

# Genetics of autoimmune disease

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## ABSTRACT

*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. 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.*

*Considerable evidence indicates that all of the common autoimmune diseases (rheumatoid arthritis, type 1 diabetes, SLE, multiple sclerosis, etc.) have a strong genetic predisposition. Much of this evidence has come from genetic epidemiology studies. Certain major histocompatibility complex (MHC) class II allotypes are strongly correlated with specific autoimmune diseases. HLA class II region contributes to most autoimmune diseases. The underlying mechanisms remain unknown but seem to be different for each disease. HLA DR2 is strongly positively correlated with systemic lupus erythematosus (SLE) and multiple sclerosis (MS), and negatively correlated with type 1 diabetes mellitus (DM 1). HLA DR3 is correlated strongly with Sjögren's syndrome, myasthenia gravis (MG), SLE and DM 1. HLA DR4 is correlated with the genesis of rheumatoid arthritis (RA), DM 1 and pemphigus vulgaris. 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). Also other genes beside the HLA genes seem to be involved in susceptibility for autoimmune diseases.*

**Key words:** genetic factors, HLA, autoimmune disease, susceptibility

**A**utoimmune diseases seem to also have a hereditary component, but mysteriously, they cluster in families as different illnesses. For example, a mother may have lupus erythematosus; her daughter, diabetes; her grandmother, rheumatoid arthritis. Autoimmune disorders have a complex genetic basis, with multiple genes contributing to disease risk,

each with generally modest effect independently. Most diseases if not all, affecting human populations are determined by genes and by the surrounding environment. The factors and the complex mechanisms that are involved in the development of pathological autoimmunity are incompletely understood. The extend to which genes are important depends on several factors such as penetrance, genetic interactions,

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and gene-environment interactions. The general concept that autoimmunity develops in the setting of genetic susceptibility, and in particular in association with a series of specific HLA alleles, applies to most human autoimmune disorders. It is important to note, however, that the same HLA allele may protect from one and yet be associated with another disorder (e.g., the HLA-DR2 associated allele, DQA1\*0102, DQB1\*0602 is rare in patients with type 1 diabetes but is associated with multiple sclerosis). It appears that susceptibility encoded by alleles within the HLA region do not globally influence the development of autoimmunity, but rather influence the likelihood of specific disorders. The genes involved are likely to play a part in immune regulation. An alternative manner by which HLA alleles may determine susceptibility for autoimmune disease is by altering the developing T cell repertoire. However, it appears to be likely that genetic as well as environmental factors are responsible for the induction, development and progression of most autoimmune diseases. Multiple genetic factors are believed to interact with environmental factors. The identification of the genes involved in complex diseases is of interest because it may lead us to the understanding of disease mechanisms. (1).

In studies of patients with autoimmune diseases, some investigators have noted that different autoimmune diseases appear to be frequent in the same families. Autoimmune diseases are complex genetic traits, in which multiple genes determine susceptibility to autoimmune disease and no particular gene is necessary or sufficient for disease expression. In the past five years, important progress has been made in identifying key genes that predispose individuals and families to autoimmune diseases. The research has focused both on how these genes may work to initiate the disease process or exacerbate symptoms and on the potential of these discoveries to lead to new interventions that minimize or reverse the negative effects of genetic influences. The disease pathways in which the genes exert their effects may also lead to the discovery of new therapeutic targets. It may change our understanding on the interactions between genes and environment (2).

The tendency to develop an autoimmune disease is in part hereditary. Initially, clinicians observed that a single patient may develop more than one autoimmune disease and that related

members of the same family may share an autoimmune diseases. These observations led to rigorously controlled epidemiologic status comparing the occurrence of autoimmune diseases in genetically identical twins to the occurrence of these diseases in nonidentical twins. In contrast, nonidentical twins have about the same risk of developing an autoimmune disease as any other sibling. In type 1 diabetes (DM 1), Graves' disease, systemic lupus erythematosus (SLE), and multiple sclerosis (MS), the increased risk for siblings of an affected individual is estimated to be 15-20-fold greater than for the general population. Gene expression patterns in blood cells may be useful in identifying patients most likely to benefit from these new therapies, and may help identify disease pathways in other autoimmune and inflammatory disorders (3-5).

Therefore heredity is estimated to account for about one-third of the risk of developing an autoimmune disease. Some genes affect the immune response itself, whereas others increase the vulnerability of the target organ to autoimmune attack. Of all such genes identified to date, the most completely characterized are members of the family of genes of the major histocompatibility complex (MHC). MHC molecules play a pivotal role in the generation of immune responses by virtue of their ability to bind antigenic fragments and present them to T cells. This group of genes – in humans referred to as human leukocyte antigens (HLA) – also controls key steps in the immune response, especially those related to recognition by T cells of specific antigens presented to them by antigen-presenting cells. The MHC repertoire seems to play an important role in the process of TCR (T cell receptor) selection (6).

However, this susceptibility is not inherited in a simple Mendelian segregation, but usually tends to be associated with more than one gene. Furthermore, data strongly suggests that alleles of genes outside the major histocompatibility complex contribute to disease susceptibility. That even genetically predisposed individuals do not always develop autoimmune diseases could only mean that the pathogenesis of such disorders must also be multifactorial (7).

The ability to develop an autoimmune disease is determined by a dominant genetic trait that is very common (10-20 percent of the general population) that may present in families as different autoimmune diseases within the same family.

Most autoimmune diseases result from the combined effects of several genes that must act in concert to determine disease susceptibility. The disease-related versions of these genes may be relatively common in the population, but unless present in combination they are not associated with disease.

Considerable advances are being made through the use of simple sequence length polymorphisms to assign chromosomal locations for the genes determining resistance or susceptibility to some autoimmune diseases (8).

The main genetic loci involved in the body's immune system include the genes for immunoglobulins and T-cell receptors, both of which are involved in the recognition of antigens, and the MHC locus. Of these, the first two are inherently variable and susceptible to recombination, and sporadic variations may give rise to lymphoid cells which may be capable of self-reactivity.

Considerable effort is being extended to establish the role polymorphisms play in influencing the binding of antigens (including autoantigens) in the peptide binding groove, for instance at DRb71 and DQb57, influence peptide binding. Although candidate autoantigenic peptides have been identified which bind to disease-associated MHC molecules, the question remains how T cells capable of interacting with such peptide-MHC complexes escape central tolerance.

Immature T cells capable of high-avidity interactions might be predicted to be deleted by central tolerance. T cells can escape central tolerance, and it is possible that autoreactive T cells in the periphery might become activated following optimal presentation with high enough concentrations of autoantigenic peptides.

Another prominent group of genes associated with the incidence of autoimmune diseases encode components of co-stimulatory pathways such as cytotoxic T lymphocyte antigen-4 (CTLA-4). T cells initiates a series of events that limit lymphocyte proliferation, so that blocking CTLA-4, or deleting it genetically, enhances autoimmune disease in experimental animals. Other genetic traits that determine inherited susceptibility to autoimmune disease act through particular cytokines, which are molecules immune system cells use to communicate among themselves.

Autoimmune diseases occur in predisposed patients. This predisposition is marked by fam-

ily histories of autoimmune diseases. Autoantibodies are often prevalent in the patient's siblings. The correlation between the presence of the histocompatibility antigens DR3, B8, and DR4 with autoimmune diseases show the importance of genes in predisposing to these diseases. HLA-DR3 appears to be a general autoimmune haplotype not only associated with DM 1 but also with SLE, Graves' disease, autoimmune hypothyroidism and Addison's disease.

The oldest and most simple way is the simple description of the same autoimmune disease occurring in different members of the same family. These multicase 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 30-70% but not 100% indicating that these diseases are a result of genetic and environmental factors.

It is likely that complement deficiencies contribute to autoimmunity by altering processing of antigen-antibody complexes (4).

Inheritance of autoimmune diseases refers to whether the condition is inherited from your parents or "runs" in families. The level of inheritance of a condition depends on how important genetics are to the disease. Strongly genetic diseases are usually inherited partially genetic diseases are sometimes inherited, and non-genetic diseases are not inherited.

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

Disease	Percent (%) concordance in twins	
	monozygotic	dizygotic
Psoriasis	65-75	15-20
Rheumatoid arthritis	12-30	4
Ankylosing spondylitis	63	23
SLE	24-69	2-9
Multiple sclerosis	30	3-4
Myasthenia gravis	40	
DM 1	53	11

TABLE I. Concordance rates in monozygotic and dizygotic twins (9)

that common genes predispose to different forms of autoimmunity.

Genetic factors are known to contribute to a broad spectrum of neurological and neurobehavioral diseases. Many single-gene neurological disorders and their familial inheritance patterns have been well characterized. Other disorders, especially the autoimmune neurological disorders, however, have much more complicated inheritance patterns, influenced by multiple genes or by a combination of genetic and environmental factors.

There is great optimism that many more susceptibility genes in these autoimmune diseases will be defined in the next few years. Since the genes that predispose to disease are related to primary events in pathogenesis, their identification will almost certainly provide important insight into the development of autoimmunity and the cause of autoimmune disease (9).

Autoimmune diseases in general are complex genetic diseases where genes and environment interact in unknown ways. □

**Systemic lupus erythematosus**

SLE shows a strong familial aggregation with a much higher frequency among first degree relatives of patients. Population studies reveal that the susceptibility to SLE involves HLA class II gene polymorphisms. An association of HLA-DR2 and -DR3 with SLE is a common finding in patients with a relative risk for the development of disease of approximately two to five. The HLA class III genes, particularly those encoding complement components C2 and C4 confer risk for SLE. Moreover, SLE is associated with inherited deficiencies of C1q, C1r/s, and C2. The discovery of multiple chromosome regions conferring risk for SLE development sup-

ports the notion that SLE is a polygenic disease (10).

**Sjögren syndrome**

Early in the course of disease, the salivary gland epithelial cells abnormally express MHC class II molecules, HLA-DR and HLA-DQ, which promote the activation of T cells and may participate in antigen presentation to T cells and B cells (6).

**Systemic sclerosis**

Genetic factors influence the development of systemic sclerosis, as well as disease manifestations. An extended HLA-DR2 (DRB1\*1602, DQA1\*0501, DQB1\*0301, DPB1\*1301) haplotype is significantly associated with scleroderma. Production of anticentromere antibodies is associated with HLA-DQB1 proteins with a glycine or tyrosine at position 26, and production of antitopoisomerase I antibodies is associated with DRB1\*1101-\*1104, DRB1\*1502, and DRB1\*1602. Scleroderma is not associated with alleles of the T-cell antigen receptor (TCR) a and b chain constant region gene complexes, although a weak association has been reported with an allele of the Cg2 TCR gene (6).

**Behçet disease**

The cause is unknown. Genetic factors also affect susceptibility to the disease, up to 80% of patients have the HLA-B51 allele (4).

Poly- and dermatomyositis

Polymyositis, dermatomyositis, and related inflammatory muscle diseases, called collectively the idiopathic inflammatory myopathies (IIM), are among the least common immunologic ill-

Systemic autoimmune diseases	Localized Autoimmune Diseases
Rheumatoid arthritis (RA) and Juvenile RA (JRA) (joints; less commonly lung, skin)	Type 1 Diabetes Mellitus (pancreas islets)
Lupus [Systemic Lupus Erythematosus] (skin, joints, kidneys, heart, brain, red blood cells, other)	Hashimoto's thyroiditis, Graves' disease (thyroid)
Scleroderma (skin, intestine, less commonly lung)	Celiac disease, Crohn's disease, Ulcerative colitis (GI tract)
Sjogren's syndrome(salivary glands, tear glands, joints)	Multiple sclerosis*
Goodpasture's syndrome (lungs, kidneys)	Addison's disease (adrenal)
Wegener's granulomatosis (blood vessels, sinuses, lungs, kidneys)	Primary biliary cirrhosis, Sclerosing cholangitis, Autoimmune hepatitis (liver)
Polymyalgia Rheumatica (large muscle groups)	Temporal Arteritis / Giant Cell Arteritis (arteries of the head and neck)
Guillain Barre syndrome (nervous system)	

TABLE II. Systemic and localized autoimmune diseases

nesses. It was demonstrated presence of tumor necrosis factor (TNF) and interleukin (IL)-10 in serum and their relation to different genotypes as well as to clinical and laboratory phenotypes in patients with polymyositis and dermatomyositis. These levels were correlated to the G-308A TNF- $\alpha$ , G-1087A IL-10 and G91C TGFB1 gene polymorphisms and haplotype frequencies, gender, autoantibody profiles and clinical manifestations. A significant higher TNF:IL-10 ratio was detected in female poly- and dermatomyositis patients carrying the TNF2 allele compared to female patients with the TNF1/TNF1 genotype (median  $\pm$  IQR 1.513  $\pm$  0.0679 vs. 0.950  $\pm$  1.173,  $p=0.021$ ). This ratio was also significantly higher in patients with the extended MICA5.1/TNF2/TNF $\alpha$ 2/DRB1\*03 haplotype compared to patients lacking this haplotype. A genetically programmed cytokine imbalance exists in patients with poly- dermatomyositis and that this imbalance is related to the presence of disease-associated autoantibodies (11,12).

### Rheumatoid arthritis

The association between rheumatoid arthritis (RA) and certain MHC alleles may be important in dissecting the pathogenesis of this disease. However, the mechanisms underlying this association remain poorly understood. There are genetic changes that influence RA. The findings suggest that distinct genetic profiles may exist that affect the age of onset and disease severity. HLA-DR4 phenotype is regarded as a genetic determinant commonly associated with 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 (2).

### Spondylarthropathies

Fewer correlations exist with MHC class I molecules, the most notable and consistent being the association between HLA B27 and ankylosing spondylitis. 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 (13).

### Myasthenia gravis

Similar to most autoimmune diseases, the MHC represents an important genetic susceptibility locus for the development of myasthenia gravis (MG). Studies indicate that the MHC haplotype with HLA-B8, -DR3 and -DQ2 is associated with early-onset MG and hyperplastic thymus in Caucasian individuals. An association with HLA-B7 and -DR2, although weaker, has also been described for patients with onset of MG after the age of 40 years associated with atrophic thymic histology (2,3).

### Multiple sclerosis

Certain histocompatibility antigen genes (HLA types) are associated with a slightly higher risk of multiple sclerosis (MS), although it has been difficult to determine precisely which alleles are involved. In MS the specific genes with increased risk are the HLA-DR and the HLA-DQ genes, the HLA-DR 15 haplotype in haplotype in Caucasians and other DRs in ethnically more distant populations. On the other hand HLA-DR2 seems to predispose to MS (2).

### Autoimmune liver diseases

Autoimmune hepatitis is a rare autoimmune disease that reflects a loss of tolerance to normal hepatic proteins. About one third of patients and one third of their first-degree relatives also are affected with a second organ-specific autoimmune disease, pointing to the existence of a common genetic predisposition to autoimmunity. 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. Part of this predisposition can be attributed to known risk factors, such as HLA-DR3 and HLA-DR4, C4A-Q0 alleles and female gender. However, other as yet unknown genetic factors are also likely to play a role in the induction of AIH (2,3).

### Type 1 diabetes

Type 1 diabetes about 34% of familial clustering is due to the MHC class II regions. HLA alleles associated with diabetes susceptibility

include HLA-DR3 and HLA-DR4 whereas others are associated with disease protection like HLA-DR2.

The protective nature of HLA-DR2 in DM 1 and the predisposing nature in MS could be the reason why it is rare to see clustering of MS in DM 1 and vice versa. Insulin gene polymorphism influence insulin synthesis and therefore may influence tolerance to insulin (4).

### Graves' disease

Its etiology is largely unknown, but it develops predominantly in genetically susceptible individuals. Family members of a patient with Graves' disease are more likely to have autoimmune thyroid disease or other organ-specific autoimmune disease than the general population. Increased expression of the MHC Class II antigens has been noted on these lymphocytes, as well as on the thyroid cells. MHC genes and their products play a crucial role in determining the immune response, particularly in antigen presentation. The HLA region on chromosome 6 is therefore an obvious candidate as a Graves' disease susceptibility gene. More recent studies indicate that HLA-DR3 is in strong linkage disequilibrium with DQB1\*0201 and DQA1\*0501, both of which are strongly associated with Graves' disease. Controversely, a few studies have implied that HLA-DQ alleles play a role in resistance to autoimmune thyroid disease. Genetic studies also support the involvement of non-MHC genes in the pathogenesis of Graves disease. CTLA-4 on chromosome 2 plays an important role in the down-regulation of T-cell activation (5,6).

### Inflammatory bowel diseases

Familial and ethnic studies indicate a high degree of heritability in inflammatory bowel diseases (IBD). The risk of disease is greater in monozygotic than dizygotic twins, in children with two affected parents rather than those with one affected parent, and in first-degree relatives of patients. Additional support for the genetic basis of IBD comes from the statistically significant association of the disease with certain HLA class II specificities [e.g. HLA-DR2 with ulcerative colitis (UC) and DR1/DQ5 with Crohn's disease (CD)].

Important clues to the pathogenesis of Crohn's disease have recently emerged from genetic research. Familial Crohn's disease has

been linked to several parts of the human genome, including a locus on chromosome 16, IBD now identified as the CARD15 gene. As many as 50 percent of patients with Crohn's disease have mutations in this gene, which appears to play a role in innate immunity, and specifically in signalling mediated by bacterial peptidoglycans. The CARD15 gene encodes the CARD15 protein, which recognizes bacterial components and activates immune response through a nuclear transcription factor called NF- $\kappa$ B. NF- $\kappa$ B is a master regulator of stress and immune responses in many cell types. Bacterial components can also activate NF- $\kappa$ B through the cell-surface Toll-like receptor 2 (TLR2). Mutations in the CARD15 gene cause loss of function of NF- $\kappa$ B in in vitro assays. However, these in vitro observations are discordant with findings in the disease, which is characterized by increased NF- $\kappa$ B activation and a marked increase in proinflammatory cytokines produced by T helper 1 cells in the mucosa (5).

### Autoimmune polyglandular syndrome

Autoimmune polyglandular syndrome is a rare autoimmune disease marked by lymphocyte infiltration and antibody deposits in multiple organs. Researchers have determined that this disorder occurs in people who carry a defective form of the AIRE (autoimmune regulation) gene on chromosome 21. The AIRE protein is a transcription factor that increases "out of place" expression of a large number of genes in the thymus, thereby promoting T cell tolerance. If T cells do not encounter these proteins-as might happen when mutations are present in the gene – autoimmune T cells survive and mature, leading to autoimmunity. These findings underscore the importance of thymically imposed "central" tolerance in the control of autoimmunity (3-5).

### Psoriasis

Psoriasis can occur among several members of the same family. This suggests that a specific gene or set of genes predisposes a family member to psoriasis. It was identified two genes associated with psoriasis on chromosome 17. the region between these two genes acts as a binding site for the protein RUNX1, which normally regulates genes involved in immune reactions. When this region is altered, susceptibility to psoriasis occurs. This defective regulation may

cause an increased activation of T cells, triggering the inflammation and rapid turnover of skin cells characteristic of the disease, and may cause skin cells known as keratinocytes to develop abnormally and divide much faster. 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 (14).

### Vitiligo

It has been discovered a connection between a specific gene and the inflammatory skin condition vitiligo, as well as a possible host of autoimmune diseases. Vitiligo, a common autoimmune disorder characterized by patchy loss of pigment in the skin and hair can be a socially devastating disease, particularly in more darkly pigmented individuals. Vitiligo often clusters in families, and frequently is seen in individuals who have multiple autoimmune diseases. In the same family, there were likely to be multiple members with vitiligo and other individuals with autoimmune thyroid disease, pernicious anemia, Addison's disease, lupus, and inflammatory bowel disease. By searching the genome, it was discovered a gene, NALP1 on chromosome 17, that was key to predisposing people to vitiligo and other autoimmune diseases, particularly autoimmune thyroid disease. About 20 percent of people with vitiligo also get autoimmune thyroid disease, and this gene may be involved in mediating both of those. This new information marks an important step in research into vitiligo prevention and treatment (15).

### Pemphigus

A number of investigators have demonstrated an increased frequency of HLA-DR4 and HLA-DR6. Additional studies have shown that a specific HLA-DR4 subtype (DRB1\*0402) is associated with pemphigus vulgaris. This DR4 subtype is distinct from those DR4 molecules associated with rheumatoid arthritis (6,7).

In recent years technologies have advanced our knowledge and new genes are being identified very rapidly.

Although it is still unclear what these diseases may have in common, they are generally grouped in the autoimmune category, as a dysregulation of the endogenous immune response (leading to damage of the patient's own tissues and organs) is thought to underlie their development and progression.

Cause and effect is still an elusive link in autoimmune diseases, and the therapies currently used reflect this lack of clear etiopathogenetic knowledge. All have a hereditary component, most probably polygenic in nature.

Some gene associations have been confirmed, while others have been proven inconsistent or restricted to a specific population. More data will come in the near future, and they are expected to help in dissecting the genetic origin of autoimmune diseases and in unravelling their causes.

In particular, the ability to scan the entire genome for common polymorphisms that associate with disease has led to the identification of numerous new risk genes involved in autoimmune phenotypes. In addition, it is now clear the common genes underlie multiple autoimmune disorders. Several themes are emerging. The genes people inherit contribute to their susceptibility for developing an autoimmune disease (16, 17). □

### CONCLUSION

It is now well-established that certain individuals are genetically susceptible to the development of autoimmune diseases. Multiple genes contribute to disease susceptibility. Type 1 diabetes, autoimmune thyroiditis, Addison's disease, autoimmune polyendocrine syndromes, vitiligo, and celiac disease may also be increased in frequency in the same families. This suggests that genetic factors play an important role in the predisposition of the disease.

Genetic complexity in autoimmunity is also determined by genetic heterogeneity, in which the same disease trait is the result of a different set of genes. The complexity of genetic analyses in autoimmunity is increased by the interaction of multiple susceptibility genes.

The genetic predisposition alone does not cause the development of autoimmune diseases. Autoimmune diseases are under polygenic control. The identification and character-

ization of these genes could provide important new insights in pathogenesis in subgroups of patients. In the future, research in this area may provide the basis for gene repair strategies.

The real challenge comes when we try to understand the mechanisms through which these genes confer disease susceptibility and how the interaction with environment takes place such that clinical expression of the disease results.

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