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GENETIC BASIS OF IMMUNE-MEDIATED DISEASE
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Introduction

The four major forms of immune-mediated disease are hypersensitivity, autoimmunity, immunodeficiency and immune system neoplasia\(^1\). These are all examples of disturbance of normal immune system homeostasis. The various immune-mediated disorders are linked together and immunological disturbance may be manifest clinically as more than a single type of disease occurring concurrently in any one individual (e.g. concurrent IgA deficiency and autoimmunity). Immune-mediated diseases are multifactorial and their clinical expression depends upon the optimum interaction of a range of predisposing factors. One of the most important of these predisposing factors is genetic background, the discussion of which forms the subject of this presentation.

Genetic Basis for Immune Disease

Immune-mediated diseases have distinct predispositions in particular races of man, and are clearly inherited through families. A similar situation exists for breeds of dog – but in feline medicine such associations are rarely documented. Examples of familial canine autoimmunity, hypersensitivity and immunodeficiency are also documented, and there are anecdotal reports of pedigrees of dog in which lymphoma occurs frequently. One factor underlying this phenomenon is likely to be the degree of inbreeding which over the past two centuries has led to the development of many of the pure breeds of dog that we recognize today\(^2\). Recent studies using microsatellite makers and investigation of specific gene polymorphisms have demonstrated the extent of inbreeding amongst some pedigrees\(^3\). Such genetic influence might also underlie the apparent geographical prevalence of some immune-mediated diseases, for example canine autoimmunity appears to arise more commonly in Australia than in the UK which may reflect a 'founder effect' in some breeds.

Despite these observations, relatively little is understood of the precise genetic basis for immune-mediated disease with the exception of the characterisation of specific molecular defects underlying certain canine immunodeficiency diseases. Some gene clusters do have strong associations with immune-mediated disease, either because the protein products of the genes are integrally involved in the aberrant immune-response, or because the genes are 'markers' of poorly defined causative 'disease genes'. Examples of this are the associations between the gene cluster that encodes the type 2 cytokines (IL-4, IL-5, IL-13) and type I hypersensitivity disease, and the association between particular genes of the Major Histocompatibility Complex (MHC) and autoimmunity. There are now two versions of the canine genome and a partial version of the feline genome available for access. This information, together with modern genomic technology, has led
to a reawakening of interest in comparative genomics and there is likely to be an explosion in knowledge of the genetic basis of canine disease in the near future.

The genetic basis for canine autoimmunity

It is now widely recognized that autoimmunity is multifactorial in aetiology. One of the most significant predisposing factors is genetic background, but human identical twin studies have repeatedly shown that this is not the sole determinant of the development of clinical autoimmune disease. In humans (but not dogs) there is a strong hormonal influence with a marked female predisposition. Lifestyle factors such as stress and diet also play a role. Additionally, a wide range of environmental influences play a part in triggering autoimmunity and these include: exposure to infectious agents, drugs, vaccines or UV light.

In humans, particular autoimmune diseases occur more frequently in certain races and are often familial in nature. Similarly, particular breeds of dog more often develop autoimmune diseases and these clearly run through pedigree groups. The genes most closely associated with genetic predisposition to autoimmune disease are those clustered on a single chromosome to form the major histocompatibility complex (MHC). The class I, II and III genes of this complex are integral to immune function and are often termed ‘immune response genes’. Moreover, these are the most polymorphic genes within the genome with several hundred alleles now documented at some human class I loci. The products of class I and class II genes are involved in the presentation of antigenic peptides by antigen presenting cells (APC) for the activation of T lymphocytes. It is likely that particular allotypic variants of these MHC molecules might be most effective at presentation of self-peptides for triggering of auto-reactive T cell populations.

In consequence of this knowledge, the science of MHC-disease association has been widely developed in human medicine where it is clear that the inheritance of particular combinations (haplotypes) of MHC alleles either predisposes to, or protects from, development of autoimmunity. Similar studies have been conducted in the dog. In the late 1970s and early 1980s, using relatively crude serological and cellular methodology, associations were shown between canine autoimmune disease and MHC gene type. Over the past decade there has been a resurgence of interest in this field with the application of sophisticated molecular technology for determining the MHC genotype of an individual dog. In the UK, these studies have been undertaken by a consortium of the veterinary schools in collaboration with the major human reference laboratory at the University of Manchester. Currently, a major European initiative is seeking funds to establish an international collaboration in studies of the genetic basis of canine disease.

MHC-disease associations have now been clearly documented for canine immune-mediated haemolytic anaemia (IMHA), lymphocytic thyroiditis, diabetes mellitus and rheumatoid arthritis (RA). Similar associations have been shown to underlie immunological susceptibility or resistance to infection.
by *Leishmania*. Both protective and susceptibility haplotypes for some of these diseases have been documented. Of greatest interest is the investigation into RA where it has been shown that there is structural similarity between the MHC class II molecule encoded by the gene most highly linked to the disease phenotype in both man and dog. This in turn suggests that a common peptide antigen might be involved in triggering the disease in both species. In the case of diabetes mellitus and hypothyroidism, a common susceptibility haplotype suggests linkage in the mechanisms underlying autoimmune endocrinopathy.

**The Genetic Basis for Canine Allergy**

There are clear breed predispositions for the development of type I hypersensitivity diseases in the dog. The most widely recognized of these would be the susceptibility of West Highland White Terriers (WHWT), and Golden Retrievers or Labradors for atopic dermatitis. Husky dogs have a predisposition to the development of the putative allergic respiratory disease, canine eosinophilic bronchopneumopathy.¹⁰

There have been two major investigations of the heritability of atopic dermatitis in WHWT and Labrador Retrievers, but these have not clearly identified a distinct mode of inheritance. To date, there has not been extensive investigation of inheritance of canine allergy at the molecular level. However, as the immunopathogenesis of these diseases is now well-defined, there are numerous ‘candidate gene’ polymorphisms that might be studied. This may not necessarily provide a clear outcome – as extensive research in humans has failed to identify an ‘allergy gene’, although numerous candidates have been investigated and show varying degrees of linkage to clinical phenotype.¹¹

**The Genetic Basis for Canine Immunodeficiency**

Primary, congenital immunodeficiency disease is most widely recognized in the dog, where approximately 20 distinct entities are documented. The majority of these remain ‘putative’ immunodeficiency disorders in which there has been relatively limited investigation of the nature of the underlying immune defect. By contrast, there is a small number of canine immunodeficiency diseases for which the inherited defect is well-characterized, and for which molecular diagnostic tests have been developed. These include: X-linked severe combined immunodeficiency (X-SCID) in the Bassett, Corgi and Jack Russell Terrier, cyclic neutropenia in the grey Collie, and canine leukocyte adhesion deficiency (CLAD) in the Irish Setter. These disorders are autosomal recessive with heterozygous carriers and homozygous affected animals. The most prevalent disease is CLAD, but active testing and controlled breeding programmes in several countries mean that this mutation is close to being eliminated.¹²

**The Genetic Basis for Canine Immune System Neoplasia**
There is clear clinical evidence that particular canine breeds are more susceptible to certain types of immune system neoplasia. For example dogs of the Boxer breed have elevated risk of developing lymphoma or mast cell tumour\textsuperscript{17} and the range of histiocytic neoplasms are well-documented in Bernese Mountain Dogs and Flat Coat Retrievers\textsuperscript{18}. These tumours are also known to arise within particular pedigrees of these breeds. Despite the clinical importance of these neoplasms, there has to date been no investigation of candidate genes that might predispose to malignant transformation.

References