**Review**

**Genetics of canine diabetes mellitus part 1: Phenotypes of disease**

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**Abstract**

This two-part article discusses the mechanisms by which genetic variation can influence the risk of complex diseases, with a focus on canine diabetes mellitus. In Part 1, presented here, the importance of accurate methods for classifying different types of diabetes will be discussed, since this underpins the selection of cases and controls for genetic studies. Part 2 will focus on our current understanding of the genes involved in diabetes risk, and the way in which new genome sequencing technologies are poised to reveal new diabetes genes in veterinary species.

*Keyword*s: Canine; Diabetes mellitus; Dog; Genetics; Genomics

**Introduction**

Unravelling the genetic basis of complex diseases such as diabetes mellitus (DM) is an important and significant challenge for human and veterinary medicine. Whilst it might not be possible to remove the risk of a disease with a complex genetic basis from a particular population, understanding the genes and mechanisms responsible for an individual’s susceptibility may reveal new drug targets for treatment or prevention of disease. Breed differences in susceptibility to DM in dogs indicate that genetic factors are likely involved in disease susceptibility (Davison et al., 2005; Fall et al., 2007; Catchpole et al., 2013; Mattin et al., 2014; Heeley et al., 2020) and new genotyping technologies are being employed to demonstrate more precisely which genetic factors are important. New high-throughput sequencing technologies, which have been invaluable in the study of human DM, hold great potential for research into the genetics of canine DM.

**Classification of diabetes mellitus in humans**

Diabetes mellitus is a clinical syndrome with several possible aetiologies, each leading to inappropriately elevated plasma glucose (hyperglycaemia; American Diabetes Association, 2014). Excluding the rare monogenic types, DM is a complex disease with risk derived from the combined action of an unknown number of genetic and environmental factors. Extensive research to identify and understand these factors aims to improve understanding of disease aetiology and inform advances in clinical care. A number of different types of DM are recognised in humans (Fig. 1; American Diabetes Association, 2014). Type 2 diabetes (T2D), associated with insulin resistance and obesity in adults, is approximately nine times more frequent than Type 1 Diabetes (T1D), an autoimmune disease most commonly diagnosed in young people (Saeedi et al., 2019). T1D and T2D are both considered to be progressive disorders, in which glycaemic control is lost over time.

The classification system outlined in Fig. 1 illustrates the complex nature of human diabetes mellitus and the different underlying causes of hyperglycaemia. T1D is characterised by absolute insulin deficiency as a result of immune-mediated beta cell destruction. Circulating autoantibodies to pancreatic autoantigens such as insulin, glutamic acid decarboxylase 65 (GAD65) and insulinoma antigen 2 (IA-2) can be identified, and may precede the onset of hyperglycaemia by months to years (Kimpimäki et al., 2001; Pietropaolo et al., 2012; American Diabetes Association, 2018). Although genetic factors play a key role in determining susceptibility to T1D, disease discordance in monozygotic twins (30 – 70%; Redondo et al., 2008) suggests that environmental factors are also important. In contrast, patients with T2D are autoantibody negative and typically demonstrate insulin resistance with residual beta cell function, as evidenced by elevated serum insulin C-peptide concentration. There has been a recent rapid growth in our understanding of genetic risk factors for both T1D and T2D (Mahajan et al., 2018; Bakay et al., 2019), although lifestyle factors such as obesity and lack of exercise are well established and important additional T2D risk factors (Kolb and Martin, 2017). The rise in incidence of both T1D and T2D is placing an increasing burden on healthcare systems worldwide (Cho et al., 2018) and is thought to be related to 20th and 21st century changes in environmental triggers of disease. There is evidence for infections, intestinal microbiota, dietary and other environmental factors affecting risk (Rewers and Ludvigsson, 2016; Paschou et al., 2018). However, given the strong genetic component to both T1D and T2D (Ashcroft and Rorsman, 2012; Nyaga et al., 2018), these factors are thought to exert their effect on genetically predisposed individuals.

In patients with T1D, there is evidence for lymphocytic infiltration of the pancreatic islets (insulitis) and dramatically reduced numbers of beta cells at the onset of disease (Gepts, 1965; Foulis and Stewart, 1984; Foulis et al., 1986). Pro-inflammatory T cells have been demonstrated in islets of T1D patients (Gepts, 1965; Bottazzo et al., 1985) and contribute to beta cell destruction, mediated by cell-cell interaction and production of cytotoxic cytokines (Roep, 2003; Kent et al., 2017). In contrast, pancreas tissue from T2D patients contains a greater number of islet-associated macrophages (Ehses et al., 2007), amyloid deposits (Clark et al., 1988) and a moderately reduced number of beta-cells, the latter likely as a result of apoptosis (Butler et al., 2003). Thus, in T1D, islet pathology is mediated by an immune-mediated process, whereas in T2D the beta cell dysfunction/destruction is more likely the result of degenerative processes, combined with peripheral tissue insulin resistance.

Monogenic forms of diabetes (Maturity Onset Diabetes of the Young – MODY, and Neonatal Diabetes Mellitus – NDM) and T1D typically present early in life, whereas the risk of T2D increases with age (American Diabetes Association, 2018). However, the age of onset does not always correlate with the underlying pathogenesis. Latent autoimmune diabetes of adulthood (LADA) has an autoimmune aetiology, with autoantibodies detectable in the blood, similar to T1D. However it is characterised by an adult age of onset, and usually occurs in individuals over the age of 30 years. Conversely, T2D is becoming increasingly common in young people, associated with higher rates of obesity in that demographic (Cho et al., 2018).

**Classification of diabetes mellitus in dogs**

Canine DM has a reported prevalence of 0.26 – 1.33% in the UK, USA, Sweden and Italy (Guptill et al., 2003; Fracassi et al., 2004; Davison et al., 2005; Fall et al., 2007; Mattin et al., 2014; Heeley et al., 2020). The annual incidence appears to be rising (McAllister et al., 2016) similar to patterns in human T1D and T2D (Cho et al., 2018). Several studies have reported a higher prevalence of DM in particular dog breeds, whereas other breeds show an apparent protection from DM (Davison et al., 2005; Fall et al., 2007; Catchpole et al., 2013), providing evidence for a substantial genetic component to disease susceptibility.

A recent study of American Eskimo dogs used a logistic regression model to estimate a heritability of 0.62 for DM in this particular breed (Cai et al., 2019) and subsequent complex segregation analysis suggested a polygenic mode of inheritance. However, this type of heritability study is yet to be replicated on a broader scale for other dog breeds at increased DM risk. In dogs, there is is an extremely wide spectrum of susceptibility for a single species, when comparing breeds at high risk, such as the Samoyed (odds ratio = 35.84), and those at low risk, such as the Boxer (odds ratio = 0.07; Table 1; Catchpole et al. 2013).

It is also notable that several breeds reported to be at low risk of DM, including the Boxer, Golden retriever and German shepherd dog, are commonly represented in studies of insulinoma, a malignant insulin-secreting tumour of the beta cells (Leifer et al., 1986; Caywood et al., 1988; Nelson, 2014). This suggests that there is diversity in the biological behaviour of pancreatic beta cells in the dog population, with breeds at the extremes of the spectrum at greater risk of either insulin deficiency (beta cell death) or excess (beta cell malignant transformation).

DM in dogs is typically diagnosed between 5 and 12 years of age (Guptill et al., 2003; Davison et al., 2005). Diagnosis of canine DM is made on the basis of hyperglycaemia, usually combined with glucosuria and clinical signs of polyuria, polydipsia, polyphagia and weight loss (Behrend et al., 2018; ESVE Project ALIVE[[1]](#footnote-1)). In contrast to human medicine, there is often very limited further investigation into the underlying aetiology of the hyperglycaemia and most diabetic dogs are treated with a similar approach. Virtually all diabetic dogs require insulin to be administered by injection (Fleeman and Rand, 2001), and careful management of diet, exercise and insulin dose is required to achieve glycaemic control (Behrend et al., 2018). A range of clinical complications can occur as a result of canine DM, such as diabetic ketoacidosis or cataracts (Nelson, 2014), and management requires significant financial and time commitment from owners.

A very small number of juvenile-onset diabetes cases (i.e. with onset in dogs < 12 months of age) have been reported, with higher prevalence in some breeds, such as Labrador retrievers (Dale, 2006; Catchpole et al., 2007; Saiz Alvarez et al., 2015), although the genetic basis of this condition has not yet been established. An inherited form of DM caused by beta cell aplasia has also been reported in Keeshond dogs (Kramer et al., 1980), but similarly, the genetic defect responsible has not been identified. In addition, a familial form of DM has been reported in two families of Samoyed dogs (Kimmel et al., 2002), although no aetiology or clear mode of inheritance was determined. The onset of DM was at a later age in the Samoyeds compared with the Keeshonds (Kramer et al., 1980; Kimmel et al., 2002), which may be due to different aetiologies for the development of DM in the two breeds.

Several classification systems for canine DM have been proposed (Catchpole et al., 2005; Gilor et al., 2016), mainly based on the underlying cause of the beta cell dysfunction. More recently, the European Society for Veterinary Endocrinology (ESVE) established Project ALIVE (Agreeing Language in Veterinary Endocrinology), with the aim of clarifying common terminology and definitions used in veterinary endocrine diseases[[2]](#footnote-2) (Fig. 2), including DM. Insulin deficiency diabetes (IDD) predominates in the canine population (Davison et al., 2005). As in humans, more detailed establishment of these definitions will offer advantages both in research and clinic settings.

Key to the establishment of useful aetiological classification is an understanding of the pathogenic mechanisms which may lead to canine DM. These have been investigated in a number of ways, often based on what is known about the pathogenesis of types of human DM. Markedly reduced beta cell mass has been reported in the pancreas of diabetic dogs (Gepts and Toussaint, 1967; Shields et al., 2015), which would lead to insulin-deficient forms of DM (Fig. 2), including in some animals euthanased relatively soon after diagnosis (0 – 63 days duration; Shields et al., 2015). However, there are insufficient published studies of pancreatic histopathology at the disease onset to enable a clear understanding of the islet microenvironment during the early stages of disease. Histopathology of the pancreas in established diabetic dogs likely represents the ‘end stage’ of the disease process.

*Immune-mediated processes*

There is limited evidence that a proportion of diabetic dogs have an immune-mediated component contributing to their beta cell loss, leading to insulin deficiency DM (Fig. 2), similar to human T1D. However, studies are conflicting and pancreatic lymphocytic infiltration has only rarely been found in diabetic dogs (Alejandro et al., 1988; Ahlgren et al., 2014; Shields et al., 2015). The presence of circulating antibodies to beta cell autoantigens, such as GAD-65, IA-2 and insulin, which are involved in human T1D, have also been investigated in dogs and were detected in a small proportion of cases of canine DM (Davison et al., 2008a, 2008b; Holder et al., 2015), although in the study by Ahlgren et al. (2014), only one of the 121 diabetic dogs tested was positive for GAD-65 autoantibodies. In another study, anti-insulin autoantibodies were detected in only three of 109 newly-diagnosed diabetic dogs (Holder et al., 2015). Taken together, these results indicate that autoantibodies to human T1D autoantigens are only present in a minority of diabetic dogs. Explanations for this may include the fact that autoimmunity is not a contributory factor in the majority of dogs, that the pathogenesis is more related to cell-mediated autoimmunity or that the autoantigens involved are different to those seen in humans. Comparison of the results of these studies is challenging, due to the use of different antibody detection methods and inclusion of dogs at different stages of disease. Furthermore, the study sample numbers have been too small to examine these findings on a breed-by-breed basis, which would be beneficial if autoimmune diabetes predominates in particular dog breeds.

*Disease of the exocrine pancreas*

Exocrine pancreatic disease, a recognised cause of human DM (Type 3C; Fig. 1) is also suspected to contribute to insulin deficient DM in some dogs. Canine DM has been diagnosed concurrently in dogs with both acute and chronic pancreatitis (Watson et al., 2010; Pápa et al., 2011). However, pancreatitis is also reported as a concurrent condition in diabetic dogs (Hess et al., 2000; Mattin et al., 2014) and it is often unclear whether DM or pancreatitis is the primary disease (Davison, 2015). Exocrine pancreatic insufficiency (EPI) can also be seen alongside canine pancreatitis and DM, with DM generally observed to develop after the diagnosis of chronic pancreatitis but before EPI in some dogs (Watson, 2003). It is likely that any inflammatory process in the exocrine pancreatic tissue (or potentially systemically) could have a negative impact on beta cell viability, as these cells seem to be particularly sensitive to the actions of pro-apoptotic mediators, such as tumour necrosis factor-alpha (Kägi et al., 1999; Eizirik et al., 2009; Pang et al., 2020).

*Insulin resistance*

Primary insulin resistance diabetes (IRD) in dogs can occur due to antagonism of insulin action by other hormones. For example, DM can develop during the progesterone-dominated phase of dioestrus or pregnancy, due to insulin resistance induced by growth hormone released from the canine mammary glands (Eigenmann et al., 1983). This form of DM might be more prevalent in certain breeds and this might explain regional variations in the breed profile of diabetic cases, arising through differences in breed popularity and neutering practices (Fall et al., 2008). DM has also been documented concurrently with hyperadrenocorticism (HAC; Hess et al., 2000; Blois et al., 2011). Glucocorticoids antagonise insulin function, but HAC does not lead to overt DM in most cases. Sustained hyperglycaemia has been shown to cause damage to canine islets and can lead to development of DM (Imamura et al., 1988), which may explain the progression to DM in some but not all dogs. Other metabolic disturbances could also play a role, directly or indirectly. For example the Miniature Schnauzer breed is predisposed to developing idiopathic hypertriglyceridaemia (Mori et al., 2010), which has been associated with both insulin resistance (Xenoulis et al., 2011) and elevated pancreatic lipase levels (Xenoulis et al., 2010), and the same breed is also predisposed to DM (Table 1).

*Role of obesity*

A T2D form of diabetes mellitus related to obesity-driven insulin resistance is considered unlikely in dogs, although this is the most prevalent form of DM in cats (Dixon et al., 2002; Nelson and Reusch, 2014). Human T2D is now understood to be primarily a condition caused by reduced/insufficient beta cell function, which fails to compensate for peripheral insulin resistance (reviewed in Ashcroft and Rorsman, 2012). In dogs, although obesity can lead to insulin resistance with some degree of impact on glucose homeostasis, most obese dogs compensate appropriately by increasing insulin secretion, preventing progression to overt DM (Verkest et al., 2011). Furthermore, a deletion in the pro-opiomelanocortin (POMC) gene, which has been associated with obesity and increased food motivation in Labrador retrievers (Raffan et al., 2016), was not found to be associated with increased risk of developing DM in this breed (Davison et al., 2017). However, an association has been shown between obesity and canine DM in some epidemiological studies in the UK and Brazil (Mattin et al., 2014; Pöppl et al., 2017), so further investigations into this relationship are warranted.

**The importance of disease phenotyping for genetic disease research**

Overall, it is clear that both genetic and environmental factors influence susceptibility to DM in dogs. However, there is still a large degree of uncertainty surrounding the heterogeneity of the disease between breeds, as well as to what extent canine DM is immune-mediated or resembles the other forms of human DM (Gilor et al., 2016). In human medicine, it is becoming increasingly recognised that, even within the standard T1D and T2D classifications, DM is heterogeneous, with different ‘endotypes’ (Arif et al., 2014; Ahlqvist et al., 2018). Incomplete or imprecise phenotyping of DM patients (based on the underlying pathogenesis of the condition) is problematic for genetic studies, introducing the risk of including phenocopies in the study population. This reduces the power to detect disease associations because not all ‘cases’ included in the study cohort have the same disease processes leading to the clinical signs. This problem is mitigated against by the large sample sizes in human genetic studies, but is a particular problem in dog studies where the sample sizes tend to be small and there is a lack of other studies to use in meta-analysis. More precise phenotyping, for example based on the presence of autoantibodies or residual insulin C-peptide secretion in T1D, has contributed to refinement of genetic studies in humans by reducing the disease heterogeneity of the study cohort. In turn, as disease-associated genetic variants are identified, genetic research has contributed to the improvement of disease classification systems (Fig. 3). Identification of specific genetic risk factors has also been used to stratify patients to assist with interpretation of the results of clinical trials, as well as to guide recruitment to such trials. For example, in the Pre-POINT study, a clinical trial of high dose oral insulin for the prevention of T1D, only children with a family history of T1D and carrying particular genetic variants associated with T1D were enrolled (Bonifacio et al., 2015).

**Mechanisms by which genetic variation can affect disease risk**

As well as precise phenotyping, understanding the types of genetic variants which may be identified and how these contribute to disease risk is key to the investigation of genetic disease. Fig. 4 further describes some of the key concepts in the study of genetic disease. There are multiple types of DNA alteration which can affect gene expression and/or protein function (Fig. 5). Once disease-associated variants have been identified, annotation software (e.g. PolyPhen-2 [[3]](#footnote-3) or SIFT [[4]](#footnote-4)) can be used to predict the impact of a variant on protein function according to the variant type and location. However, importantly, most variants impacting on risk do not change the amino acid sequence: Single Nucleotide Polymorphisms (SNPs) in non-coding regions or introns, for example, can still have important regulatory functions.

Disease risk may be influenced by a relatively small number of high impact variants, for example single genes in monogenic diabetes, in which case a classic dominant or recessive pattern of inheritance is usually evident. Alternatively, in complex genetic diseases such as T1D and T2D, small effects from a larger number of variants combine to determine the genetic risk of an individual. Subsequently, other risk factors (internal and environmental) contribute to the overall risk of that individual developing the disease. Furthermore, the effect of genetic variants alone will often not explain the full heritability of a complex disease, since there are other contributing factors, sometimes referred to as ‘missing heritability’ (Groop and Pociot, 2014). These may include heritable changes to the genome which do not alter the DNA sequence (e.g. epigenetic changes such as DNA methylation) as well as shared environmental factors such as the gut microbiome.

*Population structure of dogs*

Additional considerations for the study of genetic predisposition to diseases in dogs relate to the unique population structure of dogs. Domestication from wolves more than 15000 years ago marked the first of two major canine ‘population bottlenecks’. The second major bottleneck was selective breeding undertaken in the creation of pedigree breeds, approximately 200 years ago (Parker et al., 2004; Karlsson and Lindblad-Toh, 2008). Each bottleneck has resulted in a marked reduction in population genetic diversity and has led to long regions of linkage disequilibrium (chromosomal regions that are inherited together) across the genome. Modern dog breeds now represent genetically isolated populations with wide inter-breed but often limited intra-breed genetic variation (Lindblad-Toh et al., 2005), sometimes with a high prevalence of specific diseases within a breed. Selective breeding, whereby genes that determine desired characteristics or phenotypic traits are bred to near-homozygosity, can also lead to disease-risk alleles becoming ‘fixed’ in a breed when these are in linkage disequilibrium with the variants determining phenotypic traits. Given that most dog breeds have been established relatively recently, it is feasible that some disease-associated variants originated prior to breed creation and hence may be shared among breeds, even if the breeds do not look physically similar (Parker et al., 2017). Limited genetic divergence of breeds from different countries (Summers et al., 2014) suggests these variants may be shared worldwide. Furthermore, it is possible that a small number of genes may exert a large effect in complex phenotypes in dogs, in contrast to many genes having a small effect, as is the case in humans (Ostrander et al., 2017).

*Classes of genetic variants in dogs*

Variants that contribute to disease susceptibility in dogs can be grouped into various different classes, according to their pattern of occurrence within and between breeds. Three of the most common classes are described in Fig. 6. The first class of variant occurs at high frequency and is relatively ‘fixed’ within a breed. This type of variant contributes to the overall ‘breed risk’ of the disease. Whilst the background genetic risk for each individual within a breed is similar, the presence or absence of disease is then determined by other factors, such as environmental triggers. Importantly, disease-associated genetic variants of this type, which may have been bred to homozygosity as a consequence of selective breeding, cannot be identified by the conventional approach of comparing cases and controls within a single breed. Instead, an alternative approach is required, comparing genetic data between high risk and low risk breeds, for example using whole genome sequencing. The second class of disease-associated genetic variant occurs in a subset of individuals of a breed, modifying their disease risk. Unlike the variants that are ‘fixed’ within breeds, this category can be identified by case:control studies (for example candidate gene or genome-wide association studies (GWAS)), as they will be higher frequency in affected compared to unaffected individuals, even within breeds. The third class of variant occurs in relatively few individuals of a breed, with these rare variants, often of high impact, modifying an individual’s risk of the disease.

In a complex disease such as canine DM, with an unknown number of genetic and environmental factors expected to be involved, it is possible that multiple types of genetic variant may influence disease risk and be identified by genetic studies. Most of the research into the genetics of canine DM has so far employed candidate gene studies, based on genes involved in T1D and T2D. However, a combination of strategic study design and more recent high-throughput technologies is now allowing unbiased detection of novel variants at an affordable cost, which may elucidate the aetiology of canine DM in single or multiple breeds.

**Conclusions**

In the first of this two-part article, the classification of human and canine DM have been briefly discussed and the importance of precise classification in diabetes genetic studies has been outlined. Furthermore, the ways in which genetic variants may contribute to risk of a complex disease have been introduced. Part 2 of this article will review the genetics of DM to date, as well as the mechanisms by which genetic variation can influence gene function. In addition, some of the recent technological advances which have allowed significant progress in our understanding of human DM will be reviewed, and their potential in canine diabetes research discussed.

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**Conflict of interest statement**

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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**Table 1**

Breed distribution of diabetic dogs in the UK Canine Diabetes Register (2000–2010) compared with the breed distribution in a database from the Companion Care group of first opinion veterinary practices in the UK. For each breed, the absolute number of dogs in each database is given, as well as the proportion of each database represented by this breed. Not all breeds are included, which accounts for the differences in the reported column total and actual numbers included in the column. (Reproduced from Catchpole et al., 2013 with permission of Elsevier). ﻿

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Breed | UK Canine Diabetes Register  (*n* = 1,536) | Proportion (%) in diabetes register | Reference database (*n* = 162,000) | Proportion (%) in reference database | Odds ratio  (95% confidence interval) |
| Samoyed | 46 | 3.0 | 139 | 0.1 | 35.84 (25.58 - 50.22) |
| Tibetan terrier | 34 | 2.2 | 351 | 0.2 | 10.39 (7.28 - 14.83) |
| Cairn terrier | 50 | 3.2 | 555 | 0.3 | 9.76 (7.27 - 13.09) |
| Dachshund (all types) | 41 | 2.7 | 1080 | 0.7 | 4.07 (2.97 - 5.59) |
| Doberman Pinscher | 19 | 1.2 | 498 | 0.3 | 4.05 (2.55 - 6.42) |
| Miniature Schnauzer | 35 | 2.3 | 1034 | 0.6 | 3.62 (2.57 - 5.09) |
| Siberian Husky | 13 | 0.8 | 397 | 0.2 | 3.46 (1.99 - 6.03) |
| Scottish terrier | 10 | 0.6 | 315 | 0.2 | 3.35 (1.78 - 6.31) |
| West Highland white terrier | 140 | 9.1 | 5149 | 3.2 | 3.04 (2.55 - 3.63) |
| Miniature Poodle | 11 | 0.7 | 489 | 0.3 | 2.38 (1.3 - 4.33) |
| Border collie | 95 | 6.2 | 5093 | 3.1 | 2.02 (1.64 - 2.5) |
| Border terrier | 31 | 2.0 | 1827 | 1.1 | 1.80 (1.26 - 2.58) |
| Labrador retriever | 188 | 12.2 | 12476 | 7.7 | 1.67 (1.43 - 1.94) |
| Yorkshire terrier | 88 | 5.7 | 6088 | 3.8 | 1.55 (1.25 - 1.93) |
| Bichon Frise | 31 | 2.0 | 2179 | 1.3 | 1.51 (1.05 - 2.15) |
| Cavalier King Charles spaniel | 57 | 3.7 | 4284 | 2.6 | 1.41 (1.08 - 1.85) |
| Cocker spaniel | 65 | 4.2 | 5536 | 3.4 | 1.25 (0.97 - 1.6) |
| Beagle | 10 | 0.6 | 1066 | 0.7 | 0.99 (0.53 - 1.84) |
| Crossbreed | 283 | 18.4 | 34422 | 21.2 | 0.83 (0.73 - 0.95) |
| Golden retriever | 17 | 1.1 | 2454 | 1.5 | 0.73 (0.45 - 1.17) |
| Rottweiler | 17 | 1.1 | 2596 | 1.6 | 0.69 (0.42 - 1.11) |
| Jack Russell terrier | 69 | 4.5 | 11646 | 7.2 | 0.61 (0.48 - 0.77) |
| English Springer spaniel | 23 | 1.5 | 4127 | 2.5 | 0.58 (0.38 - 0.88) |
| German shepherd | 12 | 0.8 | 5392 | 3.3 | 0.23 (0.13 - 0.4) |
| Boxer | 2 | 0.1 | 3027 | 1.9 | 0.07 (0.02 - 0.27) |

**Figure legends**

Fig. 1. Aetiologic classification of human diabetes mellitus. (American Diabetes Association, 2014)

Fig. 2. Aetiologic classification of canine diabetes mellitus. 2

Fig. 3. Illustration of the importance of disease classification for studies of complex disease genomics and examples of the ways that genomic studies can contribute to refinement of aetiologic classification.

Fig. 4. Key concepts in study of genetic disease. (several definitions adapted from [[5]](#footnote-5))

Fig. 5. Examples of types of genetic variant (definition for ‘Delins’ taken from [[6]](#footnote-6)).

Fig. 6. Examples of three classes of disease-associated genetic variant that may be observed in dogs, each with different patterns of occurrence within and between breeds. Conventional case:control study designs are only useful to detect variants in the second and third classes shown here.

1. See: European Society for Veterinary Endocrinology, Project ALIVE, Search for a term. <https://www.esve.org/alive/search.aspx> (Accessed 7 January 2021). [↑](#footnote-ref-1)
2. See: European Society for Veterinary Endocrinology, Project ALIVE. <https://esve.org/alive/intro.aspx> (Accessed 7 January 2021) [↑](#footnote-ref-2)
3. See: PolyPhen-2 <http://genetics.bwh.harvard.edu/pph2/index.shtml> (Accessed 7 January 2021) [↑](#footnote-ref-3)
4. See: SIFT <https://sift.bii.a-star.edu.sg/> (Accessed 7 January 2021) [↑](#footnote-ref-4)
5. See: National Human Genome Research Institute, Talking Glossary of Genetic Terms. <https://www.genome.gov/genetics-glossary> (Accessed 7 January 2021). [↑](#footnote-ref-5)
6. See: DNA Recommendations. <https://varnomen.hgvs.org/recommendations/DNA/variant/delins/> (Accessed 7 January 2021). [↑](#footnote-ref-6)