**Review**

**Genetics of canine diabetes mellitus part 2: Current understanding and future directions**

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**Abstract**

Part 1 of this 2-part review outlined the importance of disease classification in diabetes genetic studies, as well as the ways in which genetic variants may contribute to risk of a complex disease within an individual, or within a particular group of individuals. Part 2, presented here, will describe in more detail our current understanding of the genetics of canine diabetes mellitus compared to our knowledge of the human disease. Ongoing work to further develop our knowledge, using new technologies, will also be introduced.

*Keyword*s: Canine; Diabetes mellitus; Genetics; Genomics; Major histocompatibility complex

**Introduction**

To date, the genetics of canine diabetes mellitus (DM) has primarily been investigated using a candidate gene approach, based on examination of susceptibility genes identified for human DM. Although this strategy historically has been rewarding in identifying mutations responsible for conditions and phenotypic traits with a monogenic basis, it is less successful for complex diseases such as DM. Introduction of 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.

**Genetics of diabetes mellitus in humans**

In the past 10-15 years, major advances have been made in our understanding of the genetic basis of complex diseases, including DM. Prior to completion of the Human Genome Project in 2003, candidate gene studies had revealed a relatively small number of type 1 diabetes (T1D) and type 2 diabetes (T2D)-associated genetic variants. Many of these studies utilised Sanger sequencing, a method of sequencing relatively short regions of the DNA using fluorescent nuceotides for sequence determination. However, improved recognition and cataloguing of single nucleotide polymorphisms (SNPs) throughout the human genome enabled the design of ‘SNP genotyping arrays’, allowing genome-wide association studies (GWAS) to be undertaken (Wellcome Trust Case Control Consortium, 2007). This approach is based on identifying SNP alleles that are present at a higher frequency in individuals with a particular condition compared to unaffected individuals from the same population, and can identify alleles with a small but significant impact on disease risk. In the post-GWAS era, more than 60 genetic regions have now been associated with T1D (Bakay et al. 2019) and there are more than 200 loci associated with T2D (Mahajan et al., 2018). However, the variants identified by GWAS are usually not themselves causal. Instead, they might simply be in linkage disequilibrium with one or more other variants, not represented on the SNP chip, that are exerting the causal effect. Similar to a lamppost, GWAS can shine a light on a disease-associated region of the genome that contains an important variant, without specifically identifying what that variant is.

Once a chromosomal region has been identified, fine-mapping of the region(s) must be undertaken to identify causal gene(s), variant(s) and mechanism(s). There are many challenges associated with moving from disease-associated SNPs to causal variants and positional candidate genes for functional studies. This process is often very time-consuming. As discussed in Part 1, many important genetic variants do not change the amino acid sequence of a protein, but are in non-coding regions and can affect gene transcription or function in a variety of different ways. Disease-associated genetic variants can even impact gene function over long distances or on different chromosomes, and may act by different mechanisms, or only in certain tissues or at a particular developmental stage.

The many methodologies currently available to study the role of genetic variation in disease suceptibililty (Fig. 1) each have their advantages and limitations. Before reference genomes were fully sequenced, it was not uncommon to use genetic markers combined with family pedigrees to conduct a linkage analysis, either in a candidate gene approach or in a genome-wide scan. Case:control GWAS is a useful unbiased approach to identify loci associated with a disease, even for complex diseases (Hayward et al., 2016). In contrast, sequencing all the coding regions (exomes) in the genome of an individual (Whole Exome Sequencing – WES) or even sequencing the entire genome (Whole Genome Sequencing – WGS) does not rely on the pre-identified regions and/or variants used in GWAS (sometimes called ‘tag-SNPs’). The high-throughput next generation sequencing (NGS) technologies and analysis tools used for WES and WGS are able to identify many types of genetic variant, however there are still some types of variant that are more difficult to detect. Most NGS technologies generate short ‘reads’ (75 – 150bp) which are assembled against a ‘reference’ genome sequence for that species during the process of bioinformatic analysis. However, assembly can be challenging or inaccurate in regions of repetitive sequences, or where a reference genome is incomplete or poorly annotated, as is the case for many species other than humans and laboratory mice. This means that some types of structural variant (e.g. gene duplication or inversion, and variations in copy-number of genes) are not easily detected. More recent NGS technologies produce longer reads (1 – 10kb) (e.g. PacBio and Oxford Nanopore), which helps to overcome these ‘short-read’ issues, although historically some long-read technologies have had a slightly higher sequencing error rate and have also been much more expensive (Reuter et al., 2015). Therefore, a number of factors must be considered when selecting the type of sequencing technology and data analysis approach to be used. Despite these caveats, recent technological advances in sequencing have allowed a rapid expansion in our understanding of all types of human DM, with beneficial clinical implications on the horizon or already in practice (Bowman et al., 2018).

*The genetics of human monogenic forms of DM*

Although not the most common form, DM can result from single gene mutations in humans (several forms of Maturity Onset Diabetes of the Young – MODY, and Neonatal Diabetes Mellitus – NDM. See Online Mendelian Inheritance in Man (OMIM) for details[[1]](#footnote-1)). Clinical signs of hyperglycaemia usually become apparent at a very early age, although some types of monogenic diabetes can manifest in later childhood (Shepherd et al., 2016). Many of the genes responsible for monogenic diabetes are important for beta cell development, membrane depolarisation and glucose metabolism or mechanisms of cell death, such as apoptosis (Misra and Owen, 2018). The most common mutations in NDM are found in the genes encoding the two subunits of the beta cell KATP channel: *KCNJ11* and *ABCC8* (Hattersley and Ashcroft, 2005; Flanagan et al., 2009). This channel is closely involved in glucose homeostasis: opening of these channels causes beta cell hyperpolarisation and suppression of insulin secretion. The insulin gene is also important: heterozygous missense mutations in the *INS* gene are responsible for ~15-20% of NDM cases (Colombo et al., 2008; Polak et al., 2008). In MODY, the most common disease-causing mutations are found in the gene encoding the enzyme glucokinase (*GCK*), and the transcription factor genes hepatocyte nuclear factors 1-alpha (*HNF1A*), 4-alpha (*HNF4A*) and 1-beta (*HNF1B*).

The study of monogenic DM has benefited greatly from recent advances in human genotyping, particularly high throughput sequencing of whole genomes (Misra and Owen, 2018). This has allowed unbiased and more rapid detection of disease-causing mutations compared to the traditional candidate gene approach. It has also facilitated discovery of novel mutations, found in a small number of individuals, highlighting new critical genes in beta cell biology. Not only has this reduced misdiagnosis of T1D and allowed precision medicine (whereby individual genetic, environmental and lifestyle factors are considered when designing a tailored prevention or treatment strategy) to be applied to affected individuals (Bowman et al., 2018; Misra and Owen, 2018), it has also revealed new genes that are criticial for pancreatic development or glucose homeostasis. In an example of genomics-led precision medicine, patients with a type of monogenic neonatal diabetes associated with a mutation in genes encoding the beta cell KATP channel have been able to replace insulin injections with oral sulphonylurea drugs, resulting in improved glycaemic control in these individuals (Pearson et al., 2006; Klupa et al., 2010; Ashcroft and Rorsman, 2012).

*The genetics of human T1D*

The contribution of genetic factors to the development of T1D was first recognised through twin concordance rates, family studies and different prevalence rates among ethnic groups (reviewed in Concannon et al., 2009; Grant et al., 2010; Bakay et al. 2019). The disease has a strong genetic component, despite no close family history in more than 85% of patients (Steck and Rewers, 2011). Early candidate gene studies identified risk alleles in a number of immune response genes, which have since been confirmed and expanded through GWAS involving thousands of individuals (Burton et al., 2007; Todd et al., 2007; Polychronakos and Li, 2011). Whilst many regions are known to contribute to genetic risk in T1D, by far the largest component of this risk is conferred by the major histocompatibility complex (MHC), a genomic region containing a large number of immune response genes, including those encoding the Human Leukocyte Antigen (HLA) proteins. This region is considered to be the most important susceptibility locus in T1D and HLA typing is used to identify children at high risk for development of diabetes for recruitment into clinical trials.

In humans, the MHC genes are located on Chromosome 6 and MHC nomenclature is complex due to the wide variety of alleles and possible haplotypes. However, due to the complexity in nomenclature, important haplotypes are often shortened for reference, e.g. *DRB1\*03--DQB1\*02:01* is shortened to DR3/DQ2. The MHC genes are divided into class I, II and III (Fig. 2). MHC class II and class I genes encode cell surface molecules which present antigen to CD4+ helper and regulatory T cells and CD8+ cytotoxic T cells, respectively. The MHC haplotype of an individual is critical to the adaptive immune response and determines the repertoire of antigenic peptides that can be presented to the immune system. As well as directing immune responses towards external antigens, the MHC haplotype is important in determining immune tolerance to ‘self’ peptides as the immune system develops.

The HLA class II genes confer approximately 50% of the genetic risk of T1D (Rotter and Landaw, 1984; Noble et al., 1996; Cucca et al., 2001; Todd et al., 1987, 2007). There are two especially important haplotypes. Either or both of the *DR3/DQ2* or *DR4/DQ8* haplotypes are found in approximately 90% of individuals with juvenile-onset T1D compared with 20% of the general population of European descent (Erlich et al., 2008). Several other HLA haplotypes (e.g. *HLA-DR2*) are associated with reduced susceptibility to T1D and are designated as ‘protective’ haplotypes. Interestingly, a MHC class II haplotype may increase risk of T1D in one particular ethnic population, yet be protective in another (Nyaga et al., 2018).

After identification of the MHC locus as a T1D genetic risk factor, candidate gene studies went on to identify important T1D-associated variants in the insulin gene itself (*INS*) as well as T1D-associated variants in four other immune response genes – *PTPN22, CTLA4, IFIH1* and *IL2RA* (Ueda et al., 2003; Bottini et al., 2004; Lowe et al., 2007; Nejentsev et al., 2009). The *INS* gene confers the greatest genetic risk outside the MHC region, with the causative locus mapped to a variable number of tandem repeats (VNTR) polymorphism in the promoter region (Bennett et al., 1995). Short VNTR alleles are associated with greater T1D risk whereas long alleles are protective by modification of *INS* gene expression in the thymus, affecting the development of T lymphocyte immune tolerance to this ‘self’ protein (Vafiadis et al., 1997). The role of the adaptive immune system in T1D is also highlighted by risk variants in *PTPN22* and *CTLA4.* These genes encode negative regulators of T cell signalling, potentially further contributing to the development of the autoimmune response towards pancreatic beta cell antigens (Polychronakos and Li, 2011).

The T1D-associated loci that have now been identified provide biological insights as to the pathogenesis of the disease (Barrett et al., 2009; Bradfield et al., 2011; Pang et al., 2020). Several loci have been linked to genes involved in interleukin-2 pathways and regulatory T lymphocyte function, providing further evidence that dysregulation of the immune system plays a major role in T1D. Many T1D variants are also implicated in other autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis (Cotsapas et al., 2011). Other important biological pathways have also now been identified, including the type 1 interferon response and beta cell apoptosis. For example, *GLIS3* (Gli-similar 3)*,* whichwas identified by GWAS as a candidate gene (Barrett et al., 2009), is thought to protect against T1D by exerting anti-apoptotic effects and maintaining beta-cell mass and function (Pang et al., 2020). The precise causal variant(s) in a number of T1D-associated regions, and the function of gene(s) in these regions, however, has yet to be established.

*The genetics of human T2D*

More than 200 T2D susceptibility loci have been identified through GWAS (Mahajan et al., 2018) and further research is underway to identify and characterise the causal genes and variants at these loci (Grotz et al., 2017; Loscalzo, 2019; Mattis and Gloyn, 2020). Similar to T1D, important biological pathways have been identified by this GWAS-led approach and, in T2D, these relate primarily to metabolism, obesity and appetite, beta cell function and development, and insulin signalling. Specific examples include genes involved in cell cycle regulation (e.g. *CDC123*) and zinc transport within insulin secretory granules (e.g. *SLC30A8*) (Zeggini et al., 2008; McCarthy and Zeggini, 2009). Other T2D susceptibility genes overlap with those also implicated in monogenic diabetes, including *KCNJ11* and *ABCC8* (Hani et al., 1998; Florez et al., 2004). However, most forms of monogenic DM are caused by rare coding variants, whereas the majority of mutations implicated in T2D are common non-coding variants (Fuchsberger et al., 2016). There is minimal overlap between the variants identified for T1D and T2D, however, beta cell fragility has been proposed as a common risk factor in both diseases, on the basis of genetic and epidemiological data, as well as laboratory animal models (Dooley et al., 2016; Liston et al., 2017).

*The genetics of human LADA*

Latent autoimmune diabetes of adulthood (LADA) shows similarities with both T1D and T2D, leading to the proposal of the alternative name ‘Type 1.5 DM’. LADA patients are seropositive for at least one of the four autoantibodies commonly found in T1D, however, the more protracted course of beta cell destruction and delayed requirement for insulin therapy mean they often present at an age typically associated with T2D (O’Neal et al., 2016). The genetics of LADA show overlap with T1D (Palmer et al., 2005), and to a lesser extent with T2D (Cervin et al., 2008; Andersen et al., 2010). For example, variation in the VNTR of the insulin gene has been found to influence susceptibility to LADA, as it does for T1D (Desai et al., 2006), while T2D-associated variants in the *TCF7L2* gene were found to be increased in LADA patients to the same degree as in T2D patients (Cervin et al., 2008). Similarly, a recent GWAS of European LADA patients found that the strongest genetic risk for LADA correlated with those for T1D, but noted a weaker correlation with T2D associations (Cousminer et al., 2018).

**Genetics of diabetes mellitus in dogs**

Published research into the genetics of canine DM has, to date, mostly been limited to functional candidate gene studies, with a case:control design within certain breeds, based on evaluating genes implicated in human T1D and monogenic diabetes (Short et al., 2014). In many cases, diabetic dogs from multiple breeds have been studied together, often due to small sample numbers, relying on an assumption, which may be incorrect, that there is little disease heterogeneity between breeds. Nonetheless, these studies have identified some important genes which may be significant in the aetiology of canine DM and pave the way for future studies. Fig. 3 illustrates some of the genes in which variants have been associated with canine DM, compared with selected genes implicated in the pathogenesis of human DM.

*The major histocompatibility complex (MHC)*

Since the MHC is such an important risk factor in T1D, finding an association of particular DLA (Dog Leucocyte Antigen) types with canine DM would support a role for the adaptive immune response in development of the canine disease. Thus, the first functional candidate gene studies in canine DM focussed on the DLA genes, encoding canine MHC Class II (Fig. 2 and 4) found on canine chromosome 12. Through DLA typing of a wide range of breeds, DLA class II alleles and haplotypes have been found to show restricted diversity within dog breeds, but wide variation among breeds (Kennedy et al., 2002; Angles et al., 2005). This restricted MHC diversity in particular dog breeds is likely to impact the immune repertoire within each breed by influencing thymic T cell development, as well as antigen presentation to naïve T cells in secondary lymphoid tissues.

Sequence-based typing of exon two (which encodes the peptide-binding groove of the MHC molecule) of the Class II DLA genes, has identified three DLA-DRB--DQA--DQB haplotypes present at increased frequency in the diabetic dog population, when comparing the genotypes of 460 diabetic dogs to 1,047 non-diabetic controls (Table 1) (Kennedy et al., 2006). Dogs from a wide range of breeds were combined for this analysis, therefore the association of these three DLA haplotypes with canine DM suggested that they may represent ‘susceptibility’ haplotypes across several breeds. However, the statistical analysis may not have compensated for analysis of multiple haplotypes within this population and the P-values stated may be higher when corrected for multiple testing. The authors went on to examine associations of two-locus haplotypes with DM in the population, given that individual or pairs of loci may also influence disease risk. One DLA-DQ haplotype (DQA1\*004--DQB1\*013) was found at lower frequency in diabetic dogs than controls, suggesting this may confer protection. Although there was insufficient power of the study to compare cases and controls within individual breeds, stratification of breeds into ‘high’, ‘moderate’, ‘neutral’ and ‘low’ risk categories, based on the calculated odds ratio for DM, was used to assess whether haplotypes would segregate with risk of DM. DLA-DRB1\*009--DQA1\*001, present in one of the three-locus ‘susceptibility’ haplotypes, was found at high frequency in those breeds at greatest risk of DM (Samoyed, Cairn terrier and Tibetan terrier) but was absent from the low-risk breeds (Boxer, German Shepherd dog and Golden Retriever) (Kennedy et al., 2006). Another of the ‘high risk’ haplotypes (DRB1\*015--DQA1\*006--DQB1\*023) was later found to be associated with development of anti-insulin antibodies, following initiation of insulin therapy (Holder et al., 2015), suggesting a role in presentation of this important pancreatic autoantigen.

Another study has suggested that the sequence-based typing approach may have identified associated, but not causative, polymorphisms (Seddon et al., 2010). This study used SNP genotyping across a wider region of the DLA (Seddon et al., 2010) and identified an area of fixed differences between ‘susceptibility’ and ‘protective’ exon 2 haplotypes across five SNPs, despite different DQA1 and DQB1 alleles. It was also noted that both protective and susceptibility haplotypes were found in diabetic dogs. Notably, the use of sequence-based typing methods have also been called into question by another study demonstrating that not all reported disease associations with DLA could be verified when an alternative SNP-genotyping method was used (Safra et al., 2011).

It is not just the MHC hypervariable region that has been associated with canine DM risk. Genotyping the MHC promoter regions has identified four novel promoter alleles which were only seen in diabetic dogs, as well as a polymorphism in the X1 box (a region upstream of the promoters which control the MHC gene expression), which might modify the expression pattern of the DQB1 haplotypes (Seddon et al., 2010).

Given the uncertain role of the immune system and the possible heterogeneity of the pathogenesis of canine DM between breeds, work is ongoing to generate extended DLA profiles of large numbers of affected and unaffected dogs within single breeds. This may identify breed-specific associations which would otherwise be masked, if they are not present in other breeds. The HLA alleles and haplotypes conferring greatest risk of human T1D differ between different ethnic groups (Zamani and Cassiman, 1998), lending support to the possibility of breed-specific DLA associations with canine DM. A recent case:control study of class II DLA haplotypes in 12 dog breeds identified diabetes-associated haplotypes in five individual breeds (Denyer et al., 2020), suggesting that a breed-specific approach will be valuable in future disease studies.

*Other immune system genes*

Recognition of the importance of T-cell signalling pathways in T1D has led to further functional candidate gene studies in dogs, examining polymorphisms in genes encoding lymphocyte cell surface molecules and cytokines (Short et al., 2007, 2009, 2010). Notably, the studies described below show disease associations, but this does not necessarily mean that the variants identified play a causal role in disease.

SNPs in the promoter region of the cytotoxic T lymphoctye-4 (*CTLA4)* gene, a negative regulator of T-cell signalling, have been associated with canine DM in crossbreed dogs and in five pedigree breeds (Short et al., 2010). Similarly, SNPs in cytokine genes, such as *IL4* and *IL10*, have been associated with ‘protection’ or ‘risk’ in single or small numbers of breeds (Short et al., 2007, 2009). In some cases, SNPs were found to be protective in one breed, but to be associated with risk in another. However, the results of these studies have not yet been replicated by other methods and the low sample numbers make it difficult to assess the significance of these findings in individual breeds. In addition, none of the identified SNPs altered the protein sequence of any of the genes, therefore these associations require further research to support causality. Nonetheless, these findings do appear to implicate the immune system in the pathogenesis of canine DM.

*Pancreatic beta cell genes*

An additional functional candidate gene study in dogs focussed on the genes implicated in human monogenic diabetes, by performing SNP genotyping in selected monogenic DM genes across a range of breeds (Short et al., 2014). Although six variants were associated with diabetes in some breeds, these generally only reached significance in a single breed (Short et al., 2014) and, similar to the cytokine gene study described above, all were either intronic or synonymous coding variants. For example, a SNP in *HNF4A* was associated with diabetes only in the Miniature Dachshund, while SNPs in three other monogenic DM genes (*INS, PAX4, MT-TL1*) were associated with DM in Cocker Spaniels but no other breeds. There was no evidence for monogenic DM in most of the breeds assessed (total n = 17), but notably the Keeshond breed, in which congenital beta cell aplasia has been reported (Kramer et al., 1980) was not included in this study.

Another SNP-based analysis examined selected SNPs in the *INS* gene in a cohort of 483 diabetic dogs and 869 controls, from 30 breeds. Of the six SNPs evaluated, associations with diabetes were found within single breeds: two conferring protection and one conferring risk of diabetes (Short et al., 2007). None of these three variants alter the amino acid sequence of insulin and it is also possible that these SNPs form protective/risk haplotypes with the adjacent *IGF2* gene, encoding insulin-like growth factor 2. Unlike in humans, there is no VNTR in the canine *INS* promoter, although a VNTR has been identified at the 5’ end of intron 2 (Catchpole et al., 2013). Dogs were found to possess either two or three copies of this VTNR, although no clear associations with diabetes have been identified (Catchpole et al., 2013).

The majority of genes/loci associated with T2D are yet to be investigated in dogs, but could hold promise for identifying novel genes and pathways involved in canine DM. The emerging concept of ‘beta cell fragility’ as a risk factor in T1D and T2D (Dooley et al., 2016; Liston et al., 2017) could be very relevant to the pathogenesis of canine DM and insulinoma, especially when considering the apparent inverse relationship of DM and insulinoma risk in breeds such as the Boxer (Catchpole et al., 2013; Caywood et al., 1988). If this theory is correct, these diabetes-resistant breeds may have beta cells with a greater resistance to apoptosis, or with a greater capacity for regeneration than other breeds, which protects from DM but predisposes them to malignant transformation. While genetic factors might determine the beta cell fragility or robustness, other genetic and environmental factors could influence the balance between apoptosis and regeneration to determine which individuals develop DM or insulinoma.

The functional candidate gene studies outlined here have made an important contribution to our understanding of canine DM, however they are inherently limited in their scope to discover new genes and regions. They implicate the immune system in the pathogenesis of disease in some breeds, but also reveal the genetic heterogeneity between breeds and therefore the likely heterogeneity in the pathogenesis of the underlying beta cell dysfunction. The LUPA consortium, a European-wide initiative using the dog as a model for the genetic basis of human diseases, employed GWAS to investigate both monogenic and complex diseases (Lequarré et al., 2011). However there are no published data using genome-wide technologies such as GWAS and NGS in canine DM to date.

**Future avenues of genetic research**

The study of DM genetics in dogs, as part of a ‘One Health’ approach, has the potential to improve both canine and human health (Karlsson and Lindblad-Toh, 2008; O’Kell et al., 2017). The advent of new technologies such as WGS of high and low DM-risk breeds, in addition to GWAS studies, should allow rapid progress to be made. Ongoing genetic studies in canine DM are benefitting from lessons learned in human DM research. These include the value of more precise phenotyping, stratification of studies by MHC haplotype and consideration of environmental factors also influencing disease risk. Since the disease is recognised as increasingly complex and heterogeneous within the human type 1 and 2 classifications (Tuomi et al., 2014), we can expect that the same may be true for canine DM, among or even within different dog breeds.

Additional challenges when studying canine genetic disease relate to the availability of data about the structure and function of the canine genome. Improved knowledge of the normal genetic variation in different dog breeds is necessary to assess the significance of potentially disease-causing variants. Progress has been made by a number of consortia in improving the availability of information, such as the Dog Biomedical Variant Database Consortium, DogSD[[2]](#footnote-2) (Bai et al., 2015; Jagannathan et al., 2019), the Give a Dog A Genome project (Mellersh C., 2008) and the Dog 10K Genomes project[[3]](#footnote-3) but the amount of available breed-specific canine reference data remains a limiting factor in research progress compared to human studies. There are still only a small number of published complete canine genomes (Boxer, Basenji, Great Dane and German Shepherd in mid-2020), therefore comparison of any canine genome with a reference sequence usually requires comparison with the genome of a dog from a different breed, with different genetic disease susceptibilities.

Another important factor in any future canine diabetes genetics studies is the availability of case samples and appropriate non-diabetic control samples from a wide variety of breeds. It is particularly important to age-match control samples to cases, since diabetes does not usually manifest until 7 years of age or older. A resource of particular value to the study of canine DM continues to be the UK Canine Diabetes Register, which has been maintained at the Royal Veterinary College (RVC) since 2000. The archive consists of clinical data and blood samples from diabetic dogs, submitted by first opinion practitioners for the measurement of serum fructosamine and HbA1c (Davison et al., 2001). During the 20 years since the establishment of this archive, clinical samples from almost 2,000 diabetic dogs have been collected and used in several of the candidate gene studies described previously (Kennedy et al., 2006; Short et al., 2009, 2010, 2014; Davison et al., 2017; Denyer et al., 2020) as well as an early epidemiological study (Davison et al., 2005). Recruitment of samples is ongoing [[4]](#footnote-4).

Many of the most successful research efforts in human T1D and T2D have been made by large consortia, including the Type 1 Diabetes Genetics Consortium (T1D) and GoT2D (T2D) among others, enabling large-scale analyses, involving tens of thousands of individuals. The power of these studies allows identification of novel risk loci, even those conferring a relatively small effect and containing genes of unknown function, which can then be investigated for their functional significance. Underpinned by the UK Canine Diabetes Register, the Canine Diabetes Genetics Partnership (CDGP) was established in November 2017, with the purpose of using WGS and other NGS techniques to explore the genetic risk of DM and insulinoma in different dog breeds[[5]](#footnote-5). Such unbiased approaches will facilitate identification of new diabetes susceptibility genes and non-coding elements of the genome which affect disease risk, and may offer new therapeutic and preventative targets.

**Conclusions**

While canine genetic research has previously been dominated by studies of monogenic disease, recent technological advances will enable rapid progress in our understanding of canine DM and other complex genetic disorders. As well as contributing to improved understanding of diabetes pathogenesis in all species, including humans, this work is also likely to reveal exciting opportunities for precision medicine in veterinary patients.

**Acknowledgements**

The members of the Canine Diabetes Genetics Partnership (in alphabetical order) are: V. Bergomi (University of Cambridge, UK), B. Catchpole (Royal Veterinary College, UK), L. J. Davison (Royal Veterinary College and University of Oxford, UK), A. L. Denyer (Royal Veterinary College, UK), M. E. Herrtage (University of Cambridge, UK), K. Hughes (University of Cambridge, UK), L. J. Kennedy (University of Manchester, UK), C. Mellersh (University of Cambridge, UK and formerly Animal Health Trust, UK), C. A. O’Callaghan (University of Oxford, UK), A. Psifidi (Royal Veterinary College, UK), I. K. Ramsey (University of Glasgow, UK), S. L. Ricketts (University of Cambridge, UK and formerly Animal Health Trust, UK), E. Schofield (University of Cambridge, UK and formerly Animal Health Trust, UK), M. D. Wallace (Royal Veterinary College, UK), P. J. Watson (University of Cambridge, UK), G. Williams (Dechra Ltd.), and D. Xia (Royal Veterinary College, UK), N. Zimmerman (Dechra Ltd.). We would also like to thank the owners of dogs with diabetes who gave permission for their dogs to participate in our studies and the veterinary surgeons who have submitted samples. The Canine Diabetes Genetics Partnership is supported by a grant from the PetPlan Charitable Trust (S17-423-461)and by Dechra Ltd. ALD is supported by a LIDo Doctoral Training Program (BBSRC funded) and by Dechra Ltd. (industrial partner for iCASE studentship). ALD is also grateful for funding from the 2018 International Canine Health Awards, administrated by [the Kennel Club Charitable Trust](http://dogcharityblog.org.uk/) and donated by Vernon and Shirley Hill of [Metro Bank](https://www.metrobankonline.co.uk/). LJD is supported by an MRC Clinician Scientist Fellowship (MR/R007977/1). The UK Canine Diabetes Register and Archive has been supported by the Kennel Club Charitable Trust, BSAVA Petsavers, the European Commission (FP7-LUPA, GA-201370) and MSD Animal Health.

**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.

**References**

Andersen, M.K., Lundgren, V., Turunen, J.A., Forsblom, C., Isomaa, B.O., Groop, P.H., Groop, L., Tuomi, T., 2010. Latent autoimmune diabetes in adults differs genetically from classical type 1 diabetes diagnosed after the age of 35 Years. Diabetes Care 33, 2062-4.

Angles, J.M., Kennedy, L.J., Pedersen, N.C., 2005. Frequency and distribution of alleles of canine MHC-II DLA-DQB1, DLA-DQA1 and DLA-DRB1 in 25 representative American Kennel Club breeds. Tissue Antigens 66, 173–184.

Ashcroft, F.M., Rorsman, P., 2012. Diabetes mellitus and the β Cell: The last ten years. Cell 148, 1160–1171.

Bai, B., Zhao, W.M., Tang, B.X., Wang, Y.Q., Wang, L., Zhang, Z., Yang, H.C., Liu, Y.H., Zhu, J.W., Irwin, D.M. et al., 2015. DoGSD: The dog and Wolf genome SNP database. Nucleic Acids Research 43, D777–D783.

Bakay, M., Pandey, R., Grant, S.F.A., Hakonarson, H., 2019. The genetic contribution to type 1 Diabetes. Current Diabetes Reports 19, 116.

Barrett, J.C., Clayton, D., Concannon, P., Akolkar, B., Cooper, J.D., Erlich, H.A., Julier, C., Morahan, G., Nerup, J., Nierras, C. et al., 2009. Genome-wide association study and meta-analysis finds over 40 loci affect risk of type 1 diabetes. Nature Genetics 41, 703–707.

Bennett, S.T., Lucassen, A.M., Gough, S.C.L., Powell, E.E., Undlien, D.E., Pritchard, L.E., Merriman, M.E., Kawaguchi, Y., Dronsfield, M.J., Pociot, F. et al., 1995. Susceptibility to human type 1 diabetes at IDDM2 is determined by tandem repeat variation at the insulin gene minisatellite locus. Nature Genetics 9, 284–292.

Bottini, N., Musumeci, L., Alonso, A., Rahmouni, S., Nika, K., Rostamkhani, M., Macmurray, J., Meloni, G.F., Lucarelli, P., Pellecchia, M. et al., 2004. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. Nature Genetics 36, 337-8.

Bowman, P., Flanagan, S.E., Hattersley, A.T., 2018. Future roadmaps for precision medicine applied to diabetes: Rising to the challenge of heterogeneity. Journal of Diabetes Research 2018, 1–12.

Bradfield, J.P., Qu, H.-Q., Wang, K., Zhang, H., Sleiman, P.M., 2011. A genome-wide meta-analysis of six type 1 diabetes cohorts identifies multiple associated loci. PLoS Genetics 7, 1002293.

Burton, P.R., Clayton, D.G., Cardon, L.R., Craddock, N., Deloukas, P., Duncanson, A., Kwiatkowski, D.P., McCarthy, M.I., Ouwehand, W.H., Samani, N.J., et al., 2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447, 661–678.

Catchpole, B., Adams, J.P., Holder, A.L., Short, A.D., Ollier, W.E.R., Kennedy, L.J., 2013. Genetics of canine diabetes mellitus : Are the diabetes susceptibility genes identified in humans involved in breed susceptibility to diabetes mellitus in dogs ? The Veterinary Journal 195, 139–147.

Caywood, D.D., Klausner, J.S., O’Leary, T.P., Withrow, S.J., Richardson, R.C., Harvey, H.J., Norris, A.M., Henderson, R.A., Johnston, S.D., 1988. Pancreatic insulin-secreting neoplasma: Clinical, diagnostic, and prognostic features in 73 dogs. The Journal of the American Animal Hospital Association 24, 577-84.

Cervin, C., Lyssenko, V., Bakhtadze, E., Lindholm, E., Nilsson, P., Tuomi, T., Cilio, C.M., Groop, L., 2008. Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes. Diabetes 57, 1433-7.

Colombo, C., Porzio, O., Liu, M., Massa, O., Vasta, M., Salardi, S., Beccaria, L., Monciotti, C., Toni, S., Pedersen, O. et al., Early Onset Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetes (SIEDP), 2008. Seven mutations in the human insulin gene linked to permanent neonatal/infancy-onset diabetes mellitus. The Journal of Clinical Investigation 118, 2148–56.

Concannon, P., Rich, S.S., Nepom, G.T., 2009. Genetics of type 1A diabetes. New England Journal of Medicine 360, 1646–1654.

Cotsapas, C., Voight, B. F., Rossin, E., Lage, K., Neale, B. M., Wallace, C., Abecasis, G. R., Barrett, J. C., Behrens, T., Cho, J. et al., 2011. Pervasive sharing of genetic effects in autoimmune disease. PLoS genetics 7, e1002254.

Cousminer, D.L., Ahlqvist, E., Mishra, R., Andersen, M.K., Chesi, A., Hawa, M.I., Davis, A., Hodge, K.M., Bradfield, J.P., Zhou, K. et al., 2018. First genome-wide association study of latent autoimmune diabetes in adults reveals novel insights linking immune and metabolic diabetes. Diabetes Care 41, 2396–2403.

Cucca, F., Lampis, R., Congia, M., Angius, E., Nutland, S., Bain, S.C., Barnett, A.H., Todd, J.A., 2001. A correlation between the relative predisposition of MHC class II alleles to type 1 diabetes and the structure of their proteins. Human Molecular Genetics 10, 2025–37.

Davison, L.J., Catchpole, B., Ristic, J., Herrtage, M.E., 2001. Research into canine diabetes mellitus. Veterinary Record 148, 352.

Davison, L.J., Herrtage, M.E., Catchpole, B., 2005. Study of 253 dogs in the United Kingdom with diabetes mellitus. Veterinary Record 156, 467–471.

Davison, L.J., Holder, A., Catchpole, B., O’Callaghan, C.A., 2017. The Canine POMC Gene, obesity in labrador retrievers and susceptibility to diabetes mellitus. Journal of Veterinary Internal Medicine 31, 343–348.

Debenham, S.L., Hart, E.A., Ashurst, J.L., Howe, K.L, Quail, M.A., Ollier, W.E., Binns M.M., 2005. Genomic sequence of the class II region of the canine MHC: Comparison with the MHC of other mammalian species. Genomics 85, 48-59.

Denyer A. L., Massey J. P., Davison L. J., Ollier W. E. R., Catchpole B., Kennedy L. J., 2020. Dog leucocyte antigen (DLA) class II haplotypes and risk of canine diabetes mellitus in specific dog breeds. Canine Medicine and Genetics 7, 15.

Desai, M., Zeggini, E., Horton, V.A., Owen, K.R., Hattersley, A.T., Levy, J.C., Hitman, G.A., Walker, M., Holman, R.R., Mccarthy, et al., 2006. The variable number of tandem repeats upstream of the insulin gene is a susceptibility locus for latent autoimmune diabetes in adults. Diabetes 55, 1890–1894.

Dooley, J., Tian, L., Schonefeldt, S., Delghingaro-Augusto, V., Garcia-Perez, J.E., Pasciuto, E., Di Marino, D., Carr, E.J., Oskolkov, N., Lyssenko, V. et al., 2016. Genetic predisposition for beta cell fragility underlies type 1 and type 2 diabetes. Nature Genetics 48, 519–27.

Erlich, H., Valdes, A.M., Noble, J., Carlson, J.A., Varney, M., Concannon, P., Mychaleckyj, J.C., Todd, J.A., Bonella, P., Fear, A.L. et al., 2008. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk analysis of the type 1 diabetes genetics consortium families. Diabetes 57, 1084-92.

Flanagan, S.E., Clauin, S., Bellanné-Chantelot, C., de Lonlay, P., Harries, L.W., Gloyn, A.L., Ellard, S., 2009. Update of mutations in the genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 ( *KCNJ11* ) and sulfonylurea receptor 1 ( *ABCC8* ) in diabetes mellitus and hyperinsulinism. Human Mutation 30, 170–180.

Florez, J.C., Burtt, N., de Bakker, P.I.W., Almgren, P., Tuomi, T., Holmkvist, J., Gaudet, D., Hudson, T.J., Schaffner, S.F., Daly, M.J. et al., 2004. Haplotype structure and genotype-phenotype correlations of the sulfonylurea receptor and the islet ATP-sensitive potassium channel gene region. Diabetes 53, 1360–1368.

Friedenberg, S.G., Buhrman, G., Chdid, L., Olby, N.J., Olivry, T., Guillaumin, J., O'Toole,

T., Goggs, R., Kennedy, L.J., Rose, R.B., et al., 2016. Evaluation of a DLA-79 allele associated with multiple immune-mediated diseases in dogs. Immunogenetics 68, 205–217.

Fuchsberger, C., Flannick, J., Teslovich, T.M., Mahajan, A., Agarwala, V., Gaulton, K.J., Ma, C., Fontanillas, P., Moutsianas, L., McCarthy, D.J. et al., 2016. The genetic architecture of type 2 diabetes. Nature 536, 41–47.

Gaulton, K.J. 2017. Mechanisms of type 2 diabetes risk Loci. Current Diabetes Reports 17,72.

Grant, S.F.A., Hakonarson, H., Schwartz, S., 2010. Can the genetics of type 1 and type 2 diabetes shed light on the genetics of latent autoimmune diabetes in adults? Endocrinology Reviews 31, 183–193.

Grotz, A.K., Gloyn, A.L., Thomsen, S.K., 2017. Prioritising causal genes at type 2 diabetes risk loci. Current Diabetes Reports 17, 76.

Hani, E.H., Boutin, P., Durand, E., Inoue, H., Permutt, M.A., Velho, G., Froguel, P., 1998. Missense mutations in the pancreatic islet beta cell inwardly rectifying K + channel gene (KIR6.2/BIR ): A meta-analysis suggests a role in the polygenic basis of type II diabetes mellitus in Caucasians. Diabetologia 41, 1511–1515.

Hattersley, A.T., Ashcroft, F.M., 2005. Activating mutations in Kir6.2 and neonatal diabetes new clinical syndromes, new scientific insights, and new therapy. Diabetes 54, 2503-13.

Hayward, J.J., Castelhano, M.G., Oliveira, K.C., Corey, E., Balkman, C., Baxter, T.L., Casal, M.L., Center, S.A., Fang, M., Garrison, S.J. et al., 2016. Complex disease and phenotype mapping in the domestic dog. Nature Communications 7, 10460.

Holder, A.L., Kennedy, L.J., Ollier, W.E.R., Catchpole, B., 2015. Breed differences in development of anti-insulin antibodies in diabetic dogs and investigation of the role of dog leukocyte antigen (DLA) genes. Veterinary Immunology and Immunopathology 167, 130–8.

Jagannathan, V., Drögemüller, C., Leeb, T., Dog Biomedical Variant Database Consortium (DBVDC), 2019. A comprehensive biomedical variant catalogue based on whole genome sequences of 582 dogs and eight wolves. Animal Genetics 50, 695-704.

Karlsson, E.K., Lindblad-toh, K., 2008. Leader of the pack: Gene mapping in dogs and other model organisms. Nature Reviews Genetics 9, 713-25.

Kennedy, L.J., Angles, J.M., Barnes, A., Carter, S.D., Francino, O., Gerlach, J.A., Happ, G.M., Ollier, W.E.R., Thomson, W., Wagner, J.L., 2001. Nomenclature for factors of the dog major histocompatibility system (DLA), 2000: Second report of the ISAG DLA Nomenclature Committee. Tissue Antigens 58, 55–70.

Kennedy, L.J., Barnes, A., Happ, G.M., Quinnell, R.J., Bennett, D., Angles, J.M., Day, M.J., Carmichael, N., Innes, J.F., Isherwood, D. et al., 2002. Extensive interbreed, but minimal intrabreed, variation of DLA class II alleles and haplotypes in dogs. Tissue Antigens 59, 194–204.

Kennedy, L.J., Davison, L.J., Barnes, A., Short, A.D., Fretwell, N., Jones, C.A., Lee, A.C., Ollier, W.E.R., Catchpole, B., 2006. Identification of susceptibility and protective major histocompatibility complex haplotypes in canine diabetes mellitus. Tissue Antigens 68, 467–476.

Klupa, T., Skupien, J., Mirkiewicz-Sieradzka, B., Gach, A., Noczynska, A., Zubkiewicz-Kucharska, A., Szalecki, M., Kozek, E., Nazim, J., et al., 2010. Efficacy and safety of sulfonylurea use in permanent neonatal diabetes due to *KCNJ11* gene mutations: 34-month median follow-up. Diabetes Technology and Therapeutics 12, 387–391.

Kramer, J.W., Nottingham, S., Robinette, J., Lenz, G., Sylvester, S., Dessouky, M.I., 1980. Inherited, early onset, insulin-requiring diabetes mellitus of Keeshond dogs. Diabetes 29, 558–65.

Lequarré, A.-S., Andersson, L., André, C., Fredholm, M., Hitte, C., Leeb, T., Lohi, H., Lindblad-Toh, K., Georges, M., 2011. LUPA: A European initiative taking advantage of the canine genome architecture for unravelling complex disorders in both human and dogs. The Veterinary Journal 189, 155–159.

Liston, A., Todd, J.A., Lagou, V., 2017. Beta-cell fragility as a common underlying risk factor in type 1 and type 2 diabetes. Trends in Molecular Medicine 23, 181-194.

Loscalzo J., 2019. Network medicine and type 2 diabetes mellitus: Insights into disease mechanism and guide to precision medicine. Endocrine 66(3), 456-459.

Lowe, C.E., Cooper, J.D., Brusko, T., Walker, N.M., Smyth, D.J., Bailey, R., Bourget, K., Plagnol, V., Field, S., Atkinson, M. et al., 2007. Large-scale genetic fine mapping and genotype-phenotype associations implicate polymorphism in the IL2RA region in type 1 diabetes. Nature Genetics 39, 1074–1082.

Mahajan, A., Taliun, D., Thurner, M., Robertson, N.R., Torres, J.M., Rayner, N.W., Payne, A.J., Steinthorsdottir, V., Scott, R.A., Grarup, N., et al., 2018. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nature Genetics 50, 1505–1513.

Mattis, K.K., Gloyn, A.L., 2020. From genetic association to molecular mechanisms for islet-cell dysfunction in type 2 diabetes. Journal of Molecular Biology 432(5), 1551-1578.

McCarthy, M.I., Zeggini, E., 2009. Genome-wide association studies in type 2 diabetes. Current Diabetes Reports 9, 164–71.

Mellersh C., 2008. Give a dog a genome. The Veterinary Journal 178(1), 46–52.

Misra, S., Owen, K.R., 2018. Genetics of monogenic diabetes: Present clinical challenges. Current Diabetes Reports 18, 141.

Nejentsev, S., Walker, N., Riches, D., Egholm, M., Todd, J.A., 2009. Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. Science 324, 387–389.

Noble, J.A., Valdes, A.M., Cook, M., Klitz, W., Thomson, G., Erlich, H.A., 1996. The role of HLA class II genes in insulin-dependent diabetes mellitus: Molecular analysis of 180 Caucasian, multiplex families. American Journal of Human Genetics 59, 1134–1148.

Nyaga, D.M., Vickers, M.H., Jefferies, C., Perry, J.K., O’Sullivan, J.M., 2018. The genetic architecture of type 1 diabetes mellitus. Molecular and Cellular Endocrinology 477, 70–80.

O’Kell, A.L., Wasserfall, C., Catchpole, B., Davison, L.J., Hess, R.S., Kushner, J.A., Atkinson, M.A., 2017. Comparative pathogenesis of autoimmune diabetes in humans, NOD mice, and canines: Has a valuable animal model of type 1 diabetes been overlooked? Diabetes 66, 1443–1452.

O’Neal, K.S., Johnson, J.L., Panak, R.L., 2016. Recognizing and appropriately treating latent autoimmune diabetes in adults. Diabetes Spectrum 29, 249–252.

Palmer, J.P., Hampe, C.S., Chiu, H., Goel, A., Brooks-Worrell, B.M., 2005. Is latent autoimmune diabetes in adults distinct from type 1 diabetes or just type 1 diabetes at an older age? Diabetes 54 Suppl 2:S62-7.

Pang, H., Luo, S., Huang, G., Xia, Y., Xie, Z., Zhou, Z., 2020. Advances in knowledge of candidate genes acting at the beta-cell level in the pathogenesis of T1DM. Frontiers in Endocrinology (Lausanne) 11, 119.

Pearson, E.R., Flechtner, I., Njølstad, P.R., Malecki, M.T., Flanagan, S.E., Larkin, B., Ashcroft, F.M., Klimes, I., Codner, E., Iotova, V. et al., 2006. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. New England Journal of Medicine 355, 467–477.

Polak, M., Dechaume, A., Cavé, H., Nimri, R., Crosnier, H., Sulmont, V., de Kerdanet, M., Scharfmann, R., Lebenthal, Y., Froguel, P. et al., 2008. Heterozygous missense mutations in the insulin gene are linked to permanent diabetes appearing in the neonatal period or in early infancy: A report from the French ND (Neonatal Diabetes) Study Group. Diabetes 57, 1115–9.

Polychronakos, C., Li, Q., 2011. Sibling relative risk understanding type 1 diabetes through genetics: Advances and prospects. Nature Reviews Genetics 12, 781-92.

Reuter, J.A., Spacek, D.V., Snyder, M.P., 2015. High-throughput sequencing technologies. Molecular Cell 58, 586–597.

Rotter, J.I., Landaw, E.M., 1984. Measuring the genetic contribution of a single locus to a multilocus disease. Clinical Genetics 26, 529–42.

Safra, N., Pedersen, N.C., Wolf, Z., Johnson, E.G., Liu, H.W., Hughes, A.M., Young, A., Bannasch, D.L., 2011. Expanded dog leukocyte antigen (DLA) single nucleotide polymorphism (SNP) genotyping reveals spurious class II associations. The Veterinary Journal 189, 220–226.

Scott, R.A., Scott, L.J., Mägi, R., Marullo, L., Gaulton, K.J., Kaakinen, M., Pervjakova, N., Pers, T.H., Johnson, A.D., Eicher, J.D. et al., DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, 2017. An expanded genome-wide association study of type 2 diabetes in Europeans. Diabetes 66, 2888–2902.

Seddon, J.M., Berggren, K.T., Fleeman, L.M., 2010. Evolutionary history of DLA class II haplotypes in canine diabetes mellitus through single nucleotide polymorphism genotyping. Tissue Antigens 75, 218–226.

Shepherd, M., Shields, B., Hammersley, S., Hudson, M., McDonald, T. J., Colclough, K., Oram, R. A., Knight, B., Hyde, C., Cox, J. et al., 2016. systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the U.K. pediatric diabetes population with monogenic diabetes. Diabetes Care 39, 1879–1888.

Shiina, T., Hosomichi, K., Inoko, H., Kulski, J.K., 2009. The HLA genomic loci map: Expression, interaction, diversity and disease. Journal of Human Genetics 54, 15–39.

Short, A.D., Catchpole, B., Kennedy, L.J., Barnes, A., Fretwell, N., Jones, C., Thomson, W., Ollier, W.E.R., 2007. Analysis of candidate susceptibility genes in canine diabetes. Journal of Heredity 98, 518–525.

Short, A.D., Catchpole, B., Kennedy, L.J., Barnes, A., Lee, A.C., Jones, C.A., Fretwell, N., Ollier, W.E.R., 2009. T cell cytokine gene polymorphisms in canine diabetes mellitus. Veterinary Immunology and Immunopathology 128, 137–146.

Short, A.D., Holder, A., Rothwell, S., Massey, J., Scholey, R., Kennedy, L.J., Catchpole, B., Ollier, W.E., 2014. Searching for ‘monogenic diabetes’ in dogs using a candidate gene approach. Canine Genetics and Epidemiology 1, 8.

Short, A.D., Saleh, N.M., Catchpole, B., Kennedy, L.J., Barnes, A., Jones, C.A., Fretwell, N., 2010. CTLA4 promoter polymorphisms are associated with canine diabetes mellitus. Tissue Antigens 75, 242–252.

Steck, A.K., Rewers, M.J., 2011. Genetics of type 1 diabetes. Clinical Chemistry 57, 176.

Todd, J.A., Bell, J.I., McDevitt, H.O., 1987. HLA-DQβ gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. Nature 329, 599–604.

Todd, J.A., Walker, N.M., Cooper, J.D., Smyth, D.J., Downes, K., Plagnol, V., Bailey, R., Nejentsev, S., Field, S.F., Payne, F. et al., 2007. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nature Genetics 39, 857–864.

Tuomi, T., Santoro, N., Caprio, S., Cai, M., Weng, J., Groop, L., 2014. The many faces of diabetes: A disease with increasing heterogeneity. Lancet 383, 1084–1094.

Ueda, H., M Howson, J.M., Esposito, L., Heward, J., Snook, H., Chamberlain, G., Rainbow, D.B., D Hunter, K.M., Smith, A.N., Di Genova, G. et al., 2003. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature 423, 506-11.

Vafiadis, P., Bennett, S.T., Todd, J.A., Nadeau, J., Grabs, R., Goodyer, C.G., Wickramasinghe, S., Colle, E., Polychronakos, C., 1997. Insulin expression in human thymus is modulated by INS VNTR alleles at the IDDM2 locus. Nature Genetics 15, 289–292.

Wellcome Trust Case Control Consortium, 2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447, 661–678.

Zamani, M., Cassiman, J.J., 1998. Reevaluation of the importance of polymorphic HLA class II alleles and amino acids in the susceptibility of individuals of different populations to type I diabetes. American Journal of Medical Genetics 76, 183–194.

Zeggini, E., Scott, L.J., Saxena, R., Voight, B.F., Marchini, J.L., Hu, Tainle, de Bakker, P.I., Abecasis, G.R., Almgren, P., Andersen, G. et al., 2008. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nature Genetics 40, 638–645.

**Table 1**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| DRB1 | DQA1 | DQB1 | Frequency in diabetic dogs (%) (*n* = 460) | Frequency in controls (%)  (*n* = 1047) | Odds ratio | 95% confidence interval | *P* |
| 002 | 009 | 001 | 11.7 | 8.1 | 1.51 | 1.03 – 2.19 | 0.03 |
| 009 | 001 | 008 | 12 | 6.2 | 2.05 | 1.38 – 3.04 | 0.0002 |
| 015 | 006 | 023 | 34.4 | 25.6 | 1.52 | 1.19-1.94 | 0.0006 |

Frequencies of three-locus DLA haplotypes found at increased frequency in diabetic dogs vs. controls (Kennedy et al., 2006).

**Figure legends**

Fig. 1. Examples of techniques for the study of genetic disease.

Fig. 2. The major histocompatibility complex (MHC).

Fig. 3. Selected examples of genes in which variants have been associated with (a) human type 1, type 2 or monogenic diabetes mellitus (DM) or (b) canine DM. Examples are not a comprehensive list since, in humans, there are more than 60 genes associated with type 1 diabetes and more than 200 associated with type 2 diabetes. Associations in dogs may have been identified in single or multiple breeds. (Short et al., 2007, 2009, 2010, 2014; Catchpole et al., 2013; Gaulton, 2017; Misra and Owen, 2018; Bakay et al., 2019). SNP, single nucleotide polymorphism; VNTR, variable number tandem repeat.

Fig. 4. Illustration of canine MHC genes and proteins. The canine MHC class I and class II genes (also known as Dog Leukocyte Antigen or DLA genes) are located on chromosome 12; functional antigen presenting genes are illustrated (Debenham et al., 2005). MHC proteins encoded by these genes are expressed on the cell surface; examples are shown. MHC class II proteins are formed by two subunits, encoded by two neighbouring genes (e.g. DLA-DRA1 and -DRB1) whereas the α-chain of a class I molecule is encoded by a single DLA gene (e.g. DLA-88). Exon 2 of the DLA genes encodes the hypervariable region of the antigen binding groove, which mediates antigen presentation to T cells, to influence the immune response.

1. See: Online Mendelian Inheritance in Man (OMIM). <https://www.omim.org/> (Accessed 7 January 2021) [↑](#footnote-ref-1)
2. See: Dog Genome SNP Database. <http://bigd.big.ac.cn/dogsdv2/> (Accessed 7 January 2021) [↑](#footnote-ref-2)
3. See: Dog 10k Genomes Project. <http://www.dog10kgenomes.org/> (Accessed 7 January 2021) [↑](#footnote-ref-3)
4. See: For submission information visit <https://www.rvc.ac.uk/diabetesregister/> (Accessed 7 January 2021) [↑](#footnote-ref-4)
5. See: Canine Diabetes Genetics Partnership. <https://www.caninediabetesgenetics.org/> (Accessed 7 January 2021) [↑](#footnote-ref-5)