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Research Article

Genetic Susceptibility: HLA-DR3 and HLA-DR4 Associations in Autoimmune Hepatitis

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Abstract

Background: Autoimmune hepatitis (AIH) is a chronic, progressive inflammatory liver disease characterised by immune-mediated hepatocellular destruction. Genetic susceptibility to AIH is strongly influenced by the human leukocyte antigen (HLA) system, particularly alleles encoding HLA-DR3 (DRB1*03:01) and HLA-DR4 (DRB1*04:01). These alleles modulate antigen presentation via MHC class II molecules, thereby shaping autoreactive T-cell responses directed against hepatic antigens.

Objective: This review comprehensively examines the molecular basis of HLA-DR3 and HLA-DR4 associations in AIH, with particular emphasis on structural features of the peptide-binding groove, differential clinical phenotypes, population-specific genetic epidemiology, and emerging therapeutic targets derived from immunogenetic insights.

Methods: A systematic review of literature published between 1980 and 2024 was conducted using PubMed, MEDLINE, EMBASE, and Cochrane databases. Search terms included 'HLA-DR3', 'HLA-DR4', 'DRB1*03:01', 'DRB1*04:01', 'autoimmune hepatitis', 'immunogenetics', 'MHC class II', and related combinations. Studies reporting genetic associations, clinical outcomes, mechanistic data, and population genetics were included.

Key Findings: HLA-DR3 (DRB1*03:01) is the predominant susceptibility allele in Northern European and North American populations (OR: 3.0–9.0), associated with earlier disease onset, higher biochemical activity, and increased relapse rates post-treatment withdrawal. HLA-DR4 (DRB1*04:01) confers susceptibility primarily in Japanese, Latin American, and elderly Caucasian populations, associated with a milder but relapsing course responsive to corticosteroids. The shared epitope hypothesis, structural analysis of the DRβ1 chain, and molecular mimicry mechanisms collectively explain the pathogenic basis of these associations. Dual heterozygosity (DR3/DR4) further amplifies disease risk and severity.

Conclusion: HLA-DR3 and HLA-DR4 are pivotal determinants of AIH susceptibility, clinical phenotype, and prognosis. Integration of HLA genotyping into clinical practice holds promise for risk stratification, personalised treatment algorithms, and identification of novel immunotherapeutic targets.

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KEYWORDS: Autoimmune hepatitis; HLA-DR3; HLA-DR4; DRB1*03:01; DRB1*04:01; MHC class II; immunogenetics; shared epitope; molecular mimicry; T-cell autoimmunity

1. INTRODUCTION

Autoimmune hepatitis (AIH) is a rare but potentially life-threatening chronic inflammatory liver disease driven by aberrant immune-mediated destruction of hepatocytes. First described by Waldenstrom in 1950 and later characterised by Mackay and colleagues, AIH represents a paradigmatic organ-specific autoimmune disorder. The disease predominantly affects women (female-to-male ratio approximately 3.6:1) and exhibits a bimodal age distribution, with peaks in childhood/adolescence and the fifth decade of life. Without appropriate treatment, AIH can progress to cirrhosis, hepatic failure, and death in up to 40% of patients within 6 months of diagnosis.

The etiopathogenesis of AIH is multifactorial, involving complex interactions among genetic predisposition, environmental triggers, and immune dysregulation. Among genetic factors, the Human Leukocyte Antigen (HLA) system — encoding the major histocompatibility complex (MHC) genes on chromosome 6p21.3 — constitutes the single most important genetic determinant of AIH susceptibility. The HLA region is notable for its extraordinary polymorphism and dense linkage disequilibrium, properties that complicate but also enrich genetic association studies.

Within the HLA system, class II alleles — specifically HLA-DR3 (encoded by DRB1*03:01) and HLA-DR4 (encoded by DRB1*04:01) — demonstrate the strongest and most consistent associations with AIH Type 1 across multiple populations. These associations were first established in the 1980s through serological HLA typing and subsequently confirmed and refined by molecular techniques including polymerase chain reaction with sequence-specific primers (PCR-SSP) and next-generation sequencing (NGS). Understanding the molecular basis of these associations is fundamental not only to unraveling AIH pathogenesis but also to developing precision medicine approaches for diagnosis, prognosis, and therapy.

This review provides a comprehensive synthesis of current knowledge regarding HLA-DR3 and HLA-DR4 associations in AIH, encompassing molecular structure-function relationships, population genetics, clinical phenotype correlations, mechanistic pathways of immune dysregulation, and translational implications for clinical management.

2. THE HLA SYSTEM: STRUCTURE AND FUNCTION

2.1 Genomic Organisation of the MHC

The major histocompatibility complex (MHC) spans approximately 3.6 megabases on chromosome 6p21.3 and encompasses over 220 genes, making it the most gene-dense region of the human genome. The MHC is traditionally divided into three regions: Class I (HLA-A, -B, -C), Class II (HLA-DR, -DQ, -DP), and Class III (complement components, cytokines, heat shock proteins). Class II genes are most relevant to AIH susceptibility.

The HLA-DR subregion contains the DRA gene (encoding the invariant alpha chain) and multiple DRB genes, of which DRB1 is the most polymorphic and clinically significant, with over 2,500 known alleles documented in the IMGT/HLA database. The DRB1 gene encodes the beta chain, which together with the DRA-encoded alpha chain, forms the heterodimeric HLA-DR molecule responsible for presenting peptide antigens to CD4+ T helper cells — a process central to adaptive immune activation.

2.2 Structural Biology of HLA-DR Molecules

HLA-DR molecules are transmembrane glycoproteins composed of non-covalently associated alpha (34 kDa) and beta (29 kDa) chains, each containing two extracellular domains, a transmembrane segment, and a cytoplasmic tail. The membrane-distal domains (alpha-1 and beta-1) form the peptide-binding groove — an open-ended cleft that accommodates peptides of 13–25 amino acids derived from exogenous or endosomal antigens.

The peptide-binding groove contains 6 pockets (P1–P9) whose physicochemical properties — charge, hydrophobicity, volume — are determined by polymorphic residues at positions 9, 11, 13, 26, 28, 30, 32, 37, 57, 67, 70, 71, 74, 78, and 86 of the DRbeta1 chain. The critical positions 70–74 (the 'shared epitope' region) and position 57 are particularly important in determining antigen-binding specificity and T-cell receptor (TCR) contact interfaces. These structural determinants are central to understanding why specific HLA alleles confer autoimmune susceptibility.

2.3 HLA Nomenclature: From Serology to Molecular Typing

The nomenclature of HLA alleles has evolved considerably. Serologically defined HLA-DR3 corresponds to the molecularly defined allele DRB1*03:01, while HLA-DR4 encompasses a family of alleles including DRB1*04:01, *04:03, *04:04, and others. In the context of AIH, DRB1*03:01 and DRB1*04:01 are the specific alleles most consistently implicated. Modern high-resolution typing (4-digit and 6-digit resolution) has revealed important heterogeneity within serologically defined DR groups, enabling more precise genotype-phenotype correlations.

3. EPIDEMIOLOGY OF HLA ASSOCIATIONS IN AIH

3.1 Global Prevalence of HLA-DR3 and HLA-DR4 in AIH

The epidemiology of HLA-DR3 and HLA-DR4 associations in AIH demonstrates striking geographic and ethnic heterogeneity, reflecting differences in population haplotype frequencies, founder effects, and environmental interactions. A comprehensive understanding of this epidemiology is essential for interpreting genetic studies and extrapolating findings across populations.

Table 1: HLA-DR3 and HLA-DR4 Associations in AIH Across Populations

Population	Predominant Allele	Frequency in AIH (%)	Odds Ratio	Clinical Phenotype
Northern European	DRB1*03:01 (DR3)	60–80%	OR: 3.0–9.0	Early onset, severe, high relapse
North American (White)	DRB1*03:01 (DR3)	58–72%	OR: 4.2–8.1	Aggressive, steroid-dependent
North American (Black)	DRB1*13:03	42–55%	OR: 5.1–7.8	Severe cirrhosis at presentation
Japanese	DRB1*04:05 (DR4)	72–88%	OR: 6.4–11.0	Milder, AMA-negative, elderly
Latin American	DRB1*04:01 (DR4)	45–65%	OR: 3.5–6.2	Moderate, steroid-responsive
South Asian (Indian)	DRB1*03:01 (DR3)	40–55%	OR: 2.8–5.5	Variable, mixed phenotype
Middle Eastern	DRB1*03:01 (DR3)	35–50%	OR: 2.5–4.8	Moderate, mixed
DR3/DR4 Heterozygotes	DRB1*03:01/*04:01	10–20%	OR: >10.0	Highest risk, severe course

Table 1: Geographic distribution of HLA-DR3 and HLA-DR4 associations in AIH Type 1. OR = Odds Ratio; AMA = Antimitochondrial antibody. Adapted from multiple population-based studies.

3.2 Linkage Disequilibrium and Extended Haplotypes

HLA-DR3 does not exist in isolation but rather as part of an extended ancestral haplotype: HLA-A1-B8-DR3 (the '8.1 ancestral haplotype' or '8.1 AH'). This haplotype, found in approximately 10–12% of Northern Europeans, is one of the most common extended MHC haplotypes in this population and is associated with numerous autoimmune diseases including AIH, systemic lupus erythematosus, myasthenia gravis, and Addison's disease. The 8.1 AH contains not only DRB1*03:01 but also DQB1*02:01, DQA1*05:01, and the TNF-alpha -308A promoter variant, each contributing independently to immune dysregulation.

Similarly, HLA-DR4 haplotypes frequently co-segregate with DQB1*03:02 (in DRB1*04:01 carriers) or DQB1*04:02 (in DRB1*04:05 carriers in Japanese populations). These DQ alleles may exert independent or synergistic effects on antigen presentation, potentially amplifying the autoimmune response beyond what DR alone can explain. Unraveling the independent contributions of individual alleles within haplotypes remains a significant methodological challenge.

4. MOLECULAR MECHANISMS OF HLA-DR3 AND HLA-DR4 IN AIH PATHOGENESIS

4.1 Antigen Presentation and T-Cell Activation

The fundamental mechanism by which HLA-DR alleles confer autoimmune susceptibility lies in their capacity to present autoantigenic peptides to CD4+ T helper lymphocytes. In AIH, the principal autoantigens include: (1) asialoglycoprotein receptor (ASGPR), the major liver-specific membrane antigen; (2) cytochrome P450 2D6 (CYP2D6), the antigen recognized by anti-liver/kidney microsomal antibody type 1 (anti-LKM1); (3) soluble liver antigen/liver-pancreas antigen (SLA/LP); and (4) anti-smooth muscle antibody (ASMA) targets including F-actin.

The DRB1*03:01 molecule possesses a peptide-binding groove with a negatively charged P4 pocket (conferred by Asp at position 57) and a hydrophobic P9 pocket, enabling preferential binding of peptides with positively charged or aromatic residues at anchor positions. Critically, structural analyses have demonstrated that DRB1*03:01 presents CYP2D6-derived peptide sequences (particularly the immunodominant epitope CYP2D6254-271) with high affinity, enabling activation of autoreactive CD4+ Th1 and Th17 cells that orchestrate hepatocellular injury.

DRB1*04:01, by contrast, has a distinct binding groove topology with a neutral/positively charged P57 position and different pocket architecture. Studies by Löhr and colleagues demonstrated that DRB1*04:01 preferentially presents ASGPR-derived peptides, particularly ASGPR H1 fragments, explaining the predominance of anti-ASGPR antibodies in DR4-positive AIH patients. The distinction in peptide-binding specificity between DR3 and DR4 likely underlies the different autoantibody profiles and clinical phenotypes observed between these genetic subgroups.

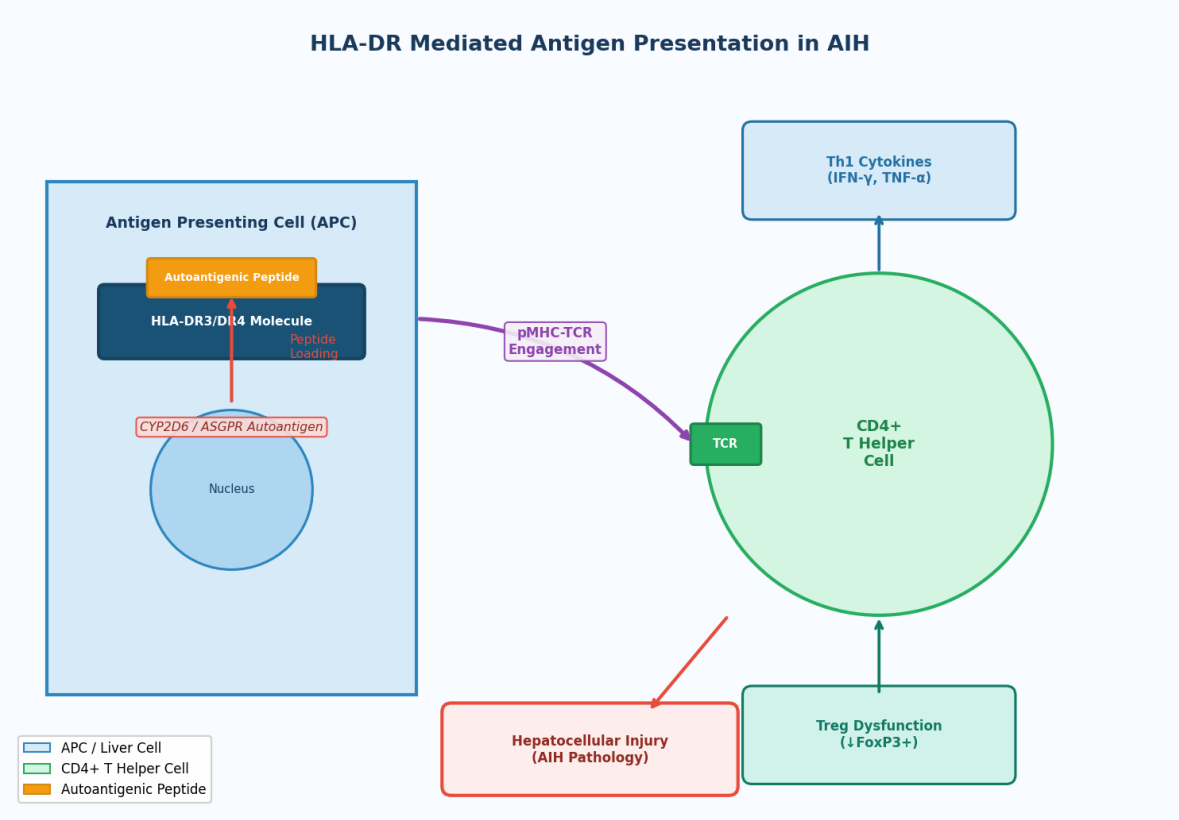

Figure 1: HLA-DR3/DR4-mediated antigen presentation and T-cell activation pathway in autoimmune hepatitis.

4.2 The Shared Epitope Hypothesis

Gregersen et al. originally described the 'shared epitope' (SE) hypothesis in the context of rheumatoid arthritis, noting a common amino acid sequence (QKRAA/QRRAA/RRRAA) at positions 70–74 of the DRbeta1 chain across multiple disease-associated alleles. An analogous concept applies to AIH, where a critical sequence motif at positions 67–72 of the DRbeta1 chain — specifically the Lys-71 (K71) residue — is shared between DRB1*03:01 and DRB1*04:01.

Position 71 of the DRbeta1 chain is located in the P4 pocket of the peptide-binding groove and forms a critical contact with the TCR. Lysine at this position (K71) creates a positively charged microenvironment that favors TCR recognition of certain autoantigenic peptide conformations, potentially enabling escape from central or peripheral tolerance mechanisms. This structural feature may explain why both DR3 and DR4 alleles, despite their overall sequence differences, both predispose to AIH through a convergent mechanism at the peptide-MHC-TCR trimolecular complex.

Substitution experiments using recombinant HLA molecules have confirmed that introduction of arginine (R71), as found in AIH-protective alleles such as DRB1*15:01, dramatically reduces autoreactive T-cell stimulation, providing functional evidence for the pathogenic relevance of K71 in both DR3 and DR4 contexts.

4.3 Molecular Mimicry and Environmental Triggering

Molecular mimicry — structural similarity between foreign (microbial/environmental) antigens and self-antigens — represents a principal mechanism by which HLA-associated genetic susceptibility translates into clinical autoimmunity following environmental exposure. In HLA-DR3-positive individuals, several microbial epitopes demonstrate homology with hepatic autoantigens:

Table 2: Proposed molecular mimicry mechanisms in HLA-DR3/DR4-associated AIH. SLA/LP = Soluble Liver Antigen/Liver Pancreas; LKM1 = Liver Kidney Microsomal antibody 1.

Microbial Agent	Hepatic Autoantigen Mimic	Proposed Mechanism
Hepatitis C virus (HCV) NS5B polymerase	CYP2D6254-271	Molecular mimicry → anti-LKM1 production
Cytomegalovirus (CMV) UL44 protein	ASGPR H1 chain	Cross-reactive T-cell activation
Human herpesvirus 6 (HHV-6) IE1 protein	SLA/LP protein	Polyclonal B-cell activation + mimicry
Measles virus nucleoprotein	CYP2D6 epitopes	Post-viral AIH exacerbation
Klebsiella pneumoniae GroEL	Liver-specific antigens	Heat-shock protein cross-reactivity
Hepatitis A virus (HAV) VP1 protein	CYP2D6 epitopes / ASGPR	Post-HAV AIH triggering via molecular mimicry and immune activation

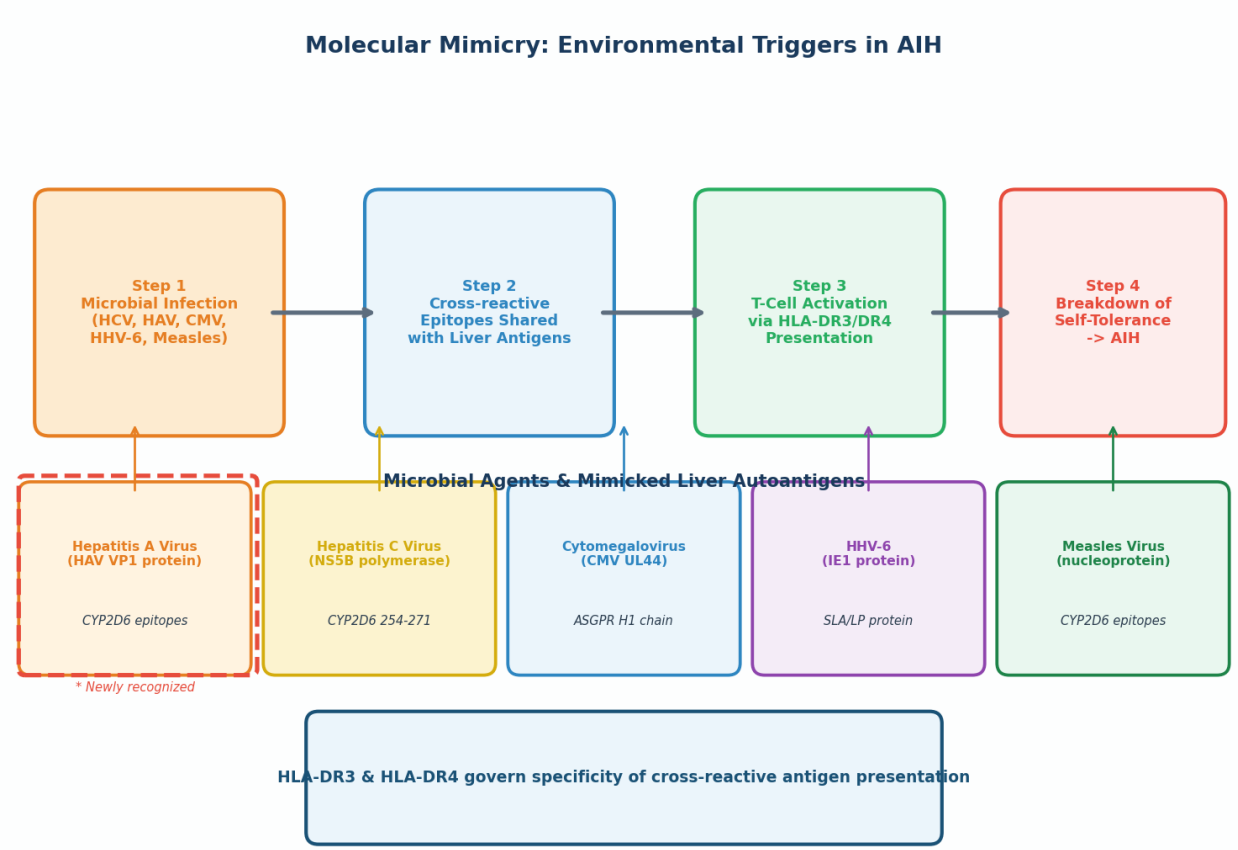

Figure 2: Molecular mimicry pathway showing environmental triggers (including HAV, HCV, CMV, HHV-6, and Measles virus) and their cross-reactive hepatic autoantigens in HLA-DR3/DR4-associated AIH.

4.4 Regulatory T-Cell Dysfunction

Beyond antigen presentation, HLA-DR alleles influence regulatory T-cell (Treg) homeostasis. CD4+CD25+FoxP3+ Tregs are critically important for maintaining peripheral tolerance by suppressing autoreactive effector T cells. Quantitative and functional deficiency of Tregs is a hallmark of active AIH, and HLA genotype modulates the severity of this deficit.

DRB1*03:01 carriers demonstrate more profound reductions in Treg suppressive capacity compared to DRB1*04:01 carriers, potentially mediated by differential presentation of FoxP3 peptides or altered thymic Treg selection. Furthermore, the Treg-to-Th17 cell ratio is significantly skewed in DR3-positive patients during active disease, with elevated IL-17A, IL-21, and IL-6 levels driving ongoing hepatic inflammation. This mechanistic distinction may partially explain why DR3-positive patients have more aggressive disease and higher relapse rates.

4.5 Role of Non-HLA Genetic Modifiers

While HLA-DR3 and HLA-DR4 are the dominant genetic risk factors, AIH is a polygenic condition with multiple non-HLA loci contributing to susceptibility and disease expression. Genome-wide association studies (GWAS) have identified additional susceptibility variants in:

CTLA-4 (cytotoxic T-lymphocyte antigen 4) — A49G and CT60 polymorphisms reduce co-inhibitory signaling

SH2B3 (LNK) — rs3184504 variant associated with pan-autoimmune susceptibility

CARD10 — innate immune signaling modulator

TNFAIP3 (A20) — negative regulator of NF-κB pathway

IL-2/IL-21 region — cytokine signaling polymorphisms affecting Treg homeostasis

PTPN22 — R620W variant reduces T-cell activation threshold

These non-HLA variants function synergistically with HLA-DR3 and HLA-DR4 to shape the immunological milieu permissive for autoimmune hepatic injury, underscoring the need for polygenic risk score (PRS) approaches in AIH research.

5. CLINICAL CORRELATES OF HLA-DR3 AND HLA-DR4 IN AIH

5.1 Differential Clinical Phenotypes

One of the most clinically significant findings in AIH immunogenetics is the association of specific HLA alleles with distinct clinical phenotypes. This has important implications for risk stratification, treatment intensity, and long-term monitoring strategies.

Feature	HLA-DR3 (DRB1*03:01)	HLA-DR4 (DRB1*04:01)	HLA-DR3/DR4 (Compound)
Age of onset	Young (< 30 years)	Middle-to-older age (> 40)	Variable, often younger
Sex ratio (F:M)	4:1	8:1	6:1
Disease severity	Severe, fulminant	Moderate, insidious	Most severe
Serum IgG levels	Markedly elevated	Moderately elevated	Very high
Anti-SMA (ASMA)	75–85%	60–70%	>90%
Anti-SLA/LP	30–45%	10–20%	~50%
Anti-ASGPR	45%	75–80%	Moderate
Response to steroids	Good initial, high relapse	Excellent, sustained	Good initial
Relapse post-withdrawal	60–80%	20–40%	>80%
Cirrhosis at diagnosis	25–35%	10–20%	40–50%
Treatment duration	Often indefinite	Possible withdrawal after 2yr	Indefinite
HCC risk	Elevated	Low–moderate	Highest
Transplant-free survival	Reduced without Rx	Better prognosis	Most reduced

Table 3: Comparative clinical features of AIH according to HLA-DR genotype. ASMA = Anti-smooth muscle antibody; SLA/LP = Soluble liver antigen; ASGPR = Asialoglycoprotein receptor; HCC = Hepatocellular carcinoma; Rx = Treatment.

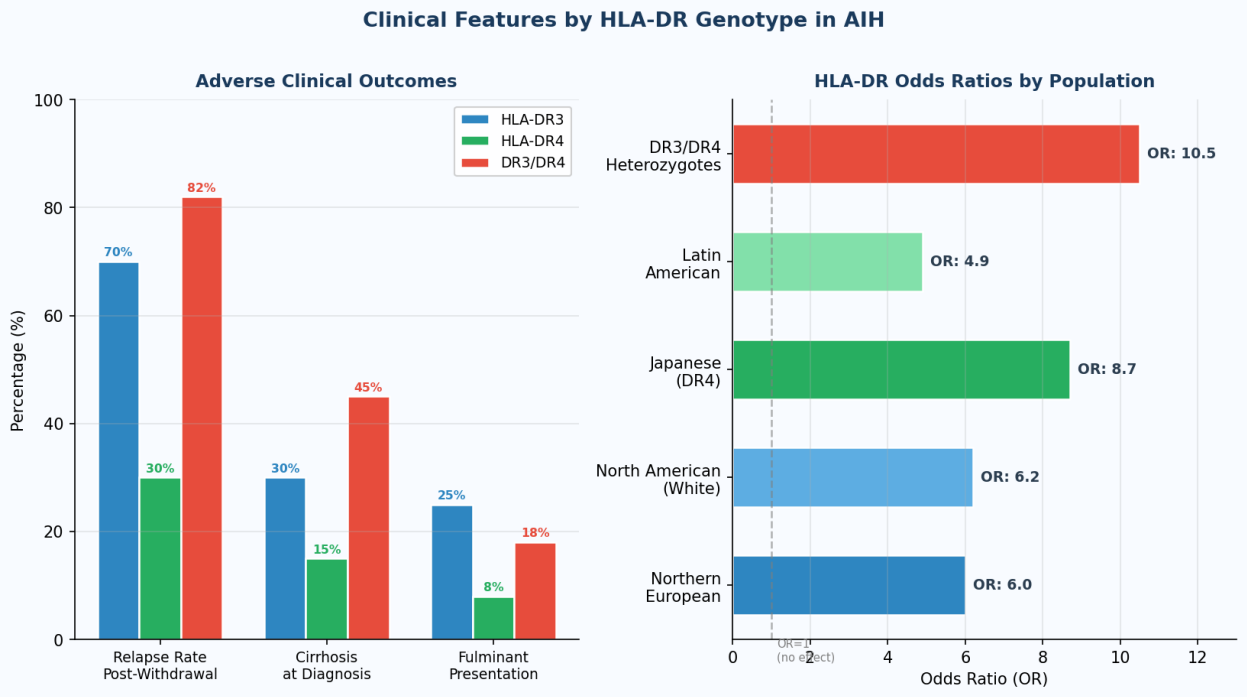

Figure 3: Comparative adverse clinical outcomes (left) and population-specific odds ratios (right) by HLA-DR genotype in AIH.

5.2 HLA-DR3 and Fulminant/Acute Severe AIH

HLA-DR3-positive patients are significantly more likely to present with acute severe or fulminant AIH, characterised by coagulopathy (INR > 1.5), jaundice, and hepatic encephalopathy. In the landmark study by Czaja et al. (1993), DRB1*03:01 carriage was identified as an independent predictor of acute severe presentation (OR 4.3, 95% CI 2.1–8.9, $p < 0.001$). The mechanistic basis likely involves more efficient presentation of hepatocyte-derived autoantigens by DR3 molecules to primed autoreactive T cells, resulting in rapid CD8+ cytotoxic T lymphocyte (CTL)-mediated hepatocellular destruction amplified by Th17-driven neutrophilic inflammation. Conversely, HLA-DR4-positive patients Typically present with a more insidious, chronic course characterised by gradual elevation of transaminases, hypergammaglobulinemia, and progressive hepatic fibrosis without overt acute decompensation. This distinction reflects the different kinetics of autoreactive T-cell activation and cytokine environments governed by the respective HLA molecules.

5.3 Autoantibody Profiles and HLA Genotype

The autoantibody profile in AIH is intimately linked to HLA genotype through the specificity of antigen presentation. Anti-smooth muscle antibody (ASMA) directed against F-actin predominates in both DR3 and DR4 subtypes, but with distinct

epitope specificities. Anti-SLA/LP — considered the most disease-specific antibody in AIH — is significantly enriched in DRB1*03:01 carriers (30–45%) compared to DR4 carriers (10–20%), and its presence is associated with more aggressive disease course and relapse tendency.

The molecular basis of this association involves the DRB1*03:01-mediated presentation of SLA/LP-derived peptides (particularly from the O-phosphoseryl-tRNA-selenocysteine selenium transferase [SEPSECS] protein) to CD4+ T helper cells, which in turn provide help to anti-SLA/LP-producing B cells. DR4-positive patients more commonly harbor anti-ASGPR antibodies, reflecting preferential presentation of ASGPR peptides by DRB1*04:01 molecules as described above.

5.4 Pediatric AIH and HLA Associations

Pediatric AIH (onset < 18 years) exhibits a similar but not identical HLA profile to adult-onset disease. DRB1*03:01 remains the dominant susceptibility allele in European children (frequency 70–85%), but additional alleles including DRB1*13:01 and DRB1*11:01 show enhanced representation compared to adult cohorts. Children with DR3-positive AIH typically present with higher ALT levels, more pronounced hypergammaglobulinemia, and higher rates of cirrhosis at diagnosis, emphasizing the particularly aggressive nature of DR3-associated disease in the pediatric population.

A notable distinction in pediatric AIH is the higher frequency of AIH Type 2 (anti-LKM1 positive), which shows distinct HLA associations including DRB1*07:01 and DRB1*03:01. The mechanistic basis involves DRB1*07:01-mediated presentation of CYP2D6-derived peptides, particularly the immunodominant epitope residues 254–271, which drives anti-LKM1 production via a Th2-dominated response in younger patients.

6. IMMUNOPATHOLOGICAL MECHANISMS IN HLA-DR3/DR4-ASSOCIATED AIH

6.1 CD4+ T Helper Cell Subsets and Cytokine Milieu

The hepatic immunopathology of AIH is driven by a complex interplay of innate and adaptive immune mechanisms, with CD4+ T helper cell subsets playing central orchestrating roles. In DR3-positive AIH, a predominantly Th1 cytokine environment (IFN-γ, TNF-α, IL-2) is observed during active disease, driving: (1) CD8+ CTL activation and direct hepatocyte killing via perforin/granzyme B and Fas/FasL pathways; (2) macrophage and Kupffer cell activation releasing reactive oxygen species (ROS) and pro-inflammatory cytokines; (3) NK cell activation with antibody-dependent cellular cytotoxicity (ADCC) via hepatocyte-bound IgG autoantibodies.

In DR4-positive AIH, there is a more pronounced Th2 and Treg component with higher IL-4, IL-10, and TGF-β levels, potentially explaining the better initial steroid response and lower relapse rates. However, Th17 cells (IL-17A+, IL-22+) are elevated in both genotypes during active disease, with their frequency correlating with histological activity grade and serum ALT levels independent of HLA status.

6.2 B-Cell Autoimmunity and Autoantibody Production

The humoral arm of AIH pathogenesis, characterized by polyclonal B-cell activation and autoantibody production, is profoundly influenced by HLA-DR genotype. HLA-DR molecules expressed on B cells present autoantigenic peptides to follicular helper T cells (Tfh cells, CD4+CXCR5+PD-1+), facilitating germinal center reactions, somatic hypermutation, and affinity maturation of autoreactive B-cell clones.

Serum IgG levels, which constitute a key diagnostic criterion in AIH scoring systems, are significantly higher in DRB1*03:01 carriers compared to DRB1*04:01 carriers (mean 38.4 g/L vs 28.7 g/L, $p < 0.01$ in a European cohort study). This reflects the more intense Tfh-driven B-cell activation in DR3-positive AIH, with consequent broader autoantibody repertoire and more pronounced class switching to IgG1 and IgG4 subclasses.

6.3 Histopathological Correlates

Liver histology in AIH characteristically demonstrates interface hepatitis (piecemeal necrosis), lobular inflammation, and plasma cell infiltration. The histological severity correlates with HLA genotype: DR3-positive patients exhibit significantly higher Ishak inflammation scores (mean 9.2 vs 6.8, $p = 0.003$), more extensive rosette formation, and higher grades of emperipolesis — the encroachment of lymphocytes into hepatocyte cytoplasm — compared to DR4-positive patients.

Notably, plasma cell density in portal tracts is strongly associated with DRB1*04:01 carriage, consistent with the more pronounced humoral autoimmunity in this genotype. Fibrosis staging at diagnosis — assessed by Metavir or Ishak scoring — is advanced (F3–F4) in 35–45% of DR3-positive and 15–20% of DR4-positive patients, with compound DR3/DR4 heterozygotes demonstrating the highest rates of cirrhosis at first presentation (40–50%).

7. DIAGNOSTIC IMPLICATIONS OF HLA-DR GENOTYPING IN AIH

7.1 HLA Typing in the Diagnostic Algorithm

The International Autoimmune Hepatitis Group (IAIHG) Simplified Diagnostic Criteria (Hennes et al., 2008) do not formally incorporate HLA genotyping. However, the Revised Original Scoring System awards 1 point for HLA-DR3 or HLA-DR4 positivity, reflecting their diagnostic relevance. In cases of seronegative AIH — where autoantibody titers are below diagnostic thresholds — HLA-DR3 or DR4 positivity provides additional supporting evidence and may appropriately lower the threshold for liver biopsy.

More importantly, HLA genotyping is invaluable in differentiating AIH from overlapping conditions, particularly primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). PBC is associated with HLA-DQB1*04:02 and HLA-DPB1*03:01, alleles distinct from the AIH-associated DR3/DR4 haplotypes. In overlap syndromes where both AIH and PBC features coexist, dual HLA typing may aid in identifying the dominant immunopathological mechanism and guiding therapy selection.

7.2 Polygenic Risk Scores and Future Diagnostics

The emergence of polygenic risk scores (PRS) — composite genetic indices integrating contributions from multiple loci — represents a promising advance in AIH diagnostics. A proof-of-concept study demonstrated that a PRS incorporating HLA-DR3/DR4 status, CTLA-4 variants, and SH2B3 polymorphisms predicted AIH diagnosis with an area under the receiver operating characteristic curve (AUROC) of 0.78, superior to any single locus. As whole-genome sequencing becomes clinically accessible, PRS-based tools may facilitate early identification of at-risk individuals before disease manifestation.

8. THERAPEUTIC IMPLICATIONS OF HLA-DR GENOTYPING IN AIH

8.1 HLA Genotype-Guided Treatment Decisions

Standard first-line therapy for AIH comprises prednisolone (or prednisone) with or without azathioprine. The decision to attempt treatment withdrawal after biochemical remission is a major clinical challenge, as relapse risks vary substantially by HLA genotype. Current evidence supports the following genotype-guided approach:

DRB1*03:01 carriers: Treatment withdrawal is generally inadvisable due to > 60% relapse risk. Consider indefinite maintenance with low-dose azathioprine (0.5–1.0 mg/kg/day) or mycophenolate mofetil (1.0–2.0 g/day).

DRB1*04:01 carriers: After sustained biochemical remission (> 2 years), careful trial of treatment withdrawal may be attempted with close monitoring (ALT every 3 months for 1 year).

DR3/DR4 compound heterozygotes: Indefinite therapy is strongly recommended; consider early transition to maintenance therapy with azathioprine or mycophenolate.

DR3-positive with anti-SLA/LP: Particularly high relapse risk subgroup; indefinite therapy with regular reassessment of fibrosis progression by Fibroscan or liver biopsy.

8.2 Emerging Immunotherapeutic Targets Derived from HLA Biology

Understanding the molecular mechanisms of HLA-DR3 and HLA-DR4 in AIH has opened exciting avenues for targeted immunotherapy beyond conventional immunosuppression:

Antigen-specific tolerization: Peptide-based tolerogenic vaccines using dominant CYP2D6 or ASGPR epitopes presented by HLA-DR3/DR4 are under preclinical investigation. Early-phase tolerance studies in murine AIH models demonstrated restoration of Treg homeostasis and reduction of liver injury without systemic immunosuppression.

CTLA-4-Ig (Abatacept): By blocking CD80/CD86-CD28 co-stimulation, abatacept may selectively interrupt HLA-DR-restricted autoreactive T-cell activation. Case series suggest potential efficacy in treatment-refractory AIH, with ongoing Phase II trials.

IL-17/IL-23 axis blockade: Given the prominent Th17 signature in DR3-positive AIH, anti-IL-17A (secukinumab) or anti-IL-23 (risankizumab) therapies represent rational targets, particularly in patients refractory to conventional therapy.

Treg expansion and adoptive transfer: Ex vivo expansion of FoxP3+ Tregs from peripheral blood of DR3/DR4-positive AIH patients, followed by adoptive transfer, is in early clinical development (ONE study, NCT02166177), with potential for antigen-specific tolerance induction.

JAK inhibitors: Tofacitinib and ruxolitinib, targeting JAK1/2 signaling, may reduce Th1 and Th17 cytokine production in HLA-DR3-associated AIH, representing a class of agents with therapeutic promise in refractory cases.

9. FUTURE RESEARCH DIRECTIONS

Despite significant advances in understanding HLA-DR3 and HLA-DR4 associations in AIH, multiple critical questions remain unresolved. The field stands at an inflection point where integration of advanced genomic, immunological, and clinical data promises transformative insights:

High-resolution HLA structural genomics: Cryo-electron microscopy studies of DRB1*03:01 and DRB1*04:01 in complex with immunodominant autoantigenic peptides and autoreactive TCRs will provide atomic-level insights into the trimolecular complex underpinning AIH susceptibility.

Single-cell multi-omics: Single-cell RNA sequencing (scRNA-seq) and ATAC-seq of hepatic infiltrating lymphocytes stratified by HLA genotype will delineate cell-type-specific transcriptional programs driving genotype-specific disease phenotypes.

Gut microbiome interactions: Emerging evidence suggests that intestinal dysbiosis interacts with HLA genotype to modulate hepatic immune responses. Characterizing the microbiome-HLA-AIH axis may identify modifiable environmental factors for disease prevention.

Global GWAS expansion: Most genetic studies have focused on European populations. Inclusion of African, South Asian, and East Asian cohorts in large-scale GWAS will identify population-specific variants that interact with HLA-DR3/DR4 to modulate AIH risk.

Epigenetic regulation: DNA methylation and histone modification patterns at HLA-DR loci and immune regulatory genes may explain discordance among HLA-identical individuals and represent novel therapeutic targets.

Artificial intelligence integration: Machine learning models incorporating HLA genotype, autoantibody profiles, transcriptomic data, and clinical parameters may enable highly accurate prediction of AIH diagnosis, treatment response, and relapse risk in individual patients.

10. CONCLUSION

HLA-DR3 (DRB1*03:01) and HLA-DR4 (DRB1*04:01) are the cardinal genetic determinants of susceptibility to autoimmune hepatitis Type 1, exerting their pathogenic influence through multiple interconnected mechanisms: allele-specific peptide presentation to autoreactive CD4+ T cells, molecular mimicry-mediated tolerance breakdown, Treg dysfunction, and qualitatively distinct cytokine environments. These mechanistic differences translate into markedly different clinical phenotypes — with DR3-associated AIH exhibiting

greater severity, earlier onset, higher relapse rates, and worse transplant-free survival compared to DR4-associated disease.

The geographic and ethnic heterogeneity of these associations underscores the need for population-specific genetic studies to fully characterize the global landscape of AIH immunogenetics. HLA genotyping already contributes to AIH diagnosis through its inclusion in the Revised IAIHG scoring system and holds growing promise for personalized treatment decisions, particularly regarding treatment withdrawal timing and maintenance therapy intensity.

Looking forward, the convergence of high-resolution structural immunology, single-cell multi-omics, polygenic risk modeling, and targeted immunotherapy development promises to transform HLA-DR biology from a diagnostic marker into a therapeutic roadmap. Antigen-specific tolerization strategies targeting the HLA-DR3/DR4 peptide-binding groove represent the most compelling frontier — offering the possibility of precision immunotherapy that restores self-tolerance without the burden of lifelong generalized immunosuppression.

In conclusion, HLA-DR3 and HLA-DR4 are not merely disease associations but are central actors in AIH pathobiology whose full clinical exploitation will require continued interdisciplinary collaboration among immunogeneticists, hepatologists, structural biologists, and clinical trialists. The study of these alleles remains at the heart of efforts to understand, diagnose, and ultimately cure autoimmune hepatitis.

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