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Advanced Medical Personalized Treatment for Autoimmune Disorders: A review Article for in-depth Insight into Personalized Autoimmune Medicine

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Abstract:

Autoimmune disorders are complex conditions that result from a combination of genetic and environmental causes and currently have no recognized therapy. Various therapeutic strategies may be used in various illnesses to promote remission or, at the very least, alleviate the symptoms. For customized therapy to be implemented, it is necessary to identify groups of individuals who are generally similar and share pathogenic signaling pathways. Therefore, research about autoimmune disorders mainly focuses on identifying new biomarkers, uncovering novel targets for therapy and agents, and understanding the processes involved in developing various disorders. We are just at the nascent phase of implementing tailored therapy for autoimmune illnesses. Hence, this research delved into the examination of several autoimmune illnesses and the impact of personalized therapy on their progression.

Keywords: Genomic analysis, Autoimmune disorders, Personalized medicine

Introduction

Millions of individuals use prescription drugs every day that do not benefit them, even if they seem to (1). Additionally, it is conceivable that such medications cause dangerous new illnesses to arise, complicating the original illness (2). Patients suffering from autoimmune illnesses experience these catastrophes to a greater extent (1, 2). Indeed, there is no general agreement about the course of therapy due to the variability of these disorders (3). More than 80 autoimmune diseases have no known cure, yet with an effective treatment plan, the symptoms may be effectively controlled (4). The majority of people with autoimmune illnesses are treated with the same restricted immunosuppressants, even though one medication does not work for everyone. Since the development of many biological medications, such as monoclonal antibodies, which target specific signaling pathways, most patients take these medications without awareness (4). Very few trustworthy indicators of treatment response that may be considered prior to therapy for autoimmune illnesses have been found (3, 4). This has produced inconsistent outcomes on the effectiveness of medications. Among the examples are tumor necrosis factor-α (TNF-α) inhibitors, which have

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been linked to insufficient response or intolerance in some autoimmune disease patients (5).

Furthermore, it has been shown that anti-TNF medications may cause psoriatic lesions in some inflammatory bowel disorder individuals (6). Rituximab, an anti-CD20 monoclonal antibody, is another frequently prescribed biological medication. It treats several autoimmune diseases, including pemphigus, RA, and systemic lupus erythematosus (SLE) (7). While almost all individuals see a decrease in B cells after using rituximab, not all benefit from the medication (8). Furthermore, after receiving rituximab, individuals with pemphigus have experienced a worsening of their condition (9). These inconsistent outcomes in individuals with the same illness classification might support the variety of autoimmune disorders, which most likely have distinct regulating signaling pathways (10). Serum autoantibodies, pathology findings, and specific clinical symptoms are employed to classify autoimmune disorders into several forms. However, that is only part of the story (8-10). Individuals who fit the exact parameters according to the methods above may not necessarily belong to the same variation. Distinct signaling pathways with the same effect may cause the illness (9, 10). Understandably, different individuals react differently to therapy in this situation. As a result, we should update our criteria to make autoimmune disorder variations more precise.

Personalized treatment for distinct autoimmune disorders

Autoimmune disorders occur when the body's immune system reacts to self-antigens due to tissue injury, malfunction, or imbalance (11). It is influenced by several variables, with host genes and the environment playing a crucial role. The immune system may target the whole body, specific systems, or specific organs based on a combination of hereditary variables, environmental influences, and self-antigens presented for identification (12).

The following autoimmune disorders' precision medications are covered in detail below (Figure 1):

1. Sjogren Syndrome
2. Myasthenia Gravis
3. Type 1 Diabetes
4. Rheumatoid Arthritis
5. Multiple Sclerosis
6. Lupus Erythematosus
7. Pernicious Anemia

Genomic analysis of multiple sclerosis

Multiple sclerosis is an inflammation and autoimmune condition that targets the myelin in the brain and spinal cord (13). It may impact individuals of all ages and lead to neurological impairment if not adequately treated. Over 200 loci have been recognized as a separate factor in the development of multiple sclerosis (14). Multiple sclerosis often presents in individuals aged 30 to 50 and is more prevalent in females than men (15). To comprehend the development of multiple sclerosis, it is necessary to analyze it using a multifactorial approach that considers the interplay of genetic, epigenetic, infectious, nutritional, climatic, and other environmental factors, along with sunlight exposure and smoking. The interaction of these elements results in self-intolerance and a decrease in immunological balance in the brain and spinal cord (15, 16). Peripheral mononuclear cells enter the brain and spinal cord organs, resulting in myelin breakdown and gliosis, which may cause neurological impairment. The individual diagnosed with multiple sclerosis has been treated using two main approaches based on the autoimmune hypothesis of the disease's development (17). The previous approach involves the administration of potent global immunosuppressive drugs. Simultaneously, the latter refers to using more specialized agents to pinpoint particular components of the body's immune response (18).

Researchers have investigated the impact of common genetic variations on multiple sclerosis, specifically focusing on various HLA alleles (19). These variants were discovered to be equally prevalent in both the control and the sample groups. Additionally, the statistical evaluation revealed that the odds ratio approaches one as the sample size increases (19). Biomarkers play a crucial role in the genetic evaluation of Multiple Sclerosis by demonstrating various features of the disease's diversity. They assist in diagnosing, categorizing, and predicting the progression of diseases, as well as in identifying effective treatments and creating tailored treatment plans based on anticipated responses (20). Since 2016, MRI has been the most suitable tool for diagnosing MS (21). The recommended field strength for brain MRI is 1.5 T. However, 3.0 T is considered superior (21). Recent research suggests that a 7 T field strength may identify central veins in brain lesions of MS patients (21, 22). However, this can also be achieved with T2-weighted sequences at 3 T, aiding in separating from microangiopathic lesions. While MRI is often used to diagnose MS, its true challenge lies in distinguishing MS from other illnesses such as neuromyelitis optical spectrum diseases (NMOSD), which similarly present with brief spinal cord lesions in the beginning (21, 22). It is advised to use T2-weighted and contrast-enhanced T1-weighted brain MRI for monitoring illness development, but an MRI of the spinal cord is not indicated. Aside from MRI biomarkers, bodily fluid biomarkers may indicate various stages of MS and

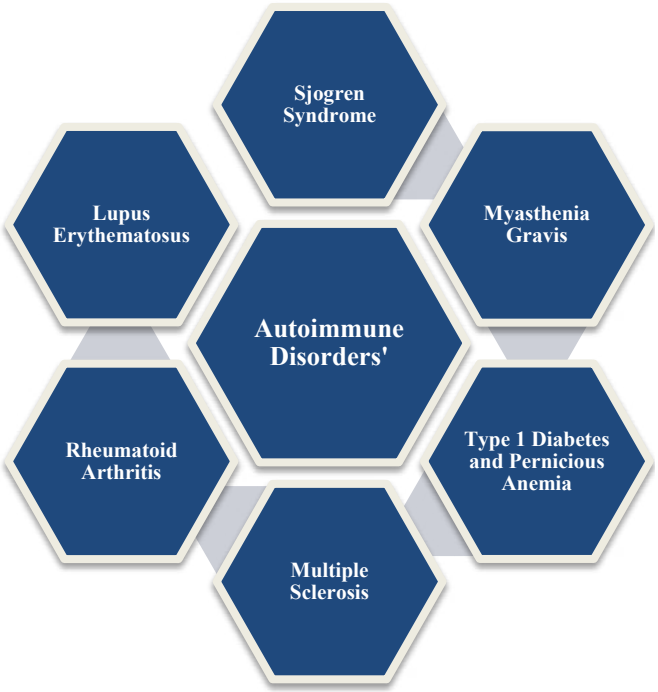

Fig1. Autoimmune disorders investigated in this study.

distinguish each stage from related diseases (23).

Body fluid indicators may be categorized into three primary groups: those indicating the initial stage of MS, those linked to the progression of the illness, and those related to the reaction to therapy (24). A low vitamin D concentration in the cerebrospinal fluid indicates the early stage of multiple sclerosis (25). A high level of Astrocyte-derived chitinase 3-like 1 (CHI3L1) in the cerebrospinal fluid (CSF) is a significant independent risk factor associated with the advancement of disability, as shown by multivariate Cox regression models (26). A proteomic method was used to establish that CHI3L1 is the strongest predictor of a transition to multiple sclerosis in individuals with clinically isolated syndrome (CIS). A multivariable analysis identified the CSF CHI3L1 level, MRI results, and age as the most significant predictors of multiple sclerosis risk. Neurofilaments (NF-L) have been suggested as a biomarker in the first stage of MS (27).

High-mobility group box protein 1, a transcriptional regulator, aids in distinguishing individuals with relapse-onset multiple sclerosis from those with primary progressive multiple sclerosis (28). Proteomic research indicates that distinguishing between multiple sclerosis patients with aggressive and benign disease courses may be achieved by analyzing two isoforms of vitamin D-binding protein and apolipoprotein E (29). Secretogranin-1, a calcium-binding protein, is reduced in the cerebrospinal fluid with the progression of the illness compared to the initial stages of multiple sclerosis (30). Stable multiple sclerosis patients have elevated B cell activating factor levels in their plasma samples compared to relapsing individuals (31). SLC9A9 is a biomarker linked to the lack of response to IFN beta (32). NLRP3 inflammasome upregulation is a biomarker for lack of response to IFN beta therapy (32). The biomarkers for predicting the response to glatiramer acetate include RGC-32, FasL, and IL-21 (33). Increased mRNA levels of RGC-32 and FasL and decreased expression of IL-21 in peripheral blood cells of responders compared to non-responders serve as the foundation for using these biomarkers (29-33).

Genetic analysis of myasthenia gravis

Myasthenia gravis (MG) is a form of autoimmune disease managed with long-term immunosuppressive therapy because of the effects of autoantibodies targeting the complex structure underlying the neuromuscular junction (34). The variability in patients' reactions to therapy and adverse effects justifies the need to identify biological indicators for predicting treatment success for every individual (35). Anti-AChR antibodies are a valuable biomarker for diagnosing MG. However, it cannot assess illness severity since no direct association was shown between MG severity and levels of anti-AChR antibodies (36). MiR-323b-3p, MiR−409-3p, MiR−485-3p, MiR−181d-5p, and MiR−340-3p have been identified as potential biomarkers for predicting and indicating immunosuppressive medication sensitivity in individuals with myasthenia gravis (37).

miRNAs may be analyzed in the blood as a robust

Table 1. Genetic factors involved in myasthenia gravis from the perspective of personalized medicine

Row	Genetic factor of myasthenia gravis	Role
1	miR-323b-3p	Decreased in non-responsive individuals
2	miR−409-3p	Decreased in non-responsive individuals
3	miR−485-3p	Decreased in non-responsive individuals
4	miRNA-181d-5p	Increased in non-responsive individuals
5	miR−340-3p	Increased in non-responsive individuals
6	*SPP1 gene*	Increased/ decreased non-responsive group

biomarker for therapy response (38). Patients who do not react as anticipated can be directed to other therapies, enhancing cost-effectiveness. MiR-323b-3p, MiR−409-3p, and MiR−485-3p were decreased in non-responsive individuals, but miRNA-181d-5p and MiR−340-3p were increased in non-responsive individuals (38, 39). An important link has been found between a patient's reaction to azathioprine and two specific genetic variations: the TPMT3E haplotype in the thiopurine S-methyltransferase and a haplotype in the ATP-binding cassette sub-family C member six transporter (40). MG individuals who did not respond to glucocorticoid medication were discovered to have a genetic variation in the *SPP1* gene expressing osteopontin, linking them to the non-responsive group (Table 1) (38-40).

Evaluating the genome in cases of pernicious anemia

Pernicious anemia (PA) is an inflammatory illness caused by a chronic Helicobacter pylori disease and atrophic body gastritis (ABG) (41). The ongoing disease is being progressively eliminated by an autoimmune response that permanently depletes the stomach mucosa (42). Vitamin B12 insufficiency has also been linked to the cause. Hence, the clinician's objective in treating severe anemia is to prevent anemic symptoms, address consequences, including nerve and heart muscle damage, and pinpoint the exact cause using precision medicine (43). The National Heart, Lung, and Blood Institute (NHLBI) is doing fundamental and clinical research to integrate personalized medicine and enhance the medical management of the illness (44).

Genetic analysis of rheumatoid arthritis

Rheumatoid arthritis (RA) is a varied condition that may manifest as either mild, self-limiting arthritis or rapid progressive joint deterioration (45 ,46). An intricate interplay between human genetic composition and environmental factors initiates the phenomenon (47). Environmental factors and genetics are insufficient to explain the diverse clinical characteristics of the illness fully. The condition is also defined by synovial hyperplasia and joint damage, potentially resulting in joint deformity (48).

The treatment of RA focuses on controlling inflammation. Early and effective medication significantly reduces the risk of joint damage, death, and disability (49). In 2017, significant research has concentrated on identifying biomarkers that might predict a patient's response specifically to Methotrexate (MTX), the first non-biologic treatment drug given (50). Approximately 30% of patients do not respond to TNF inhibitors (TNFi), but they are still often used as the first option among biological treatment medicines (51). The gene *SLC19A1* from the solute carrier family 19 member 1 shows the most reliable and significant evidence. It is a transport carrier that facilitates the entry of MTX into the cell (52).

Anti-CCP antibodies are a genetic marker linked to an unfavorable prognosis regarding disease severity and joint destruction. HLA-DRB1 alleles encoding common epitopes are also a signal for disease severity in RA (53).

Genomic evaluation of Sjogren's syndrome

Sjögren's syndrome (SS) is a kind of B cell hypersensitivity characterized by the production of too many autoantibodies and a high likelihood of developing B cell non-Hodgkin lymphoma (NHL) (54). Approximately 5% of primary Sjögren's syndrome individuals are susceptible to developing lymphoma (55). It is crucial to have a particular biomarker to identify patients early to monitor and detect them early and choose the proper treatment (54, 55). Diagnostic biomarkers aid in diagnosis, whereas predictive biomarkers provide further insights for clinical decision-making. Cytopenias are a recognized predictive indicator for the onset of lymphoma (56). Many suggested biomarkers for evaluating SS still need validation via more

comprehensive investigations before being used in clinical practice (57).

Genomic analysis of systemic lupus erythematosus

SLE presents many signs and symptoms that differ across individuals and affect several organs, including the joints, skin, kidneys, lung capacity, and CNS (58). It is a persistent inflammatory, immunological condition. A link has been identified between Systemic Lupus Erythematosus (SLE) and particular human leukocyte antigen (HLA) haplotypes, including HLA-DR3, DR9, DR15, and DQA1*0101 (59). A considerable correlation has been discovered between vitamin D levels in the blood and the genomic binding domains of vitamin D receptors of systemic lupus erythematosus (60).

Genomic analysis of type 1 diabetes

Type 1 diabetes (T1D) occurs due to the death of beta cells by the immune system, causing a decrease in insulin production and leading to high blood sugar levels (hyperglycemia) (61). The impact of precision medicine on type 1 diabetes is not well established (62). Patients with type 1 diabetes exhibit varying severity based on differences in their pancreatic autoantibody profile and the pace of beta cell destruction (62, 63).

Genetic research in precision medicine has identified over 50 genetic markers, particularly in the HLA area, that impact the propensity to T1D (64). Diagnostic indicators for T1D include a mix of glucose, C-peptide, glycated compounds, and autoantibodies. However, these molecules often indicate the advanced phase of the illness (65).

Recent advancements in genomic research include administering islet autoantigens or peptides to individuals at risk of Type 1 Diabetes, showing potential effects on immune modulation of islet autoimmunity (66). The issues persist in terms of dosing frequency, dose, method of administration, and the use of adjuvants (Figure 2).

Future outlook

Researchers should thoroughly study the systemic monitoring of variant genes such as *TNFRSF1A*, which is associated with the risk of multiple sclerosis. This gene might provide crucial insights into the cause of multiple sclerosis and novel approaches to therapy (67).

Myasthenia gravis-related genetic regions may contribute to the development of immune diseases by enhancing immune response, inhibiting immune suppression mechanisms, and modifying the process that distinguishes between self and non-self-molecular structures via immune tolerance. Therefore, studying single nucleotide polymorphisms (SNPs) linked to myasthenia gravis in the broader population can enhance the accuracy of diagnosis, treatment, and prognosis (68).

Genome editing techniques have successfully treated sickle cell disease and β-thalassemia. This approach might cure pernicious anemia by studying the gene responsible for the mitochondrial transportation of vitamin B12 (69).

Studies on rheumatoid arthritis should prioritize discovering additional genes linked to the condition

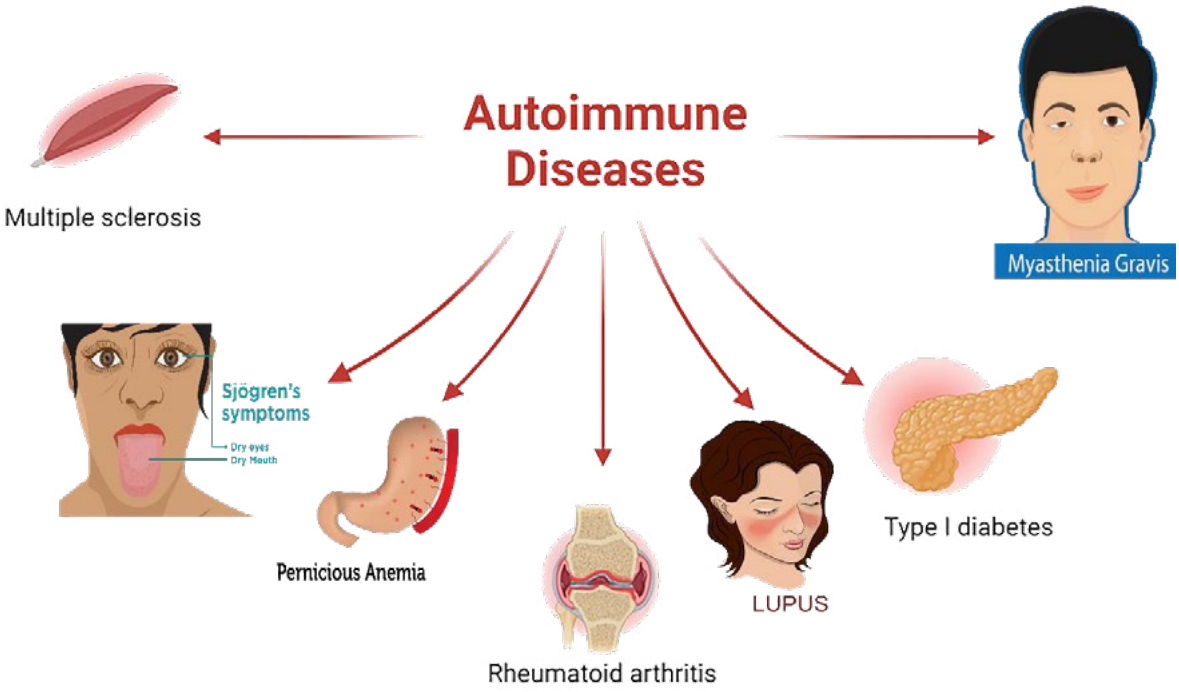

Fig2. Autoimmune diseases and their symptoms

and their corresponding impacts. Transcriptomic and epigenomic approaches should be utilized to identify indicators for reaction to treatment and pathways associated with therapy. Integrating genetic, clinical, and environmental information is essential for developing personalized medicine in treating rheumatoid arthritis (70).

Novel therapeutics for Sjogren syndrome might be discovered by identifying genetic risk factors, such as the significant interferon signaling pathway, including *IRF5* and *STAT4* genes (71).

The future therapy of systemic lupus erythematosus involves preventing the disorder by analyzing genetic profiles and creating novel biomarkers for immunological activation and modification (72).

Studying genes and pathways related to type 1 diabetes may uncover the timely involvement of the death of β-cells and the development of clinical illness by the innate and adaptive immune system. The Type 1 Diabetes Genetics Collaboration (T1DGC) globally provides materials that may assist in diagnosing, intervening, and monitoring the effects of treating type 1 diabetes (73).

In the age of 'Big Health Data,' using various algorithms for machine learning and deep learning is crucial for improving the diagnosis, prognosis, and therapy monitoring of autoimmune disorders by identifying patterns and clusters among distinct disease groups. This will facilitate the discovery of more relevant indicators and streamline the translation of biomarker research to clinical practice. The advancement of personalized healthcare in autoimmune illnesses relies on developing next-generation sequencing technology, which aims to provide a comprehensive, cost-effective analysis of the exome or transcriptome (74,75).

Conclusions

Genomics information is crucial for precision healthcare since it helps explain individual variability and development. However, the practical use of chromosomal information in clinical settings must be enhanced to address issues identified by researchers, such as the disparity between the molecular and medical data forms poses a challenge due to the vast amount of genomic information, making it difficult to handle clinical data in practice without further manipulation. Genomic and observational information utilized in clinical contexts varies due to the vast amount of data in genomic operations, making it distinct from data in clinical systems. Challenges arise when aligning genomic and clinical information for medical interpretation, particularly in specific sequencing, where information is often processed before medical analysis. There needs to be more global validation for the biomarkers being used, highlighting the need for international cooperation to evaluate the existing biomarkers. Conquering these obstacles will provide further possibilities for using genetic data in therapeutic settings.

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Authors' Contribution

Zahra Azami and Mahnaz Piri-Gharaghie were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare they have no conflicts of interest regarding the publication of this article.

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