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GENETIC AND MOLECULAR BIOMARKERS OF AUTOIMMUNE DISEASES: FROM IMMUNE DYSREGULATION TO PERSONALIZED THERAPY

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ABSTRACT

Autoimmune diseases are heterogeneous disorders caused by the interaction of inherited susceptibility, epigenetic remodeling, environmental exposure, and dysregulated innate and adaptive immunity. The rapid development of genome-wide association studies, next-generation sequencing, single-cell technologies, and high-throughput proteomics has expanded the spectrum of candidate biomarkers that can be used for risk prediction, early diagnosis, assessment of disease activity, prognosis, and treatment selection. This narrative review summarizes the clinical significance of HLA alleles, non-HLA susceptibility genes, polygenic risk scores, DNA methylation patterns, non-coding RNAs, autoantibodies, cytokines, complement components, and multi-omics signatures in major autoimmune diseases. Particular attention is given to the translation of biomarkers into personalized therapeutic strategies, including patient stratification for biologic agents, Janus kinase inhibitors, B-cell-targeted therapy, and cellular approaches. The main limitations remain population heterogeneity, insufficient external validation, pre-analytical variability, and the lack of standardized multi-marker panels. Integration of genetic, epigenetic, transcriptomic, proteomic, and clinical data is the most promising route toward reproducible biomarker systems and precision medicine in autoimmunity.

KEYWORDS: autoimmune diseases; genetic biomarkers; HLA; single-nucleotide polymorphisms; epigenetics; microRNA; autoantibodies; cytokines; multi-omics; precision medicine.

INTRODUCTION

Autoimmune diseases comprise more than 80 clinically distinct conditions in which immune tolerance to self-antigens is impaired. Their phenotypes range from organ-specific disorders, such as autoimmune thyroid disease and type 1 diabetes, to systemic diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjögren disease, and multiple sclerosis. A common pathogenic feature is the interaction of genetic predisposition with epigenetic and environmental influences, followed by persistent activation of autoreactive lymphocytes and inflammatory effector pathways [1–4].

Conventional laboratory indicators, including C-reactive protein, erythrocyte sedimentation rate, and broad autoantibody panels, are useful but frequently lack sufficient disease specificity or predictive power. Modern biomarker research therefore focuses on combinations of genomic variants, transcriptional signatures, cellular phenotypes, proteins, metabolites, and clinical variables. Such integrated profiles may identify individuals at risk before irreversible organ damage develops, distinguish molecular subtypes within a single diagnosis, and predict response or toxicity during targeted therapy [5–8].

The aim of this review is to analyze genetic and molecular biomarkers involved in autoimmune disease susceptibility and progression and to assess their potential use in diagnosis, prognosis, monitoring, and personalized treatment.

MATERIALS AND METHODS

A narrative literature review was performed using publications indexed in PubMed, Scopus, Web of Science, and major biomedical journal platforms. Search terms included "autoimmune disease", "genetic biomarker", "HLA", "single-nucleotide polymorphism", "polygenic risk score", "epigenetic biomarker", "microRNA", "autoantibody", "cytokine signature", "multi-omics", and "precision medicine". Priority was given to systematic reviews, consensus statements, genome-wide association studies, and translational studies published from 2018 to 2025. Earlier landmark studies were included when they defined established mechanisms or biomarkers. Candidate biomarkers were evaluated according to biological plausibility, reproducibility, analytical feasibility, and potential clinical utility.

GENETIC SUSCEPTIBILITY AND HERITABLE BIOMARKERS

Genome-wide association studies have identified hundreds of susceptibility loci for autoimmune diseases. The strongest effects are concentrated in the major histocompatibility complex, where specific HLA class I and class II alleles alter antigen presentation and shape the autoreactive T-cell repertoire. HLA-DRB1 shared-epitope alleles are strongly associated with seropositive rheumatoid arthritis, HLA-DQ2 and HLA-DQ8 with celiac disease and type 1 diabetes, and HLA-B27 with ankylosing spondylitis. Nevertheless, HLA variants are neither necessary nor sufficient for disease development, and their predictive value varies across populations [3,9,10].

Non-HLA genes usually confer smaller individual effects but reveal key pathogenic pathways. PTPN22 influences lymphocyte receptor signaling; CTLA4 regulates T-cell co-stimulation; STAT4 participates in cytokine signaling; IL2RA affects regulatory T-cell homeostasis; IRF5 contributes to type I interferon responses; and TYK2 is involved in signaling through several cytokine receptors. A biomarker panel that combines these variants can provide more information than any single locus [4,11,12].

Polygenic risk scores aggregate the effects of many susceptibility alleles and may help identify individuals with a high inherited risk. Their translation into routine care is currently limited by ancestry-dependent performance, incomplete representation of rare variants, and the need to combine genetic risk with age, sex, family history, exposures, and immunological data [13].

Table 1: Selected genetic biomarkers associated with autoimmune diseases

Biomarker / gene	Biomarker type	Associated disease(s)	Potential clinical significance
HLA-DRB1 shared epitope	HLA allele group	Rheumatoid arthritis	Susceptibility, association with anti-CCP-positive disease and severity
HLA-DQ2 / HLA-DQ8	HLA haplotypes	Celiac disease; type 1 diabetes	Risk assessment and diagnostic support in appropriate clinical settings
HLA-B27	HLA allele	Axial spondyloarthritis	Supports diagnosis; limited value as a stand-alone screening test
PTPN22 rs2476601	SNP	RA, T1D, autoimmune thyroid disease	Altered lymphocyte signaling; pleiotropic autoimmune risk
STAT4 variants	SNPs	SLE, RA, systemic sclerosis	Association with interferon-related and Th1 pathways
CTLA4 variants	SNPs	T1D, autoimmune thyroid disease, SLE	Impaired co-inhibitory signaling and loss of tolerance
IRF5 variants	SNPs	SLE, Sjögren disease	Type I interferon pathway activation
TYK2 variants	SNPs	Psoriasis, IBD, SLE	Cytokine signaling; therapeutic relevance for TYK2 inhibition
Polygenic risk score	Composite genomic score	Multiple autoimmune diseases	Risk stratification; currently population- and method-dependent

EPIGENETIC AND NON-CODING RNA BIOMARKERS

Epigenetic mechanisms connect environmental exposure with persistent changes in immune-cell function. DNA methylation, histone modification, chromatin accessibility, and non-coding RNAs influence the expression of genes

involved in antigen presentation, lymphocyte activation, cytokine production, and regulatory T-cell stability. In systemic lupus erythematosus, widespread hypomethylation of interferon-regulated genes in T cells and other leukocyte populations is associated with disease activity. In rheumatoid arthritis, disease-related methylation patterns have been described in peripheral blood and synovial tissue, although tissue specificity remains an important limitation [14,15].

MicroRNAs are particularly attractive biomarkers because they are stable in serum, plasma, and extracellular vesicles. miR-146a, miR-155, miR-21, and miR-223 have been linked to inflammatory signaling in several autoimmune diseases. Circular RNAs and long non-coding RNAs may also contribute to disease classification and therapeutic monitoring, but most proposed markers still require prospective validation, standardized normalization, and replication across ethnic groups [16–18].

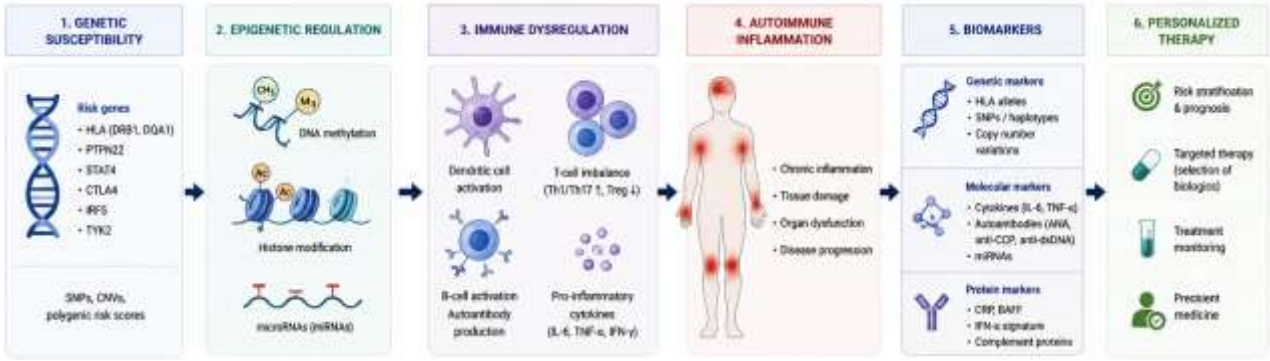

Figure 1. From inherited susceptibility to biomarker-guided personalized therapy in autoimmune diseases

IMMUNOLOGICAL AND PROTEIN BIOMARKERS

Autoantibodies remain among the most clinically mature biomarkers in autoimmunity. Anti-cyclic citrullinated peptide antibodies support early diagnosis and prognosis in rheumatoid arthritis; anti-double-stranded DNA antibodies and complement consumption are used in systemic lupus erythematosus; anti-thyroid peroxidase and anti-thyroglobulin antibodies characterize autoimmune thyroid disease; and disease-specific antibodies such as anti-AQP4 and anti-MOG define clinically relevant neuroinflammatory subgroups. However, antibody positivity can precede symptoms by years and must be interpreted within the clinical context [19,20].

Cytokines and soluble mediators reflect pathway activity rather than inherited risk. Type I interferon signatures are prominent in systemic lupus erythematosus and subsets of Sjögren disease and systemic sclerosis. IL-6, TNF-α, IL-17, BAFF, CXCL10, and complement fragments are candidate markers of disease activity or therapeutic response. A single cytokine is rarely sufficient because concentrations vary according to sampling time, comorbidity, medication, and assay platform. Multi-analyte panels are therefore more promising than isolated measurements [5,21,22].

Table 2: Molecular and immunological biomarkers with potential clinical utility

Biomarker	Class	Disease(s)	Proposed use
Anti-CCP antibodies	Autoantibody	Rheumatoid arthritis	Early diagnosis; prognosis of erosive disease
Anti-dsDNA antibodies	Autoantibody	Systemic lupus erythematosus	Diagnosis and activity monitoring, especially with complement
C3, C4, cell-bound complement products	Complement biomarkers	SLE and immune-complex diseases	Activity assessment and flare monitoring
Type I interferon gene signature	Transcriptomic signature	SLE, Sjögren disease, systemic sclerosis	Molecular stratification and potential prediction of targeted response
IL-6 and CRP	Cytokine / acute-phase protein	RA and other inflammatory AIDs	Activity monitoring; limited disease specificity
BAFF	Soluble protein	SLE, Sjögren disease	B-cell pathway activity; therapeutic target
miR-146a / miR-155	microRNAs	SLE, RA, MS	Candidate diagnostic and activity biomarkers
AQP4-IgG	Autoantibody	Neuromyelitis optica spectrum disorder	Disease-defining diagnostic biomarker
MOG-IgG	Autoantibody	MOG antibody-associated disease	Diagnostic classification and relapse-risk assessment

MULTI-OMICS AND CELLULAR BIOMARKER DISCOVERY

The heterogeneity of autoimmune disease cannot be adequately described by one molecular layer. Multi-omics approaches combine genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiome data, and immune-cell phenotyping. Single-cell RNA sequencing and spatial technologies reveal disease-associated cell states that may be hidden in bulk tissue analysis, including pathogenic T-cell subsets, age-associated B cells, interferon-responsive monocytes, and activated fibroblast populations [6,7,23].

Machine-learning models can integrate high-dimensional molecular profiles with clinical and laboratory data. Such systems may classify disease subtypes, identify patients at risk of organ damage, and predict response to therapy. Nevertheless, apparent model accuracy can be inflated by small cohorts, batch effects, data leakage, and limited external validation. Transparent model design, preregistered analysis, independent cohorts, and calibration across clinical settings are essential before implementation [8,24].

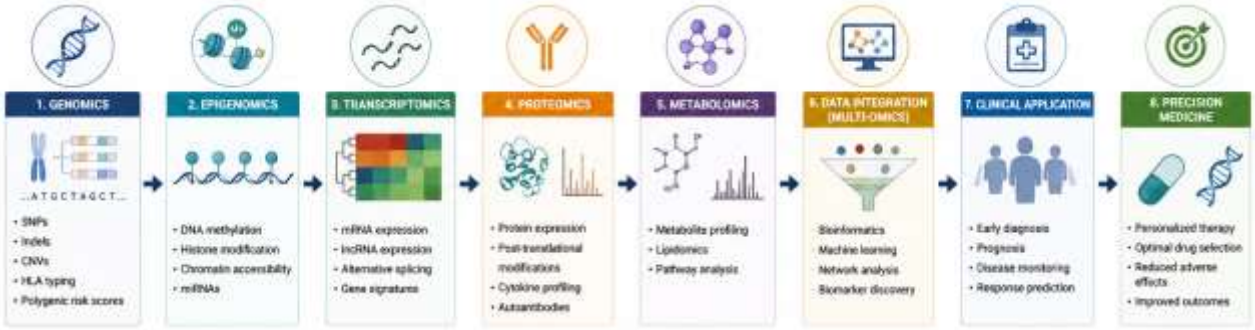

Figure 2. Multi-omics pipeline for biomarker discovery, validation, and clinical translation.

BIOMARKERS FOR PERSONALIZED THERAPY

Biomarkers can support personalized therapy at several decision points: selection of a molecular target, estimation of benefit, prediction of toxicity, monitoring of pharmacodynamic effects, and early detection of relapse. In rheumatoid arthritis, baseline serostatus, inflammatory burden, and molecular profiles may help refine the choice among TNF inhibitors, IL-6 receptor blockade, B-cell depletion, T-cell co-stimulation modulation, and Janus kinase inhibitors. In systemic lupus erythematosus, complement levels, anti-dsDNA antibodies, interferon activity, and B-cell pathway markers may contribute to treatment selection and monitoring, although no single panel is universally accepted [20–22].

Pharmacogenomic markers may identify patients at increased risk of adverse reactions or altered drug metabolism. HLA testing is already clinically established for selected immune-mediated drug hypersensitivity reactions, demonstrating that genomic biomarkers can directly improve safety. In autoimmune disease, emerging cellular therapies, including CAR T-cell and regulatory T-cell approaches, further increase the need for biomarkers that define disease mechanisms, treatment eligibility, depth of immune reset, and long-term remission [25–27].

Table 3: Biomarker-guided therapeutic applications in autoimmune disease

Clinical task	Candidate biomarker category	Example	Current status / limitation
Risk prediction	HLA and polygenic scores	HLA-DQ2/DQ8; multi-locus PRS	Useful in selected contexts; ancestry dependence limits generalization
Early diagnosis	Disease-specific autoantibodies	Anti-CCP; AQP4-IgG; MOG-IgG	Clinically established for selected diseases
Disease activity	Autoantibodies, complement, cytokines	Anti-dsDNA + C3/C4; CRP; IFN signature	Often requires combinations and longitudinal interpretation
Therapy selection	Pathway and cell-state biomarkers	Interferon, B-cell, IL-6, or TNF-related profiles	Promising; few fully validated companion diagnostics
Safety	Pharmacogenomic markers	HLA-associated drug hypersensitivity	Established for selected drugs; underused in some settings
Response monitoring	Transcriptomic/proteomic panels	Decline in IFN or B-cell pathway activity	Research use; assay harmonization required
Cellular therapy follow-up	Immune-cell repertoire and minimal residual autoimmunity	B-cell reconstitution, autoantibody kinetics	Emerging field with limited long-term evidence

LIMITATIONS AND FUTURE DIRECTIONS

The main barrier to clinical translation is the gap between biomarker discovery and validation. Many studies are cross-sectional, single-center, and underpowered. Differences in ancestry, age, sex, disease duration, treatment exposure, sample processing, and assay platform reduce reproducibility. The clinical meaning of a biomarker may also change over time; therefore, serial measurement and dynamic models are often more informative than a single baseline value.

Future studies should use prospective multicenter cohorts, common data standards, predefined analytical plans, and external validation. Biomarker panels should be evaluated not only for statistical association but also for incremental clinical value, cost, turnaround time, and impact on patient outcomes. Integration of multi-omics with electronic health records and interpretable artificial intelligence may allow clinically useful risk and response models, provided that fairness, privacy, and transparent reporting are maintained.

CONCLUSION

Autoimmune diseases arise from a multilayered interaction between inherited susceptibility, epigenetic remodeling, immune-cell dysfunction, and environmental exposure. HLA alleles, non-HLA susceptibility variants, polygenic risk scores, DNA methylation patterns, non-coding RNAs, autoantibodies, complement components, cytokines, and transcriptional signatures represent complementary biomarker classes. Their greatest clinical value will likely be achieved through validated multi-marker panels rather than isolated tests. The integration of genomic and molecular biomarkers with clinical phenotyping can improve early diagnosis, identify biologically distinct patient subgroups, guide targeted therapy, and support longitudinal monitoring. Large, diverse, prospective studies and standardized analytical pipelines remain essential for converting biomarker discovery into reliable personalized medicine.

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