders were categorised by system in the gastrointestinal, immune, integument, nervous-sensory and respiratory systems. Gastrointestinal disorders were positively correlated with the
number of dogs registered with the KC. Taller and heavier breeds had more immune and musculoskeletal D disorders.

Of the top 50 breeds, 33 were categorised as brachycephalic (14 breeds), mesocephalic (15 breeds) or dolichocephalic (4 breeds). References for the skull morphology of the remaining 17 breeds could not be sourced. Skull shape affected the total number of D disorders and the number of D nervous-sensory disorders to which breeds were predisposed. Mesocephalic breeds had more immune and musculoskeletal D disorders.

Discussion

Of almost 400 inherited disorders identified in the 50 most popular UK dog breeds investigated, over 300 were classified as not directly linked to breed standards (D disorders). These disorders have emerged without a link to specific physical attributes specified in the breed standards and as such they can be seen as inherently unpredictable mutations occurring throughout the genome. McGreevey and Nicholas (1999) stated that in breeds with low numbers of registrations, it is likely that inbreeding is a causative factor behind the relatively high prevalence of certain inherited disorders.

Inbreeding may result from repeated mating of any closed group of dogs and their offspring. Within the pedigree dog industry the approach taken to breeding puppies varies markedly. Producers range from experienced, responsible breeders producing puppies from health-screened parents, to so-called ‘puppy-farmers’ breeding puppies, often in large numbers, from unregistered and sometimes closely related parents.

Some non-conformational disorders affect a wider variety and greater number of breeds than others, though it should be noted that a disorder affecting many breeds is not necessarily highly prevalent within any given breed or in the canine population as a whole. The number of D disorders to which a breed was predisposed (in total and by body system affected) was found to negatively correlate with the percentage increase in registrations over the past decade. Initially this finding would appear to show that traditionally popular breeds have more associated disorders than those whose popularity has increased only in recent years. However it is considered by the authors that this finding is suggestive....
of a time lag in reporting i.e. a temporal delay between an increase in breed popularity (hence population size) and the appearance, documentation and investigation of breed-associated conditions.

The most severe D disorders (maximum GISID score 15 or above) give rise to the most serious welfare consequences for affected individuals. Of the 18 diseases of this type identified in this study, a high degree of breed specificity was clear, none affected more than nine breeds of the top 50 (Table 3). However, as prevalence data were often completely absent, unreliable or biased, it is difficult to assess the overall welfare impact of these diseases and the likely cost-benefit implications of control strategies to the pedigree canine population. The number of disorders associated with a breed does not appear to correlate with the breed cumulative GISID score (Fig. 4). We can therefore conclude that breeds with fewer total D disorders but higher cumulative severity scores are predisposed to disorders of relatively high average severity, for example Dogue de Bordeaux (cumulative GISID 168–441; three disorders) and Flat coated retriever (cumulative GISID 162–381; five disorders) (Table 1).

The most common mode of inheritance reported amongst D disorders was autosomal recessive. This finding is in agreement with other reports (Meyers-Wallen, 2003; Ostrander et al., 2000). Such information is relevant in assessing the potential for success of planned breeding programmes and in the development of DNA screening tests within breed populations (Traas et al., 2006).

The relationships seen between breed build characteristics and numbers of disorders of various body systems are worthy of note: taller and heavier breeds had more associated immune and musculoskeletal disorders. This distribution of disease predisposition may suggest that some disorders considered by the authors as not directly related to breed standard requirements are actually the clinical manifestation of a genetic predisposition exacerbated by a certain specified phenotype, for example height. Hence certain diseases considered in the literature to be D-type conditions may be better classified as CD conditions. Alternatively, conditions of these body systems may exhibit some as yet un-described form of genetic linkage with the inheritance of genes related to height and build, or occur in certain lines or distantly related breeds which share a common characteristic. For example, lines of heavy dog breeds may have developed from common founder dogs thus sharing genetic similarity (Wayne and Ostrander, 2007). Within the 33 breeds which could be categorised by cephalic index as brachycephalic, mesocephalic or dolichocephalic, the apparent effect of skull shape on the total number of D and D nervous sensory disorder predispositions could be explained by a similar common ancestral theory. It is also feasible that the reporting time-lag previously discussed contributes to this finding.

Published studies on inherited D diseases in dogs are numerous. By the very nature of the topic these studies are varied in their approach, ranging from case series reporting of a given condition in dogs of the same breed, to pinpointing specific disorder-causing genetic defects at the molecular level in individual breeds. This reflects the natural progression in understanding of a condition as it is subjected to ongoing study, and with the development of new investigative techniques (Banning and Hughes, 2006). However, some breed-associated conditions have received extensive research attention whilst others have remained at an earlier stage of the investigative process. Breed-associated disorders that are models of an equivalent human disease, and diseases of breeds currently popular for working purposes (guide dogs, armed forces or police dogs) are often the subject of more advanced research (Breen, 2008; Olson et al., 2004; Wayne and Ostrander, 2007). It is these projects which would be expected to attract increased funding compared with conditions considered to affect only dogs kept as companions animals. Diseases for which screening schemes produce regular, comparable data over time also lend themselves to more frequent study (Leppanen and Saloniemi, 1998; Wallin-Hakanson et al., 2000). Among individual breeds these factors are likely to have a considerable influence on the number of NC disorders reported and the depth of their investigation. The impression that only pedigree dogs are at significant risk of inherited diseases likely results from the current lack of studies looking at the cross-breed canine population in terms of general disease prevalences.

<table>
<thead>
<tr>
<th>Breed Group</th>
<th>Number of Kennel Club registrations</th>
<th>Percentage increase in registered dogs (1998–2007)</th>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>$\rho = 0.179$, $P = 0.22$</td>
<td>$\rho = -0.140$, $P = 0.34$</td>
<td>$\rho = -0.018$, $P = 0.46$</td>
<td>$\rho = 0.093$, $P = 0.53$</td>
</tr>
<tr>
<td>Endocrine</td>
<td>$\rho = -0.067$, $P = 0.65$</td>
<td>$\rho = -0.207$, $P = 0.16$</td>
<td>$\rho = 0.073$, $P = 0.62$</td>
<td>$\rho = 0.093$, $P = 0.53$</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>$\rho = 0.322$, $P = 0.026^{*}$</td>
<td>$\rho = -0.356$, $P = 0.01^{**}$</td>
<td>$\rho = 0.325$, $P = 0.08$</td>
<td>$\rho = 0.178$, $P = 0.23$</td>
</tr>
<tr>
<td>Immune</td>
<td>$\rho = 0.033$, $P = 0.82$</td>
<td>$\rho = 0.382$, $P = 0.01^{**}$</td>
<td>$\rho = 0.285$, $P = 0.05^*$</td>
<td>$\rho = 0.322$, $P = 0.03^*$</td>
</tr>
<tr>
<td>Integument</td>
<td>$\rho = 0.112$, $P = 0.45$</td>
<td>$\rho = -0.401$, $P = 0.01^{**}$</td>
<td>$\rho = 0.323$, $P = 0.12$</td>
<td>$\rho = 0.230$, $P = 0.12$</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>$\rho = 0.267$, $P = 0.06$</td>
<td>$\rho = -0.229$, $P = 0.12$</td>
<td>$\rho = 0.365$, $P = 0.01^{*}$</td>
<td>$\rho = 0.380$, $P = 0.01^{*}$</td>
</tr>
<tr>
<td>Nervous-sensory</td>
<td>$\rho = 0.040$, $P = 0.78$</td>
<td>$\rho = -0.32$, $P = 0.03^{*}$</td>
<td>$\rho = -0.028$, $P = 0.85$</td>
<td>$\rho = 0.01^{*}$</td>
</tr>
<tr>
<td>Respiratory</td>
<td>$\rho = 0.054$, $P = 0.71$</td>
<td>$\rho = -0.321$, $P = 0.03^{*}$</td>
<td>$\rho = 0.001$, $P = 0.99$</td>
<td>$\rho = 0.052$, $P = 0.73$</td>
</tr>
<tr>
<td>Urogenital</td>
<td>$\rho = 0.27$, $P = 0.12$</td>
<td>$\rho = -0.195$, $P = 0.18$</td>
<td>$\rho = -0.262$, $P = 0.07$</td>
<td>$\rho = 0.211$, $P = 0.15$</td>
</tr>
</tbody>
</table>

Statistically significant values are marked.

* $P < 0.05$

** $P < 0.01$
The degree of accuracy in our enumeration of inherited canine diseases in total and within breeds studied was likely influenced by several factors related to the use of terminology in the veterinary literature. Widespread use of non-standardised terminology may have led to underestimation of the number of inherited D diseases in dogs due to the potential for erroneous grouping of similar conditions as one disease. Conversely, the total may have been overestimated if an individual disorder referred to by several different names in various studies was counted as multiple distinct conditions. As far as possible, we attempted to categorise each disease accurately to ensure a lack of repetition.

Overall, there was an alarming lack of reliable, country-specific prevalence data for inherited diseases in the canine population as a whole, in individual breeds, and in crossbreeds for comparison to pedigree populations. Few purpose-designed prevalence studies have been reported concerning either the overall or breed-specific canine populations. Prevalence data were reported for only 21 D disorders across a wide variety of breeds. Within-breed estimates varied substantially and were generally not comparable, having been calculated from studies with poor design, insufficient sample sizes or lack of baseline canine population data and disease prevalence for comparison with breed-specific equivalents (for summary of prevalence data collected, see online Supplementary material).

Case definition disparities across countries, over time and between practitioners also reduced the quality of available prevalence data. Furthermore, bias within the prevalence estimates must also be considered when interpreting reliability. Screening for a limited number of canine inherited diseases takes place around the globe, particularly in Europe, USA, and Australasia, and disorder prevalence estimates are often derived from the findings of these existing schemes. The vast majority of these are voluntary schemes whereby owners or breeders elect to participate by presenting dogs for examination or other testing in order to detect the presence of a particular disorder. Thus, the reliability of any resulting disorder prevalence estimates in a given canine population is likely to be low if fundamental differences exist between dogs presented for testing and those not presented. Demographic and epidemiological research based on the owned dog populations presenting to first opinion practice may help to counter any bias introduced by the predominance of studies using patients at the referral level (McGreevy, 2007).

Conclusions

This study identified that the top 50 most popular breeds of pedigree dog in the UK are predisposed to over 300 inherited disorders not linked to the KC breed standards. Breeds affected by large numbers of disorders, and disorders affecting large numbers of breeds were identified and the clinical severity of disorders was compared using the GISID system. However, without sufficient, reliable information on country-specific, within-breed disease prevalence and national breed population sizes, we were unable to provide a definitive quantitative assessment of the overall welfare impact of these inherited diseases on the canine population of the UK. Future research in this area should allow effective comparison and extrapolation of key information, such as sample population description, prevalence of disorders in this baseline population, and details of selection processes for dogs of a given breed screened for a given condition.

Conflict of interest statement

This work was funded by the Dogs Trust but was commissioned as an independent review. As such, none of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary material


References