

GENETIC BASIS OF AUTOIMMUNE HEPATITIS AND THE IMPACT OF HLA ALLELES ON DISEASE SUSCEPTIBILITY

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Abstract: Autoimmune hepatitis (AIH) is a chronic autoimmune inflammatory liver disease characterized by an immune response directed against hepatocytes. The disease develops through the interaction of genetic and environmental factors. Studies indicate that genes of the human leukocyte antigen (HLA) system play a significant role in the development of AIH. Specific alleles of the HLA-DRB1, HLA-DQB1, and HLA-B genes increase susceptibility to the disease. This article analyzes the genetic basis of AIH, the association between HLA alleles and disease predisposition, as well as ethnic differences among populations.

Keywords: autoimmune hepatitis, HLA alleles, genetic predisposition, ethnic differences, liver.

Autoimmune Hepatitis (AIH) is a chronic disease characterized by the production of autoantibodies against liver tissues due to a dysfunction of the immune system. AIH occurs more frequently among women and, if left untreated, can lead to liver cirrhosis and liver failure.

Genetic factors play a crucial role in the development of autoimmune hepatitis, among which the **major histocompatibility complex (MHC)** genes are the most significant. In humans, the MHC system is known as the **Human Leukocyte Antigen (HLA)** complex, which regulates the immune system's ability to recognize foreign antigens. HLA molecules present antigens that enter the body to T-lymphocytes, thereby activating the immune response.

However, certain HLA alleles disrupt the immune system's tolerance toward its own tissues. As a result, liver cells are mistakenly recognized as “foreign,” leading to an autoimmune attack. Studies have shown that **HLA-DRB1*03:01**, **HLA-DRB1*04:01**, and **HLA-B*35:01** alleles are significantly associated with a predisposition to AIH.

Therefore, HLA system genes form the genetic basis of autoimmune hepatitis and play a central role in its pathogenesis.

The HLA system represents the most important genetic complex responsible for regulating the immune response. It activates T lymphocytes by presenting antigens to them. The HLA system is divided into Class I (A, B, C) and Class II (DR, DQ, DP) molecules. Among these, Class II molecules—particularly HLA-DR and HLA-DQ—play a central role in autoimmune diseases by mediating immune activation in response to specific antigens.

HLA-DR Genes and Autoimmune Hepatitis (AIH)

Studies conducted in populations of European descent have demonstrated a strong association

between the **HLA-DRB1*03:01** and **HLA-DRB1*04:01** alleles and Type 1 Autoimmune Hepatitis (AIH-1) (Bittencourt et al., 1999; Higuchi et al., 2020). Individuals carrying these alleles have a 4–6 times higher risk of developing AIH compared to those without them.

In populations of Latin American descent, the **HLA-DRB1*13:01** and **HLA-DRB1*04:04** alleles have been identified as the major genetic risk factors. Meanwhile, in Asian populations—particularly those of Japanese and Chinese ancestry—the **HLA-DRB1*04:05** and **HLA-B*35:01** alleles show the strongest association with AIH.

HLA-DQ and DR-DQ Haplotypes

Several studies (Czaja et al., 1995) have indicated that Type 1 Autoimmune Hepatitis (AIH-1) is associated with the **DR3-DQ2 haplotype**, while Type 2 Autoimmune Hepatitis (AIH-2) is linked to the **DR7-DQ2 haplotype** or the **DRB1*07:01** allele. These haplotypes are believed to increase immunological susceptibility to the disease and influence the antigen presentation process, thereby contributing to the development of autoimmune reactions in the liver.

HLA Class I Genes (HLA-B) and Autoimmune Hepatitis (AIH)

A large-scale study conducted in China (Li et al., 2023) revealed that the **HLA-B*35:01** allele shows the strongest association with Type 1 Autoimmune Hepatitis (AIH-1) (OR = 7.32; $p < 10^{-304}$). Patients carrying this allele demonstrated elevated liver enzyme levels (AST and ALT) but lower serum immunoglobulin G (IgG) concentrations.

The HLA alleles associated with autoimmune hepatitis vary considerably among different ethnic groups. The main alleles of the HLA system, their associations with AIH types, and the corresponding relative risk ratios are summarized in **Table 1**.

Table-1.

HLA Allele	AIH Type	Population	Odds Ratio (OR)	Reference
HLA-DRB1*03:01	AIH-1	Europe	5.2	Higuchi et al., 2020
HLA-DRB1*04:01	AIH-1	Europe	4.7	Bittencourt et al., 1999
HLA-DRB1*13:01	AIH-1	Latin America	3.9	Bittencourt et al., 1999
HLA-B*35:01	AIH-1	China (Han)	7.3	Li et al., 2023
HLA-DRB1*07:01	AIH-2	Yevropa	4.5	Czaja et al., 1995

According to the data presented in Table 1, the HLA-DRB1*03:01 and HLA-DRB1*04:01 alleles show the strongest association with Type 1 Autoimmune Hepatitis (AIH-1) in populations of European descent. In contrast, the HLA-B*35:01 allele in the Chinese population increases the risk of developing AIH by approximately 7.3-fold.

These variations highlight the genetic heterogeneity of AIH and suggest the presence of ethnic predisposition in the disease's development.

Non-HLA Genetic and Epigenetic Factors

In addition to HLA genes, several non-HLA genetic variations have been identified that may contribute to the development of Autoimmune Hepatitis (AIH). For instance, polymorphisms in the **CTLA4**, **TNF**, and **IL2RA** genes can alter immune regulation and influence the severity of the disease.

Moreover, **epigenetic modifications**—such as DNA methylation and microRNA expression changes—are also believed to play a significant role in the pathogenesis of AIH by modulating gene activity without altering the DNA sequence itself (Zachou et al., 2021).

The genetic basis of Autoimmune Hepatitis (AIH) is complex and is primarily associated with polymorphisms in HLA system genes. The observed allelic variations among different ethnic groups reflect the **regional and genetic heterogeneity** of AIH.

In the future, conducting comprehensive genome-level studies on AIH will be crucial for improving early disease detection and developing personalized therapeutic strategies, ultimately enhancing patient outcomes.

Conclusion

The analyses indicate that **genes belonging to the HLA system** represent one of the key genetic determinants in the development of Autoimmune Hepatitis (AIH). In particular, the **HLA-DRB1*03:01**, **HLA-DRB1*04:01**, and **HLA-B*35:01** alleles show a strong association with Type 1 AIH, while HLA-DRB1*07:01 is highly associated with Type 2 AIH. These findings confirm the presence of **ethnic and genetic diversity** in disease susceptibility. Furthermore, polymorphisms in genes such as **CTLA4**, **TNF**, and **IL2RA**, along with **epigenetic modifications**, play a role in modulating the immune response and influencing the severity of disease progression. Collectively, these data suggest that a complex genetic network underlies the pathogenesis of AIH. Therefore, future studies should focus on **genetic diagnostics**, the identification of **molecular markers** for early detection, and the development of **personalized therapeutic approaches** for more effective disease management.

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