

GENETICS OF AUTOIMMUNE DISEASE

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Autoimmune diseases are common conditions which affect up to 10% of the general population. The reasons why individuals develop an autoimmune disease are largely unknown. It seems to develop in genetically susceptible individuals and the course of the disease can be influenced in a permissive or in a protective way.

To study the genetic risk of getting an autoimmune disease several approaches have been used. The oldest and most simple way is the simple description of the same autoimmune disease occurring in different members of the same family. These multicaser families with autoimmunity suggest a genetic modified etiology as well as the possibility of shared environmental factors in the pathogenesis of these diseases. Other approaches are concordance studies in monozygotic and dizygotic twins. Concordance rates for autoimmune diseases in monozygotic twins are between 30% and 70% but not 100% (Table 1) indicating that these diseases are a result of genetic and environmental factors.

Table 1. Concordance rates in monozygotic and dizygotic twins

Disease	Percent (%) concordance in twins	
	monozygotic	dizygotic
Psoriasis	65 - 70	15 - 20
Rheumatoid arthritis	12 - 30	4
Ankylosing spondylitis	63	23
SLE	24 - 69	2 - 9
Multiple sclerosis	30	3 - 4
Myasthenia gravis	40	
IDDM	53	11

In addition that these observations of finding the same autoimmune diseases within families also a tendency for multiple different autoimmune diseases can be seen with

increased frequency among first and second degree relatives of a person with a given autoimmune disease. These observations imply the possibility that common genes predispose to different forms of autoimmunity. There are two ways in humans which have been used to identify susceptibility genes of common diseases either by testing hypothesized candidate genes or by whole genome scanning methods. Candidate genes are genes located in a chromosome region suspected of being involved in a disease. Candidate gene studies using cohort comparisons between affected patients and racially and geographically matched healthy controls have shown that the major histocompatibility complex (MHC) region on chromosome 6 has the strongest association with most immune-mediated diseases. Also other polymorphic genetic loci including genes encoding cytokines and cytokine receptors, T-cell receptors, immunoglobulins, Fc receptors and autoantigens have been identified as risk factors for various autoimmune diseases but their statistical association with disease has been found to be weaker than those of the MHC complex. Nevertheless these other genetic loci are involved in autoimmune diseases as secondary risk factors.

The HLA region on chromosome 6p21 can be split into three different parts called class I, class II and class III. The class I region encodes HLA-A, HLA-B and HLA-C molecules which are expressed on the cell surface of nucleated cells involved in the presentation of endogenous antigens to CD8+ cytotoxic T (Tc) cells. The class II region encodes many membrane-bound proteins expressed on the cell surfaces of B-lymphocytes, macrophages, dendritic cells and activated T lymphocytes, which are involved in the processing and presentation of exogenous antigens to CD4+ T-helper (Th) cells. The class III region is located between the class I and class II regions and contains genes encoding components of the complement region (C2 and C4), the heat shock protein (HSP70) and the tumour necrosis factors (TNF).

HLA class I antigens have been associated with psoriasis. According to the age of onset psoriasis has been subdivided into a familial early age (< 40 years) of onset form (type I) and a sporadic late onset form with no family history (type II). Type I psoriasis has a high association to genes of the MHC complex most strongly with HLA-Cw6 and HLA-B57. HLA-Cw6 seems to influence the age of disease onset with concordance rates of 80% in developing the disease before 20 years of age. Up to 30% of psoriasis patients develop psoriatic arthritis (PsA) making PsA to one of the most often spondylarthropathies. PsA patients with psoriasis type I show similar HLA associations as type I patients without arthritis but different from patients with arthritis and late onset disease. HLA-B27 has been related to spine involvement and HLA-B39 to polyarthritic disease in PsA patients.

HLA-B27 is found in a healthy white population in about 8% but in patients with spondylarthropathies with increased rates (ankylosing spondylitis 95% of patients, reactive arthritis 70%, psoriatic arthritis 60%, psoriatic arthritis with peripheral arthritis 25%, spondylitis with inflammatory bowel disease 70%, acute anterior uveitis without any other stigmata of spondyloarthritis 50%). The exact mechanism underlying the effect of HLA-B27 on disease susceptibility is still unknown. Interestingly no association of HLA-B27 is seen in patients with spondylarthritis in Africa.

HLA class II region contributes to most autoimmune diseases. The underlying mechanisms remain unknown but seem to be different for each disease.

In insulin-dependent diabetes mellitus (IDDM) about 34% of familial clustering is due to the MHC class II region. HLA alleles associated with diabetes susceptibility include HLA-DR3 and HLA-DR4 whereas others are associated with disease protection like HLA-DR2. On the other hand HLA-DR2 seems to predispose to multiple sclerosis (MS). The protective nature of HLA-DR2 in IDDM and the predisposing nature in MS could be the reason why it is rare to see clustering of MS in IDDM and vice versa. In MS the specific genes with increased risk are the HLA-DR and the HLA-DQ genes, the HLA-DR15 haplotype in Caucasians and other DRs in ethnically more distant populations.

HLA-DR4 phenotype is regarded as a genetic determinant commonly associated with rheumatoid arthritis (RA). The major susceptibility alleles associated with RA are the HLA-DR4 alleles DRB1*0401 and DRB1*0404. Caucasians with DRB1*0401/0404 seem to have a higher risk of a more severe form of RA.

HLA-DR3 appears to be a general autoimmune haplotype not only associated with IDDM but also with systemic lupus erythematoses (SLE), Graves' disease, autoimmune hypothyroidism and Addison's disease. Among all immunogenes tested in complex and autoimmune liver diseases strongest disease associations were found with the MHC HLA class II genes DR and DQ.

The HLA class III region contains many genes encoding proteins which are unrelated to cell-mediated immunity but modulate or regulate immune responses in some way, including tumour necrosis factor, heat shock proteins and complement proteins (C2, C4). The complement genes C2 and C4 have shown to be associated with SLE with an incidence of 75% of C4 homozygous subjects and 33% of C2 homozygous subjects developing SLE. The hierarchy of susceptibility amongst these components is C1q>C4>C2 in disease risk order.

Also other genes beside the HLA genes seem to be involved in susceptibility for autoimmune diseases. Organ specific autoimmune disease susceptibility loci are for example the insulin gene (INS) region on chromosome 11p15 or the cytotoxic T-lymphocyte-associated-4 (CTLA-4) gene on chromosome 2q33. CTLA-4 was first identified as a candidate gene in Graves' disease but is an equally strong candidate for other T-cell mediated autoimmune diseases like IDDM. Non-organ specific autoimmune disease susceptibility loci are for example genes for proinflammatory cytokines like TNF or IL-1.

Genetic susceptibility to the development of autoimmune disease is a complex subject with many different genes and their products interacting with each other and interacting with external stimuli. Certain gene regions, especially HLA, are likely to cause susceptibility to more than one autoimmune disease and might explain the clustering of diseases within the same families and individuals.

Literature

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