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Role of genetics in eleven of the most common autoimmune diseases in the post genome-wide association studies era

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Abstract. – Autoimmune diseases (ADs) are common conditions in which an individual's immune system reacts against its healthy cells. This condition is a common cause of morbidity and mortality, with an estimated prevalence ranging from 5 per 100,000 to more than 500 per 100,000. According to the National Stem Cell Foundation (NSCF), ADs are prevalent in about 4% of the world's population, which creates a burden on society due to the high treatment cost. ADs show a clear gender bias with a higher prevalence among women, occurring at a rate of 2:1 female-to-male ratio. The etiology of ADs includes genetic and environmental factors. ADs are more likely to develop in genetically susceptible individuals. The higher concordance ratio between monozygotic twins compared to dizygotic twins or other siblings validates the role of genetic factors in the pathogenesis of many ADs. ADs diagnosis includes conventional immunoassay such as indirect immunofluorescence, complement fixation, passive agglutination, autoantibodies detection, and most recent advances, including multiplex platforms such as microspots, line-blot, addressable microbeads and barcoded nanoparticles that allow multiplex parallel testing of autoantibodies. ADs treatment includes biological and synthetic drugs that block many pathways and components of the immune system, including Janus kinase (JAK) inhibitors, non-receptor tyrosine-protein kinase (TYK2), and other cytokines. Generally, recent immune-modulatory drugs used in ADs treatment are non-disease specific with broad action and are associated with many side effects like infection and malignant diseases. Furthermore, gene therapy seeks to control the levels of proinflammatory cytokine molecules and lymphocyte infiltration through the delivery and expression of therapeutic genes. Recent genomic-wide association studies (GWAS) have allowed the identification of various genetic loci associated with disease susceptibility and have revealed candidate genes that can be used in targeted therapeutics. This review summarizes recent literature on the genetic factors associated with susceptibility to the 11 most common ADs, namely: Type 1 diabetes mellitus (T1DM), Multiple sclerosis (MS), Grave's disease, Sjögren's syndrome (SS), Celiac disease, Hashimoto's thyroiditis (HT), Anti-phospholipid syndrome (APS), Autoimmune hemolytic anemia, Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), and Scleroderma (systemic sclerosis).

Key Words:
Autoimmunity, Genetics, SNPs, Markers, GWAS.

Introduction

The immune system is smartly designed to elicit inflammatory responses against potentially harmful foreign materials while avoiding self-tissue damage. However, an uncontrolled inflammatory response might lead to tissue or organ damage and, eventually, death. Self-recognition is essential for shaping immune receptors on both T and B cells as well as clearing the body of apoptotic cells and other tissue debris. The development of harmful autoimmunity reactions with self-antigens is prevented under healthy conditions. Yet, if an immunological reaction of an organism occurs against its own cells, tissues, and other body constituents, autoimmunity can develop and lead to serious illness. With an estimated prevalence of 3,225 per 1,000, autoimmune diseases (ADs) are a common cause of morbidity and mortality[1]. The causes of AD could be genetic and environmental[1]. ADs are common pathologi-

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cal conditions that form in genetically susceptible individuals[2]. Autoimmunity is described as the existence of antibodies or T-cells that react with self-proteins. Autoimmunity is seen in all individuals, yet autoimmune disease (AD) happens when one or more of the basic regulatory mechanisms of immune tolerance break down and lead to self-reactivity, causing tissue damage[3]. In AD, the individual's immune system attacks its own healthy cells, tissue, and other constituents[4,5]. As a consequence, this leads to pathological changes and dysfunction of the tissue that is targeted by a self-immune response[6]. In this review paper, we discuss the genetic basis of the 11 most common ADs around the world, namely: Type 1 diabetes mellitus (T1DM), Multiple sclerosis (MS), Grave's disease, Sjögren's syndrome (SS), Celiac disease, Hashimoto's thyroiditis (HT), Anti-phospholipid syndrome (APS), Autoimmune hemolytic anemia, Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), and Scleroderma (systemic sclerosis). Table I summarizes the prevalence, gender ratio, affected organs/systems, pathology, and autoantigen mechanisms underlying these diseases.

Immune Tolerance (IT)

In 1948, Macfarlane Burnet and Eliza Hall[7] proposed that immune tolerance is acquired during the development of immune cells. Immunological tolerance or immune tolerance (IT) is achieved by several conditions that suppress the immune reaction[7]. Self-tolerance is known as the lack of specific immune responses of lymphocytes to self-antigens[8]. Tolerance to self-antigens is observed in the healthy immune state. Importantly, immune tolerance to self-antigens is regulated and maintained by multiple mechanisms that prevent the maturation and activation of self-reactive lymphocytes[9]. This includes central and peripheral tolerance (Figure 1), T regulatory cells (Tregs), and the homeostasis produced by the cytokines and chemokines and their cognate receptors[10]. Central tolerance refers to the process of removing self-reactive lymphocytes, including B- and T-cells, from the bone marrow or thymus before they enter circulation. On the other hand, peripheral tolerance is the process of additional tolerance in the peripheral tissue, targeting self-reactive T-cells that are able to escape the initial elimination in the thymus[11]. Clonal deletion is a process of elimination of immature B cells bearing IgM that recognize ubiquitous self-surface antigens. Autoreactive B cells can be modified responses called receptor editing rather than being deleted[10]. Receptor editing is the main process for the removal of autoreactive T or B-cells, yet this system is not perfect[12]. Inactivating *recombination-activating gene 1 (RAG 1)* and *recombination-activating gene 2 (RAG 2)* protein expression, which promotes positive selection, regulates receptor editing[13]. If the receptor editing fails, the autoreactive T or B cells undergo clonal deletion. Although there are several processes for controlling autoreactive lymphocytes, they can still escape and leak out into the periphery, even in healthy individuals. The presence of autoreactive lymphocytes or their ability to generate autoantibodies does not always result in pathology[14]. Several studies[15-17] have shown the presence of autoantibodies or autoreactive T cells in normal physiological conditions. Autoreactive T cells in healthy individuals' peripheral blood can react with several body structures, including myelin basic protein (MBP) of the myelin sheath and type II collagen of cartilage. Moreover, autoimmunity can be beneficial in some biological processes such as tissue repair, stroke, and Alzheimer's disease[18]. For that reason, it is believed that the presence of autoantibodies or autoreactive T-cells is not sufficient to elicit ADs. It has been proposed that the presence of low-level auto-reactivity is physiological and necessary for a normal immune response. It has been reported to ensure homeostasis and the survival of mature T-cells in the peripheral blood, weak reactivity of autoantigen reactivity is important[19]. Self-immune tolerance plays an important role in the treatment and prevention of ADs[7]. ADs arise from one or a combination of the following factors: genetic, immunological, and environmental factors[11].

Mechanism of Autoimmunity

The endocrine system, connective tissue, gastrointestinal tract, heart, skin, kidneys, and other body sites can all be affected by ADs. The mechanism of most ADs remains incompletely defined. Despite that, much progress has been made in understanding the processes involved in the development of self-sustaining, anti-host immune responses[3]. All ADs are believed to go through three major phases: initiation, propagation, and resolution[20]. A combination of genetic factors, genetic predisposition, and environmental fac-

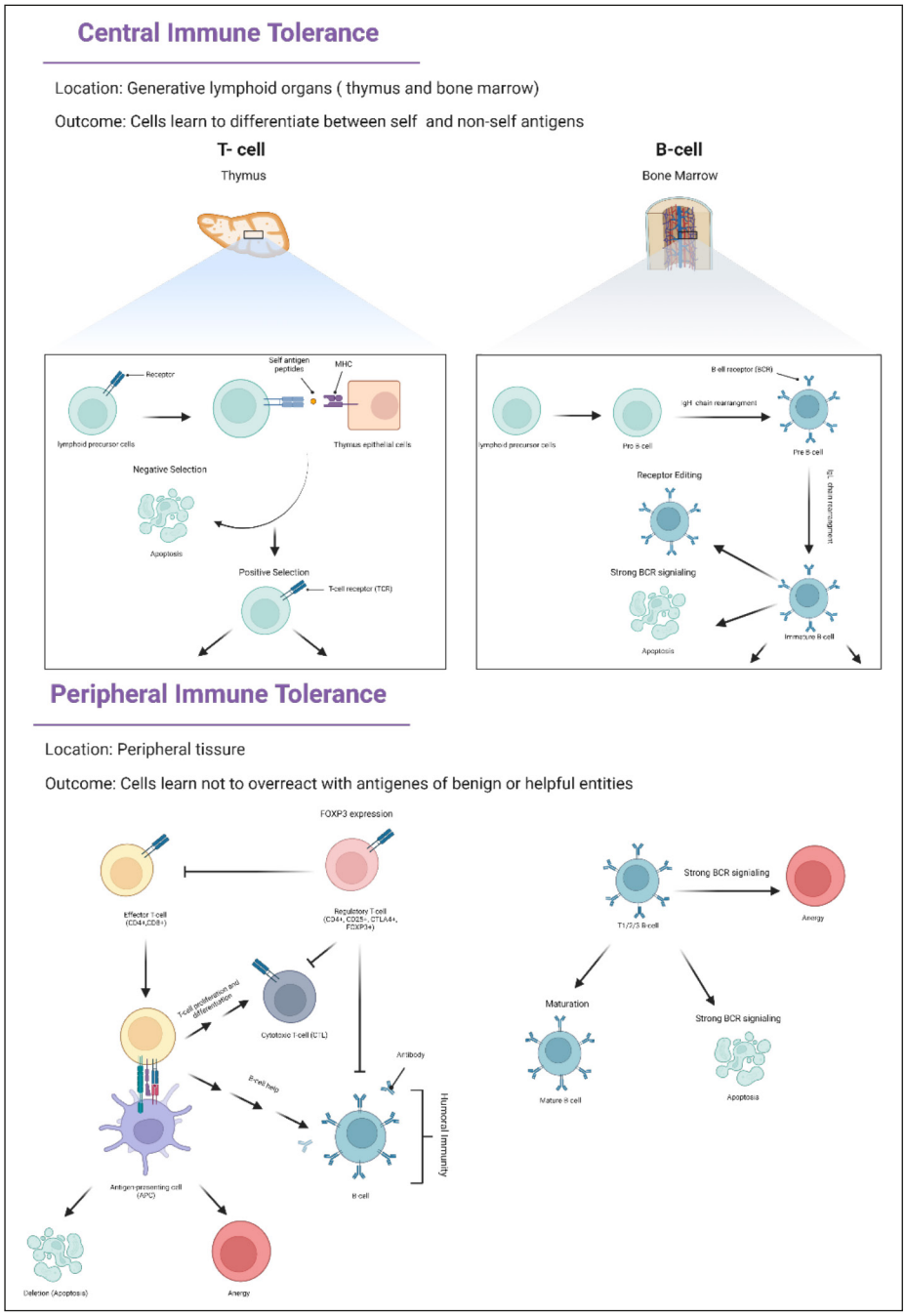

Figure 1. Central and peripheral immune tolerance. The top panel shows events involved in central tolerance that take place in generative lymphoid organs (thymus for T-cells and bone marrow for B-cells). Lymphoid precursor cells undergo a maturation and selection process determined by the interaction with major histocompatibility complex (MHC) proteins and self-peptides. Positive selection occurs when double-positive T-cells (having $CD4^+$ and $CD8^+$ receptors) bind to thymus cortical epithelial cells having MHCI or MHCII along with self-antigen peptides with a sufficient enough affinity to get the survival signal. Strongly self-reactive lymphoid precursor cells are deleted and undergo apoptosis (negative selection). Pro B-cell undergoes Immunoglobulin heavy chain rearrangement (IgH). Followed by the Immunoglobulin light chain rearrangement (IgL). Auto-reactive B-cell in central immune tolerance can undergo receptor editing to lower the reactivity (strong BCR signal) of B-cell to self-antigen. On the other hand, lymphoid precursor cells with auto-reactivity below a certain threshold can migrate into the periphery as mature lymphoid cells (T-cells or B-cells). The majority of T-cells develop into effector T-cells (Teff) expressing $CD4^+$ and $CD8^+$ surface receptors. Teff mediates both humoral (antibody-mediated) and cellular immune responses. The minority of T-cells are differentiated into regulatory T-cells (Treg) having $CD4^+$, $CD25^+$, and $CTLA4^+$ surface receptors. They mediate peripheral immune tolerance, yet their mechanism is not fully understood; it involves many levels of effector immune response. Treg can prevent T-cell activation by antigen-presenting cells (APCs), which prevents T-cell differentiation into cytotoxic T-cells. Also, preventing T-cells from helping B-cell in the production of antibodies. Peripheral tolerance contributes to the induction of anergy (functional unresponsive T or B-cell), apoptosis, and suppressive action machined by Treg. Adopted from[138]. Created using BioRender.com.

tors causes autoimmunity. Individuals with ADs are typically unaware of any clinical symptoms in the initiation stage. Self-perpetuating inflammation and tissue damage caused by cytokine production, epitope spreading, and a disrupted effector T-cell to regulatory T-cell (Teff/Treg) balance characterize the propagation stage. The resolving stage then initiates with the activation of cell-intrinsic (inhibitory pathways) and cell-extrinsic (Tregs) mechanisms. This limits the effector response and restores the Teff/Treg balance[21]. Patients frequently encounter relapsing and remitting disease as a result of the ongoing battle between pathogenic effector responses and regulation. The failure of regulatory mechanisms and the short-term ability to maintain the equilibrium between effector and regulatory responses are associated with the initiation and propagation stages of ADs. ADs are hypothesized to be initiated by polymorphisms in different genes, leading to defects in the regulation or reducing the threshold for lymphocyte activation[22]. Besides that, environmental factors initiate the activation of self-reactive lymphocytes and react with self-tissues, as illustrated in Figure 2[20].

Autoimmune Diseases (ADs)

ADs result from autoimmune reactions with self-tissue. An autoimmune response is known to cause approximately 15 diseases. ADs can affect any site in the body, and their clinical manifestations are highly variable. They affect around 3% to

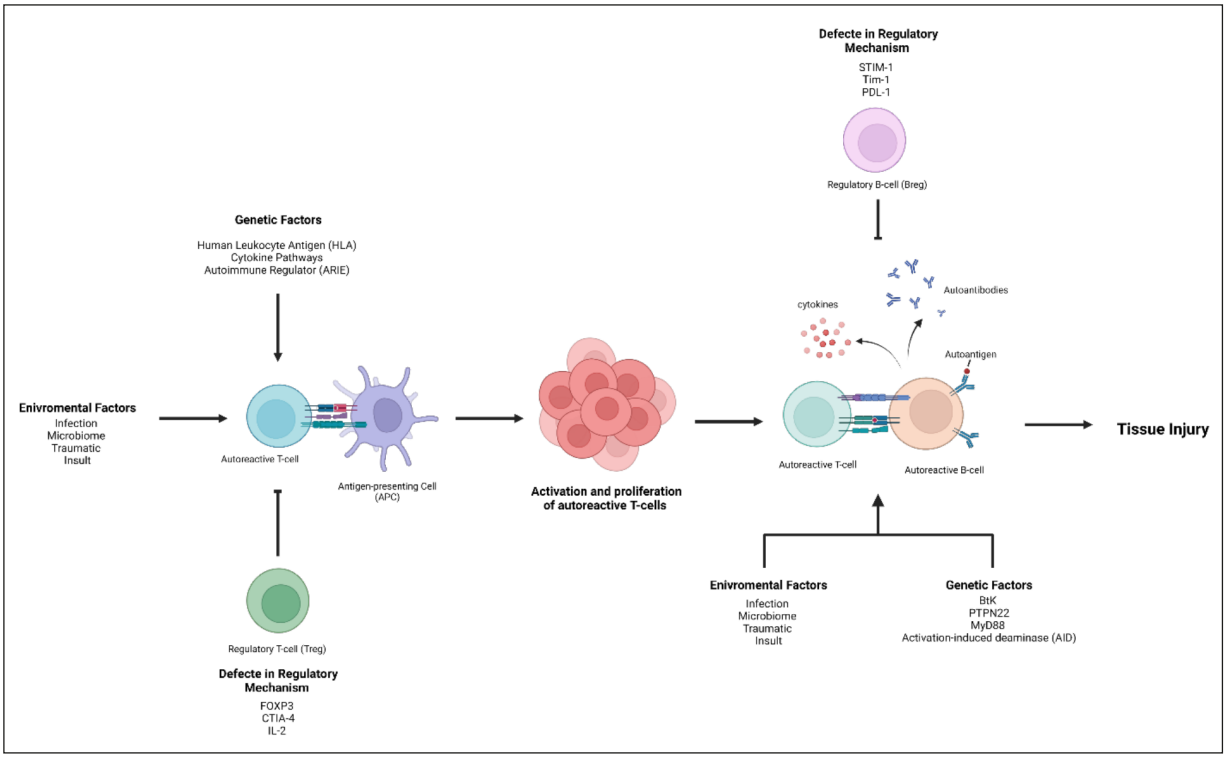

Figure 2. Factors affecting the initiation of autoimmunity. Genetic polymorphisms (genetic factors) in gene-related to immunity, including HLA, cytokines, autoimmune regulators or receptors, and genes involved in central tolerance such as the *AIRE* and *AID* genes, can lower the threshold for the activation of autoreactive T cells that activate autoreactive B-cells leading to the production of autoreactive antibodies. Environmental factors including infection, microbiomes, insult, and trauma [central nervous system injury, stress, reactive oxygen species (ROS), and posttraumatic stress disorder (PTSD)] can generate a proinflammatory environment that supports the initiation of autoreactive T and B-cells. Regulatory T-cells (Treg) suppress the autoreactive T-cells in a normal situation. Any defect resulting from the inability to control autoreactive T-cells responses. Regulatory B cells (Breg), like regulatory T cells (Treg), regulate the activity of T and B cells. Normally, Breg contributes to immunomodulatory processes and suppression of immune responses by the production of the anti-inflammatory cytokine, mainly IL-10, and inhibition of T cell activation, and induction of Tregs. Any defect in regulatory B-cells leads to decreased IL-10 production, creating a proinflammatory environment that amplifies the effect of autoreactive T and B cells. One or several of these factors can contribute to autoreactive T and B cell escape, activation, and proliferation, resulting in tissue damage and clinical disease, including autoimmunity diseases (ADs). Adopted from[20]. Created with BioRender.com.

9% of the population or 14-22 million individuals, 78% of whom are females[5,23]. The majority of ADs are rare, yet they are the most common disease in industrialized societies[24]. Organ-specific ADs, such as Hashimoto's thyroiditis, Graves' disease, multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), antiphospholipid syndrome (aPL), and autoimmune hemolytic anemia[5], affect a specific organ or target in the body. On the contrary, systemic ADs affect multiple organs, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and scleroderma[5,25]. RA is considered to be a systemic inflammatory disease that commonly affects synovial tissues and can involve other tissues and organs. For example, non-articular muscular structures include tendons, ligaments, and fascia[26]. Some of the least common ADs include bullous pemphigoid (BP) and autoinflammatory syndromes such as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE) and stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI)[27]. ADs can cause significant mortality and morbidity rates[10]. Most ADs show a clear sex difference in their prevalence. ADs are one of the leading causes of death among young and middle-aged women (less than 65 years old) in the United States[28]. Notably, epidemiological studies[28] showed that thyroid disease and type I diabetes are the most common ADs[10]. According to Cooper et al[28], the differences in gender and age at the diagnosis or onset of specific ADs may provide evidence for different disease pathways. SLE, for example, occurs 5-10 years earlier among women in comparison to men. Nevertheless, this may be limited to white ethnicity patients[28]. On the contrary, hyperthyroidism occurs earlier among men, with 35-year mean onset age for men compared to 48 years for women. In addition to that, there are differences in the risk factors of specific ADs among different countries and different ethnicities living in the same geographical area. The pattern of ADs is not consistent as some ethnic groups have a higher risk than others of acquiring a disease but a lower risk of acquiring others[28] (Table I).

Genetic Factors in ADs

Susceptibility to ADs is associated with different factors that include genetic, epigenetic, and environmental components[57]. Chemical and physical agents, dietary components, gut microbiota, and infections such as viral infections are all environmental factors that may contribute to immune tolerance loss[58]. Viral infections are the main environmental factor that can induce ADs among genetically susceptible individuals[59]. Viruses such as Parvovirus, Epstein-Barr virus (EBV), Hepatitis C virus (HCV), and Mumps have been shown to induce ADs, including rheumatoid arthritis (RA), thyroid diseases, primary biliary cirrhosis (PBC), type I diabetes, and autoimmune hepatitis (AIH)[60]. Several mechanisms utilized by viruses can initiate ADs, including molecular mimicry, epitope spreading, bystander activation and stimulation of pattern recognition receptors, viral persistence, and polyclonal activation of B cells, and autoinflammatory activation of innate immunity[59,60]. Different genetic factors are interconnected with disease susceptibility, specific autoantibodies, and disease phenotypes[61]. Genetic risk contributes to all ADs with varying penetrance, ranging from monogenic to polygenetic disease. Monogenic diseases are caused by a single deleterious gene variant with minimal or no environmental influence. On the contrary, polygenetic diseases are caused by multiple variants in combination with environmental influences causing autoimmunity[62]. ADs can be caused by a change or defect in a single gene, affecting specific immune mechanisms needed to maintain tolerance[63]. Genetic polymorphisms are inherited sequence variants in the genome that lead to phenotypic variability and regulate the expression and function of genes. Consequently, they can affect biological pathways and alter the magnitude of susceptibility to ADs[57]. Immune regulatory genes or immunogenetic loci are genes that encode MHC class I and II proteins, complement components, immunoglobulins, cytokines or chemokines and their receptors, transporters associated with antigen processing genes, T-cells receptors genes, and minor histocompatibility markers. The MHC genes in humans are located on the short arm (p) of chromosome 6[64,65]. The MHC genes class I (A, B, C) and class II (DR, DQ, DP) genes are highly polymorphic. They encode the Human leukocyte antigens (HLA) that consist of light and heavy chains that combine, forming peptide binding sites, and it is represented on the T-cell receptor. Consequently, any difference in the amino acid sequence can alter the peptide-binding site, leading to a difference in binding affinity. This change in amino acid was shown to affect the peptide binding and can be related to the autoantigen presentation. The MHC class III involves signaling molecules (heat-shock proteins) and in-

Table I. Summary of the most common autoimmune diseases (ADs) worldwide.

Classification	Disease	Organ/System	Mechanism	Pathology	Autoantigen	Mechanism of damage	Prevalence (per 100,000 per year)	Gender ratio (female/male)	Ref.
Organ-specific autoimmune diseases	Type 1 diabetes mellitus (T1DM)	Pancreas β cells.	Autoantibodies and autoreactive T-cells that react to pancreatic islet cells.	Extermination of islet cells and failure of insulin production.	Pancreatic β-cell antigens and insulin	Antibodies and T-cells	15	1/1	5,10,29-31
	Multiple sclerosis (MS)	Brain and, or spinal cord	T-cell response against myelin basic protein.	Demyelination of neurons, marked by patches of hardened tissue in the brain or the spinal cord; partial or complete paralysis and jerking muscle tremors.	Myelin basic protein and proteolipid protein.	T-cells	35.9	2/1	10,29,30,32
	Grave's disease	Thyroid	Autoantibodies against receptors for thyroid-stimulating hormone (TSH).	Stimulation of the increased release of thyroid hormone causes hyperthyroidism.	Thyroid-stimulating hormone receptor (TSHr).	Antibodies	21	5/1	10,29,30,33
	Sjögren's syndrome (SS)	salivary glands	CD41 cells react with self-antigens (M3 muscarinic acetylcholine receptor). lymphocytic infiltration into the salivary and lacrimal glands and attack the glands.	Reduction and inflammation of exocrine glands secretion.	Sjögren's-associated antigen A or B.	Lymphocytes.	13.1	9/1	10,30,34-37
	Celiac disease	Small bowel	Antibodies made to gliadin (gluten), cross-reactive to tissue transglutaminase.	Gluten-sensitive enteropathy, villous destruction, and gastrointestinal manifestations.	Transglutaminase	T-cells and antibodies.	17.4	1.85/1	29,30,38,39
	Hashimoto's thyroiditis (HT)	Thyroid	Autoreactive T-cells and autoantibodies to thyroglobulin and thyroid microsomal antigens.	Hypothyroidism.	Tg-antibodies, Thyroid peroxidase, thyrotropin receptor, and sodium iodide symporter.	T-cells and antibodies.	0.3 to 1.5 per 1,000.	10.3/1	30,40-44
	Anti-phospholipid syndrome (APS)	Vascular system	Presence of lupus anticoagulant (aPL), anticardiolipin, or anti- β2-glycoprotein I antibodies.	Obstetric morbidity (mainly pregnancy losses) and or vascular thrombosis.	anticardiolipin and anti-β2-glycoprotein I.	Antibodies.	40-50	2/1 to 5/1	45-47
	Autoimmune hemolytic anemia	Red blood cells	Autoantibodies to RBC antigens.	Lysis of red blood cells (RBC) and anemia.	RBC surface antigen.	Antibodies	17	60/40	5,30,48
Systemic autoimmune diseases	Rheumatoid arthritis (RA)	joints, lungs, heart, etc.	Autoantibodies to IgG (rheumatoid factor). In addition, the deposition of immunocomplexes in the synovium of joints, lungs, heart, etc. The infiltrating of autoreactive T-cells in the synovium.	Inflammation of joints and deformation in cartilage and bones.	IgG, filaggrin and fibrin.	T-cells and antibodies.	43.3	2/1	10,29,30,49,50
	Systemic lupus erythematosus (SLE)	Kidney, skin, heart, joint, etc.	Immunocomplex circulating in the body formed by autoantibodies to nuclear antigens (antinuclear antibodies), including anti-DNA.	Glomerulitis, arthritis, vasculitis, skin rash, etc.	Nucleic acid (DNA, histones, ribonucleoproteins), and others.	Antibodies	48.0	9/1	29,30,51,51
	Scleroderma (systemic sclerosis)	Connective tissue, the microvasculature, and the small arteries.	Antibodies against topoisomerases, fibrillarin, and polymerase.	Damage to arteries and skin-related fibrosis.	Jo-1, histidyl RNA synthetase; Ku, autoantibody, and others.	T-cells and B-cells.	17.6	5/1	30,53-56

flammatory responses (the complement proteins), and macrophage activation [tumor necrosis factor (TNF)][66]. Moreover, other cytokines that are not encoded by the MHC play an important role in stimulating T-cells and B-cells, including Interleukin-2 (IL-2), IL-6, IL-12, and interferons. Genetic variability of the immunoglobulin structure (immunoglobulin allotypes) and T-cells receptors may influence the immune response to self-antigens leading to ADs[21]. Other non-MHC genes have a minor contribution to ADs susceptibility[67]. Another gene that, when altered, can lead to ADs is the prolactin gene located near the MHC, and is important as an immune-modulating influencer[64]. Any variation in *MHC* genes, including a single amino acid change, results in genetic susceptibility to ADs. The protein encoded by the gene linked to ADs is elaborated in several inflammatory mechanisms like antigen presentation, type I interferon, Toll-like receptors, NF-κB signaling, B-cell and T-cell functions, apoptosis, and clearance of cellular debris and immune complexes[68].

Genomic-Wide Association Study (GWAS) on ADs

Genomic-wide association study (GWAS)[69,70] is a genetic study estimating the association of genetic variants with human complex diseases or quantitative traits like height, weight, and age. GWASs typically concentrate on single-nucleotide polymorphisms (SNPs), yet other types of variants can be included, such as copy number variation, indels, and genetic variations. GWASs inspect variants across the whole human genome; thus, it gives a way to study human autoimmunity diseases with complex mechanisms. Apart from biological experiments, GWAS is a hypothesis-free driven approach. Therefore, it is unbiased, providing a way to find clues for novel biological mechanisms of specific diseases. GWASs were applied to identify many risk variants associated with autoimmune diseases[69]. GWASs have been used as a tool for discovering polymorphic genes that cause genetic susceptibility[70]. According to the GWAS catalog, there are 291 studies and 4,417 associations related to differences in autoimmune diseases. Table II lists selected common and rare variants causing autoimmunity disease arranged from the most common to least common. Notably, a genetic variant can be related to more than one AD. For instance, an SNP (rs6457617) was found to be associated with Grave's disease and scleroderma. The Ensembl Variant Effect Predictor (VEP) tool (Figure 3) was used to predict the consequences of SNPs causing ADs. Results had shown around 38% are intronic variants, 16% are upstream gene variants, 14% are downstream gene variants, 12% are non-coding transcripts,

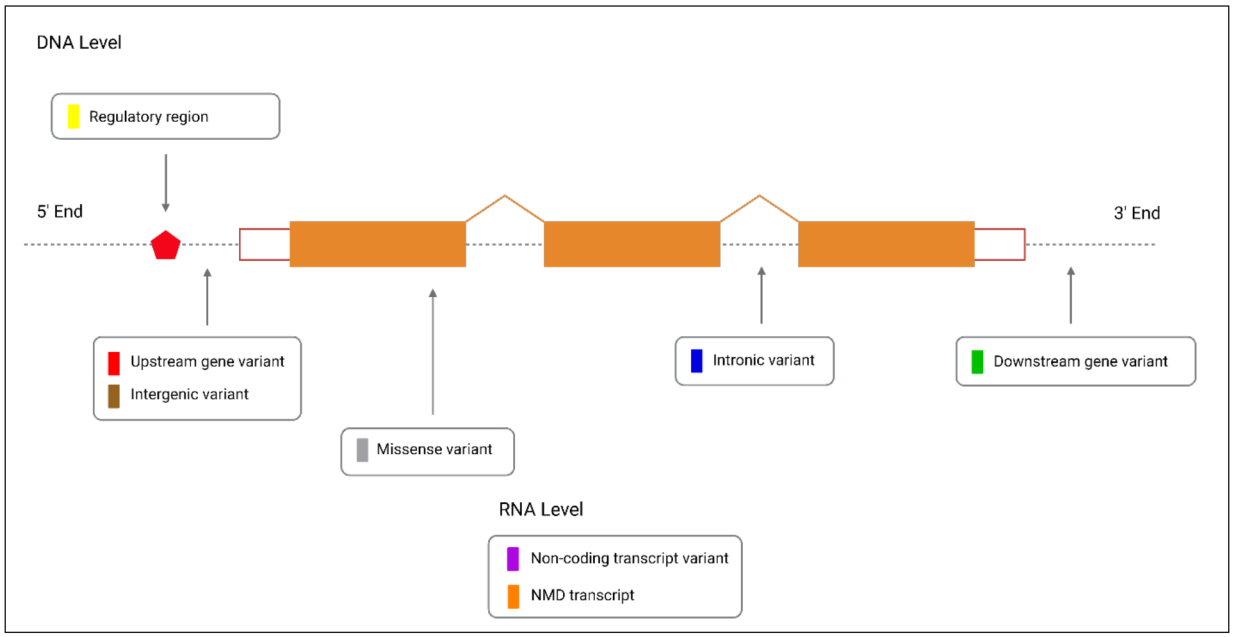

Figure 3. ADs-related SNPs Location as retrieved from the GWAS catalog, using Variant Effect Predictor (VEP) tool provided by Ensembl Variant Effect Predictor[139].

4% are NMD transcripts, 3% are regulatory region variants, 3% are intergenic variants, 2% are missense variant, 2% are non-coding transcript exon variant, and 4% other types of variants (Figure 4). Moreover, among all SNPs associated with these 11 ADs, there are 2,072 overlapped genes and 10,087 overlapped mRNA transcripts. Overlapping genes are defined as pairs of genes with partially overlapping genomic regions[71]. These overlapping genes are frequently encoded on opposing DNA strands and are often associated with specific disease phenotypes[72]. They are remarkable for their potential intricate regulation, such as cis-regulation of nested gene-promoter configurations and post-transcriptional regulation of natural antisense transcripts[71]. Complex transcriptional regions will arise from overlapping transcripts[73]. They can influence the expression of their complementary genes at various levels, including transcription, mRNA stability, and translation[74]. Intergenic variants are responsible for gene expression modulation by altering chromatin states and promoter or enhancer-associated activity[75]. On the other hand, intronic variants mainly regulate biological activity by dysregulating mRNA splicing processes[76]. For example, over 20,000 disease-causing variants in the Human Gene Mutation Database (HGMD) have shown an impact on the splicing processes, and the majority of these pathogenic variants are located close to splice-junction boundaries[77]. This emphasizes the impact of intronic variants and their role in causing pathogenic effects, including ADs. Intergenic variants are a subclass of non-coding RNA variants that were previously identified as junk DNA, and they are located within two coding genes. Their roles are not fully known yet. They are believed to have a trans-regulatory effect within some ribonucleoproteins[78]. Furthermore, a considerable number of genetic variants are linked to susceptibility to ADs[2]. An upstream gene variant is a sequence variant located in 5' of a gene region. This variation can include variation in the promoter region or regulatory regions such as the 5' UTR and 3'UTR regions. Promoter regions consist of transcription factor binding sites (TFBS) and RNA polymerase II binding sites[79]. Variation in the promoter region can affect the level of mRNA and, thus, proteins. The regulatory region plays an important role in gene expression regulation, including cis- and trans-regulatory elements, binding transcription factors (TFs), enhancers, promotes, and transcribed non-coding regions with a regulatory role like micro RNAs (miRNAs), and long non-coding RNAs (IncRNAs)[77]. SNPs in the 3' UTR disrupt mRNA stability and translation by affecting polyadenylation, regulatory protein mRNA, and miRNA-mRNA interaction[81]. Many variants in the 3' UTR that affect ADs risk have been identified in preliminary human studies[81]. On the other hand, 5' UTR variants account for 1% of ADs

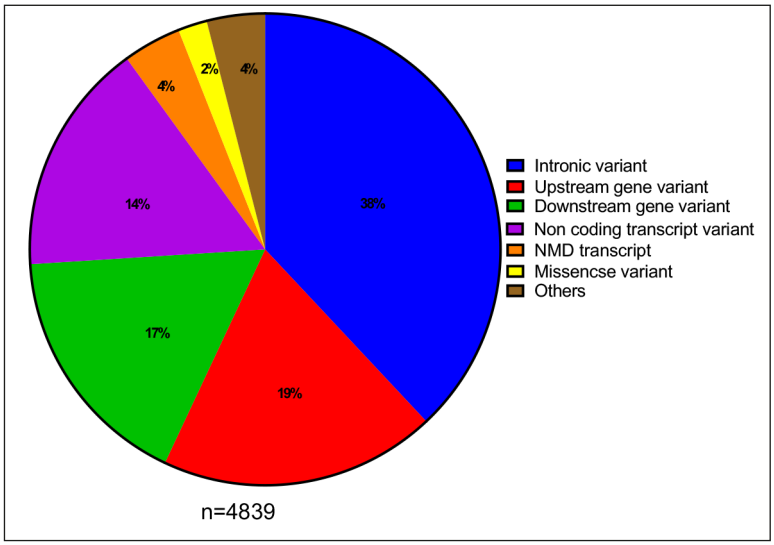

Figure 4. Pie chart of variants consequences of the SNPs related to AD retrieved from the GWAS catalog, using Variant Effect Predictor (VEP) tool provided by Ensembl Variant Effect Predictor[139]. N represents the total number of SNPs. Only SNPs with $p \leq 5 \times 10^{-8}$ were selected.

Table II. Summary of selected common and rare variants causing autoimmunity disease (ADs).

ADs	SNPs	Alleles	Minor allele	Risk allele	Variant type	Genes	Region	SINP localization	Ref.
Type 1 diabetes mellitus (T1DM)	rs9272346	A/G/T	G	G	Common	*MHC*	6p21.32	Intron variant	[88]
	rs2476601	A/G/T	A	A	Common	*PTPN22*	1p13.2	Missense variant	[89,90]
	rs1770	G/A	G	G	Common	*HLA-DQB1*	6p21.32	Splice region variant	[91]
	rs689	A/G/T	A	A	Common	*INS*	11p15.5	Splice region variant	[89,92]
	rs192324744	T/A/G	G	G	Rare	*LRP1B*	2q22.2	Intron variant	[93]
	rs142823282	T/C	G	G	Rare	*TAMM41*	3p25.2	Intron variant	[94]
	rs149641852	G/T	T	T	Rare	*SNCAIP*	5q23.2	Intron variant	
Multiple sclerosis (MS)	rs10801908	C/G/T	T	C	Common	*CD58*	1p13.1	Intron variant	[95]
	rs11256593	C/T	T	T	Common	*IL2RA*	10p15.1	Regulatory region variant	
	rs438613	T/C	C	C	Common	*EOMES*	3p24.1	Intron variant	
	rs1800693	T/C	C	C	Common	*TNFRSF1A*	12p13.31	Noncoding transcript exon variant	
	rs9271366	A/G/C/T	G	G	Common	*HLA-DRB1*	6p21.32	Intergenic variant	[96]
	rs77017041	A/G	G	NA	Rare	*ANKRD55*	chr5:56111622	Missense Variant	[97]
	rs61734100	C/G/T	C	NA	Rare	*NLRP8*	19q13.43	Missense variant	[98]
	rs147248515	G/T	T	NA	Rare	*MMEL1*	chr1:2598730	Missense Variant	[97]
Grave's disease	rs6457617	T/C/A	C	T	Common	*HLA- DRB1 HLA-DQA1 HLA-DQB1*	6p21.32	Intergenic variant	[99]
	rs312729	G/A/T	A	NA	Common	*KCNJ2 CTD-2378E21.1*	17q24.3	Intergenic variant	[100]
		T/C	C	G	Common	*CTLA4 ICOS*	2q33.2	Regulatory region variant	[101]
Sjögren's syndrome (SS)	rs116232857	A/G/T	G	G	Common	*HLA-DQA1*	6p21.32	Intron variant	[102]
	rs9271573	C/A	A	NA	Common	*HLA-DQA1 HLA-DQB1 HLA-DRB1*	6p21.32	TF binding site variant	[103]
Celiac disease	rs1464510	C/A/G/T	A	A	Common	*LPP*	3q28	Intron variant	[104]
	rs2030519	G/A	G	NA	Common	*LPP*	3q28	Intron variant	[105]
	rs2030519	G/A	G	A	Common	*LPP*	3q28	Intron variant	[106]
	rs1359062	C/A/G/T	C	NA	Common	*RGS1*	1q31.2	Intron variant	[105]
	rs17264332	A/G/T	G	G	Common	*OLIG3 TNFAIP3*	6q23.3	Intron variant	[106]
Hashimoto's thyroiditis (HT)	rs13093110	C/T	T	T	Common	*LPP*	3q28	Intron variant	[101]
	rs11571297	T/C	C	G	Common	*CTLA4 COS*	2q33.2	Regulatory region variant	
	rs10738556	T/A/C/G	T	T	Common	*SMARCA2*	9p24.3	Intron variant	[107]
	rs7212416	T/A	A	T	Common	*AATF*	17q12	Intron variant	
	rs7537605	G/A/T	A	NA	Common	*VAV3*	1p13.3	Intron variant	[108]

Table continued

Table II *(continued)*. Summary of selected common and rare variants causing autoimmunity disease (ADs).

ADs	SNPs	Alleles	Minor allele	Risk allele	Variant type	Genes	Region	SINP localization	Ref.
Anti-phospholipid syndrome (APS)	rs1024843	C/A/T	C	T	Common	*PTPRO*	12p12.3	Intron variant	[109]
	rs2395166	G/T/A	C	T	Common	*HLA-DRA*	6p21.32	Intergenic variant	
	rs1020096	G/A	A	A	Common	*GATA3*	10p14	Intergenic variant	
	rs1443267	A/C/G/T	A	A	Common	*MRPS23*	17q22	Intron variant	
	rs2288493	C/T	T	T	Common	*TSHR*	14q31.1	3 prime UTR variant	
	rs1225763	G/A	A	A	Common	*SYCP2L*	6p24.2	Intron variant	
	rs79154414	C/T	T	T	Rare	*C1D*	2p14	Regulatory region variant	
	rs145365907	A/T	T	T	Rare	*NGF*	1p13.2	Intergenic variant	
Autoimmune hemolytic anemia (sickle-cell anemia)	rs11886868	C/T	T	NA	Common	*BCL11A*	2p16.6	Intron variant	[110]
	rs7557939	G/A	A	NA	Common	*BCL11A*	2p16.1	Intron variant	[111]
	rs10195871	A/G/T	G	NA	Common	*BCL11A*	2p16.5	Intron variant	[112]
	rs10172646	G/A	A	NA	Common	*BCL11A*	2p16.4	Intron variant	[113]
	rs2445284	C/T	C	G	Common	*OR51L1*	11p15.4	Intergenic variant	[114]
	rs887829	C/T	T	A	Common	*U G T 1 A 1 UGT1A10*	2q37.1	Intron variant	[115]
Rheumatoid arthritis (RA)	rs6457620	C/G	G	NA	Common	*HLA-DRB1*	6p21.32	Intergenic variant	[116]
	rs9268839	G/A/C	G	G	Common	*HLA-DRB1*	6p21.32	Intron variant	[117]
	rs7743761	C/A	A	NA	Common	*MHC*	6p21.33	Intron variant	[118]
	rs112062732	T/C/G	C	NA	Common	*HLA-DRB1*	6p21.32	Intergenic variant	[119]
	rs660895	G/A	G	G	Common	*HLA*	6p21.32	Intron variant	[120]
	rs2234163	G/A	A	NA	Rare	*TNFRSF14*	1 : 2 5 5 9 8 6 7 (GRCh38)	Noncoding transcript variant	[121]
	rs2066845	G/C/T	C	NA	Rare	*NOD2*	16q12.1	Missense variant	[122]
Systemic lupus erythemato-sus (SLE)	rs3757387	T/C	C	T	Common	*IRF5*	7q32.1	Regulatory region variant	[123]
	rs7568275	G/C/T	G	NA	Common	*STAT4*	2q32.3	Intron variant	[124]
	rs11889341	C/T	T	T	Common	*STAT4*	2q32.2	Intron variant	[125]
	rs9268807	G/C/A/T	C	C	Common	*HLA*	6p21.32	Intergenic variant	[123]
	rs7800325	T/C	C	T	Common	NR	7q11.23	Intergenic variant	
	rs34572943	G/A	A	NA	Common	*ITGAM*	16p11.2	Intron variant	[124]
	rs34572943	G/A	A	A	Common	*ITGAM*	16p11.2	Intron variant	[125]
	rs114092478	C/T	T	T	Common	*HLA-DQB1*	6p21.32	Intergenic variant	
	rs9494894	T/C	C	T	Common	NR	6q23.3	Intergenic variant	[123]
	rs199789198	C/A	A	A	Rare	NR	7q11.23	Intron variant	
	rs77009341	G/C	C	C	Rare	NR	7q11.23	Intron variant	
	rs143176121	T/C	C	T	Rare	NR	7q11.23	Intron variant	
	rs587680541	CCC/CC	NA	T	Rare	NR	7q11.23	Intron variant	

Table continued

Table II *(continued)*. Summary of selected common and rare variants causing autoimmunity disease (ADs).

ADs	SNPs	Alleles	Minor allele	Risk allele	Variant type	Genes	Region	SINP localization	Ref.
Scleroderma (systemic sclerosis)	rs3129882	C/T/G	G	NA	Common	*HLA-DRA*	6p21.32	Intron variant	[126]
	rs6457617	T/C/A	C	T	Common	*HLA-DQB1*	6p21.32	Intergenic variant	[127]
	rs10174238	G/A	G	NA	Common	*STAT4*	2q32.3	Intron variant	[128]
	rs9275390	C/T	C	NA	Common	*HLA-DQB1*	6p21.32	Regulatory region variant	[126]
	rs3821236	G/A	A	A	Common	*STAT4*	2q32.2	Intron variant	[129]
	rs77583790	G/A/C	A	A	Rare	*SCHIP1 IL12A*	3q25.33	Intron variant	[130]
	rs193107685	T/C	C	C	Rare	*LIMK1*	7q11.23	Intergenic variant	[128]

pathogenesis, yet they play a role in gene regulation and translation efficiency[82].

A downstream gene variant is a sequence variant located at 3' of a gene. Any alteration in these genes can affect the regulation of transcription elongation by altering the catalytic activity of RNA polymerase[83]. Nonsense-mediated mRNA decay (NMD) is a mechanism that degrades targeted mRNA transcripts with a premature stop codon. NMD removes aberrant mRNA that emerges from mutations, alternative splicing, and other events[84]. If the NMD is not working well, this will lead to the expression of truncated proteins, causing severe phenotypes[82]. Recent research[86] has revealed that NMD plays a much broader role in gene expression by regulating the stability of numerous normal transcripts. Missense or nonsynonymous variants cause single amino acid (AA) substitution with the protein sequence that can affect the protein structure and function[87]. Other genetic variants include splice donor variants, splice region variants, stop lost, and synonymous variants, which all account for 4% of SNPs associated with these 11 ADs.

Genes Associated with ADs and Their Interactions

SNPs are the most common form of genetic variation at a single position in the DNA sequence. Specific alleles are known as risk alleles associated with several diseases, including ADs. In addition to their association with disease susceptibility, variants could also enhance the severity of ADs. The GeneMANIA prediction server (https://genemania.org/) was used to generate a gene-gene interaction network[131]. It was used to analyze gene lists and gene prioritization based on functional assays using data sets collected from GEO, BioGRID, I2D, and others[131]. Maximum resultant gene attribution was ten genes in the advanced setting of the network used in GeneMANIA except for Grave's disease, SS, Autoimmune hemolytic anemia (sickle-cell anemia), RA, SLE, and Scleroderma (systemic sclerosis). The maximum resultant gene attribution was five genes. The query gene sets, including gene symbols of disease-related genes, were submitted as the input. Interaction data categories, including co-expression, co-localization, genetic interactions, pathways, physical interactions, and shared protein domains, were selected to build a network model to illustrate the gene-gene interaction. The line thickness between the nodes represents the accounted percentage among each gene interaction category. The generated network (Figure 5) illustrates ADs gene-gene interaction of the selected set of genes and SNPs retrieved from the GWAS catalog (Table II) and linked to different ADs.

In T1DM, four genes were found to be associated with this disease, including the HMC genes such as the HMC *class II DQ beta 1* (*HLA-DQB1*), *insulin* (*INS*), *synuclein alpha interacting protein* (*SNCAIP*), *protein tyrosine phosphatase non-receptor type 22* (*PTPN22*), *low-density lipoprotein receptor-related protein 1B* (*LRP1B*), *transmembrane protein 42* (*TAM42*) *mitochondrial translocator assembly and maintenance homolog* gene. The most common type of gene-gene interaction within genes causing T2DM was found to be co-expression interaction. Genes that are controlled by the same transcriptional regulatory factor, the co-expression network, enable their identification. Also, their gene product shares common biological processes[132]. Moreover, the

interaction within genes related to T1DM showed a direct physical interaction within *HLA- DQB1* and *INS*. Furthermore, there was a direct co-expression interaction within the *HLA-DQB1* and *PTPN22* genes. All these genes are known to contribute to T1DM susceptibility[133]. Other gene-gene interactions are indirect interactions linking genes associated with ADs with each other, forming a complex network, and emphasizing the complexity of different genes' roles in ADs.

In MS, eight genes were found to be associated with this disease, including *CD58*, *MHC class II DR beta 1* (*HLA-DRB1*), *ankyrin repeat domain 55* (*ANKRD55*), *TNF receptor superfamily member 1A* (*TNFRSF1A*), *interleukin two receptor subunit alpha* (*IL2RA*), *eomesodermin* (*EOMES*), *NLR family pyrin domain containing 8* (*NLRP8*), and *membrane metalloendopeptidase like 1* (*MMEL1*). The most common type of gene-gene interaction within genes causing MS was found to be the co-expression of genes within *IL2RA- HLA- DRB1*, followed by genetic interaction within *IL2RA- NLRP8* and *ANKRD55- EOMES*, lastly, shared protein domains interaction within *SNCAIP- ANKRD55.*

In Grave's disease, five genes were found to be associated with this disease, including *MHC*

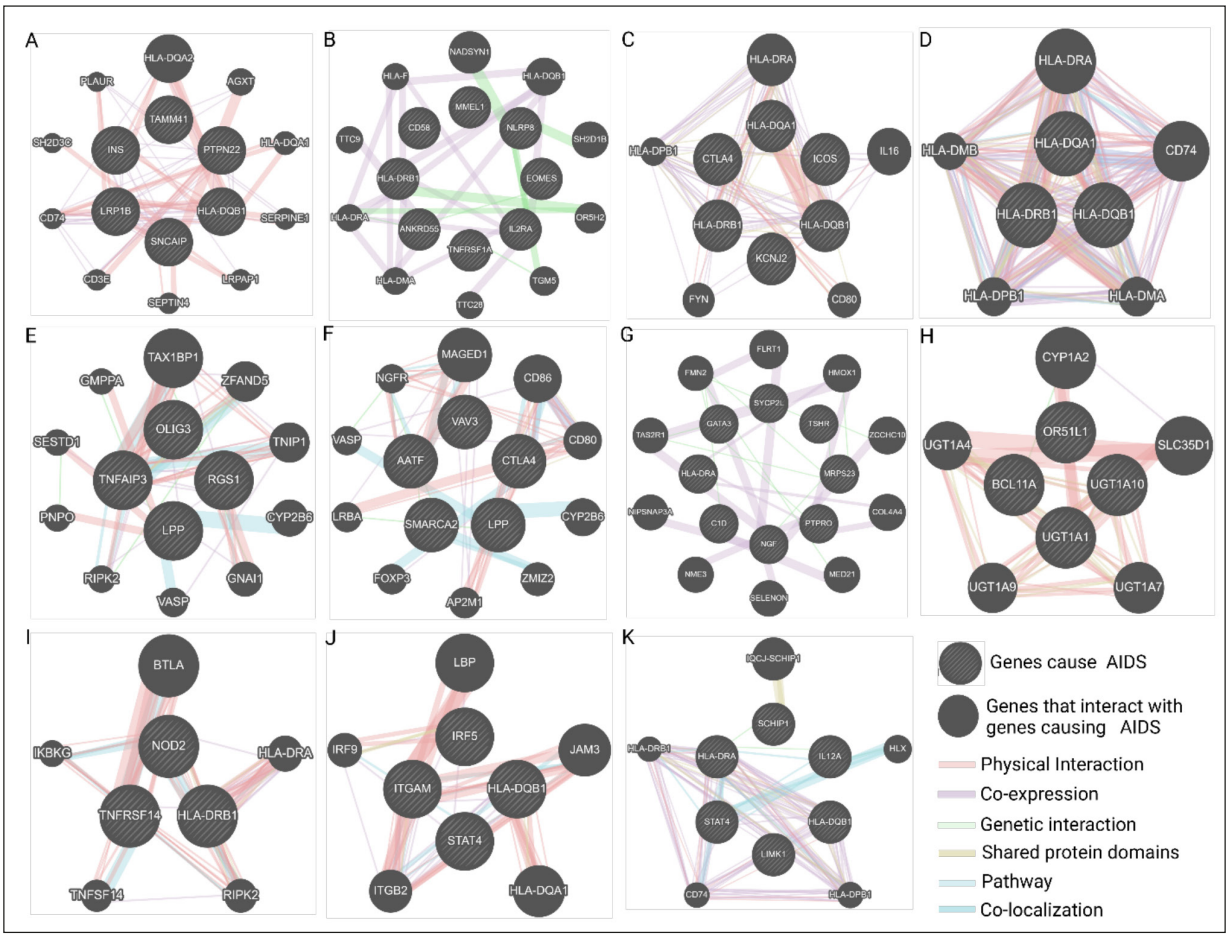

Figure 5. Gene-gene interaction of the most frequent genes in different ADs. **A**, Type 1 diabetes mellitus (T1DM), (**B**) Multiple sclerosis (MS), (**C**) Grave's disease, (**D**) Sjögren's syndrome (SS), (**E**) Celiac disease, (**F**) Hashimoto's thyroiditis (HT), (**G**) Anti-phospholipid syndrome (APS), (**H**) Autoimmune hemolytic anemia (sickle-cell anemia), (**I**) Rheumatoid arthritis (RA), (**J**) Systemic lupus erythematosus (SLE), and (**K**) Scleroderma (systemic sclerosis). Interaction data categories, including co-expression, co-localization, genetic interactions, pathways, physical interactions, and shared protein domains, were selected to build a network model to illustrate the gene-gene interaction. The Maximum resultant gene attribution was ten genes in an advanced set of networks that were used in GeneMANIA except for Grave's disease, SS, Autoimmune hemolytic anemia (sickle-cell anemia), RA, SLE, and Scleroderma (systemic sclerosis). The maximum resultant gene attribution was five genes. Genes that cause ADs are listed in Table II (center striped, gray nodes), and other genes that interact with genes associated with ADs (circumference gray nodes). The line thickness between the nodes represents the accounted percentage among each gene interaction category. The network was generated using GeneMANIA[131].

class II DQ alpha 1 (*HLA-DQA1*), *inducible T cell costimulatory* (*ICOS*), *MHC class II DQ beta 1* (*HLA-DQB1*), *potassium inwardly-rectifying channel subfamily J member 2* (*KCNJ2*), *MHC class II DR beta 1* (*HLA-DRB1*), *cytotoxic T-lymphocyte associated protein 4* (*CTLA4*) and *MHC class II DR alpha* (*HLA-DRA*). Physical interaction was found to be the most common interaction within proteins produced from genes linked with Grave's disease, followed by co-expression and shared protein domain interaction. *HLA-DQA1- HLA-DQB1* genes exhibit physical gene interaction. Furthermore, *HLA-DRB1* and *HLA-DQB1*, *HLA-DRB1* and *CTLA4*, and *HLA-DQB1* and *ICOS*. *HLA-DQA1- HLA-DRB1*, *HLA-DQA1- HLA-DQB1*, *HLA-DRB1- HLA-DQB1*, and *ICOS- CTLA4* were found to have shared protein domains. Apart from *KCNJ2*, all genes interact with each other.

Three genes were found to be associated with SS, including *MHC class II DR beta 1* (*HLA-DRB1*), *MHC class II DQ beta 1* (*HLA-DQB1*), and *MHC class II DQ alpha 1* (*HLA-DQA1*). The most common gene interaction among genes associated with SS is physical interaction, followed by co-expression, and finally, shared protein domains interaction. Physical interaction was found among *HLA-DQA1- HLA- DQB1* and *HLA- DQA1- HLA-DRB1*. The *HLA-DQB1* and *HLA-DRB1* genes were found to be co-expressed. All selected sets of genes have a shared protein domain gene interaction.

In Celiac disease, four genes were found to be associated with this disease including *oligodendrocyte transcription factor 3* (*OLIG3*), a *regulator of G protein signaling 1* (*RGS1*), *LIM domain containing preferred translocation partner in lipoma* (*LPP*), and *TNF alpha-induced protein 3* (*TNFAIP3*). The most abundant type of interaction among genes associated with celiac disease was found to be the co-expression of genes such as the one found among *TNFAIP3* and *RGS1*, followed by genetic interaction between *TNFAIP3* and *LPP*. On the contrary, *OLIG3* did not show any interaction with other genes related to celiac disease.

In HT, five genes were found to be associated with this disease, including *vav guanine nucleotide exchange factor 3* (*VAV3*), *cytotoxic T-lymphocyte associated protein 4* (*CTLA4*), *LIM domain containing preferred translocation partner in lipoma* (*LPP*), *SWI/SNF related matrix-associated actin-dependent regulator of chromatin subfamily a member 2* (*SMARCA2*), and *apoptosis antagonizing transcription factor* (*AATF*). The only gene interaction among those genes is genetic interaction among *SMARCA2* and *AATF*.

In APS, eight genes were found to be associated with this disease, including *synaptonemal complex protein two like* (*SYCP2L*), *thyroid-stimulating hormone receptor* (*TSHR*), *mitochondrial ribosomal protein S23* (*MRPS23*), *protein tyrosine phosphatase receptor type O* (*PTPRO*), *nerve growth factor* (*NGF*), *C1D nuclear receptor corepressor* (*C1D*), *MHC class II DR alpha* (*HLA-DRA*), and *GATA binding protein 3* (*GATA3*). The most abundant type of interaction within genes associated with APS was found to be co-expression interaction, such as the interaction between *HLA-DRA and PTPRO*. The second most abundant interaction is genetic interaction, such as *NGF* and *MRPS23*, P*TPRO* and *GATA3*, and *MRPS23* and *TSHR*. Both *SycP2L* and *C1D* genes do not interact with each other or other selected gene sets.

In Sickle-cell anemia, four genes were found to be associated with this disease, including *olfactory receptor family 51 subfamily L member 1* (*OR51L1*), *UDP glucuronosyltransferase family one member A10* (*UGT1A10*), *UDP glucuronosyltransferase family one member A1* (*UGT1A1*), and *BAF chromatin remodeling complex subunit BCL11A* (*BCL11A*). The most abundant interaction is the physical interaction between *UGT1A10* and *UGT1A1*. The second interaction is the shared protein domains interaction that is also between *UGT1A10* and *UGT1A1*. Other genes (*OR51L1* and *BCL11A*) do not interact with any gene.

In RA, three genes were found to be associated with this disease, including *nucleotide-binding oligomerization domain containing 2* (*NOD2*), *MHC class II DR beta 1* (*HLADRB1*), and *TNF receptor superfamily member 14* (*TNFRSF14*). The only interaction is the co-expression interaction between *HLA-DRB1* and *TNFRSF14*. The *NOD2* gene does not interact with other genes.

In SLE, four genes were found to be associated with this disease, including *interferon regulatory factor 5* (*IRF5*), *MHC class II DQ beta 1* (*HLADQB1*), signal transducer and activator of *transcription 4* (*STAT4*), and *integrin subunit alpha M* (*ITGAM*). The only interaction is co-expression between *IRF5- ITGAM*, *ITGAM- HLA-DQB1*, and *HLA-DQB1- STAT4*.

In Scleroderma, six genes were found to be associated with this disease, including *schwannoma interacting protein 1* (*SCHIP1*), *interleukin 12A*

(*IL12A*), *MHC class II DQ beta 1* (*HLA-DQB1*), *LIM domain kinase 1* (*LIMK1*), signal transducer and activator of *transcription 4* (*STAT4*), and *MHC class II DR alpha* (*HLA-DRA*). The most abundant interaction is co-expression between *HLA-DQB1* and *HLA-DRA* and *HLA-DQB1-STAT4*. Another interaction is pathway interaction between *IL12A* and *HLA-DRA*, *IL12A* and *STAT4*,

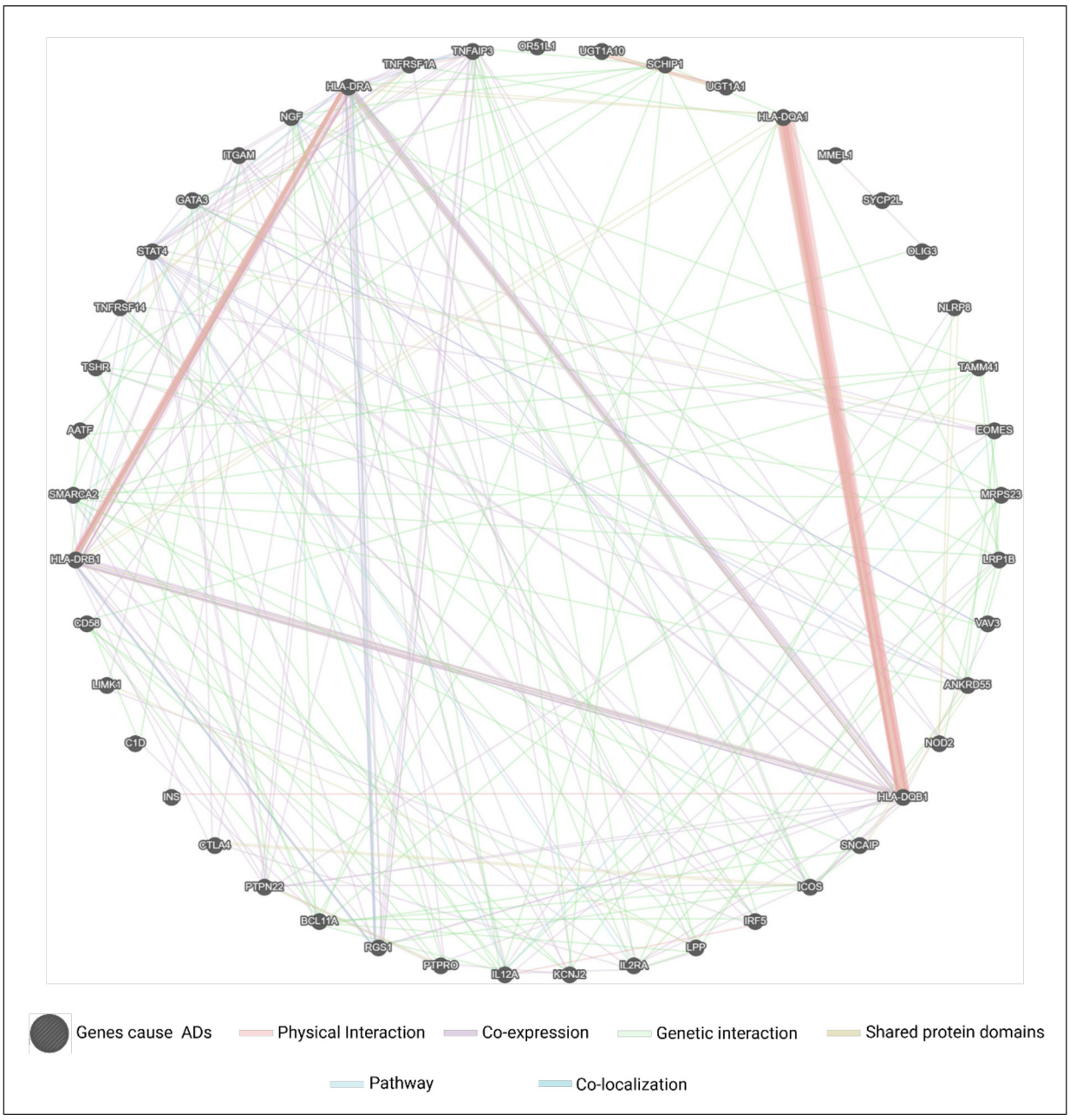

Figure 6. Overall ADs gene-gene interaction. The dominant interaction is physical gene-gene interaction and co-expression interaction. The most abundant interaction is among MHC genes, such as the physical interaction between *HLA-DQB1* and *HLA-DQA1, HLA-DRA- HLA*-and *DRB1*, and the co-expression interaction between *HLA-DQB1* and *HLA-DRA*, and *HLA-DQB1* and *HLA-DRB1*. Interaction data categories, including co-expression, co-localization, genetic interactions, pathways, physical interactions, and shared protein domains, were selected to build a network model to illustrate the gene-gene interaction. The Maximum resultant genes were 0 genes in the advanced setting of the network that were used to generate gene-gene interaction networks. Genes that cause ADs are listed in Table II (center striped, gray nodes), and other genes that interact with genes associated with ADs (circumference gray nodes). The line thickness between the nodes represents the accounted percentage among each gene interaction category. The network was generated using GeneMANIA[131].

and *HLA-DRA* and *STAT4*, followed by shared protein domains interaction between *HLA-DQB1-HLA-DRA*. Next is the physical interaction between *HLA-DQB1* and *HLA-DRA*. Finally, the genetic interaction between *IL12A- HLA-DRA* and *HLA-DRA- SCHIP1* was observed. Genetic integration refers to the pair of genes that are functionally associated when the effect of perturbing one gene is found to be altered by the perturbations of another gene[131].

Figure 6 illustrates the overall interaction of all genes listed in this paper, showing that co-expression and physical interaction are the most dominant interaction among all ADs associated genes. The most frequent interaction is within the MHC coding genes (*HLA-DQA*, *HLA-DQA1*, *HLA-DRB1*, and *HLA-DQB1*).

Alongside gene-gene interaction, gene-environmental interaction is becoming increasingly recognized in causing ADs[134]. It has the potential to efficiently explain disease risk profiles and uncover underlying molecular mechanisms contributing to disease pathogenesis by identifying gene-environment interactions. Recently, a gene-environmental interaction was recognized between smoking and *HLA-DRB1* shared epitopes. Moreover, cigarette smoking can affect the mRNA expression of *NOD2*, causing impairment of *NOD2* function[135]. Another study[136] linked the *LRP1B* gene with obesity. A study[137] conducted in a Southern Chinese population showed a possible interplay between *STAT4* and alcohol drinking. Understanding these interactions is likely to contribute significantly to the development of personalized medicine and targeted preventative approaches[134].

Conclusions

The past decades have brought a considerable understanding of genetic factors associated with ADs. The development of this field depends upon the growth and reinforcement of more refined measurement tools ranging from serologic or phenotypic assessment to DNA sequencing. The utilization of different databases capturing GWAS approaches has helped us gain a better knowledge of the genetics of many ADs and bring to light many candidate genes and biological pathways. This knowledge will help clinicians to intervene more efficiently and successfully than they are now. Future studies should investigate the underlying molecular mechanisms associated with these ADs risk variants using *in vitro* and *in vivo* models to help quantify the phenotypic consequences of these variants and gain a better understanding of these diseases. The incorporation of population genetic studies to study human genetics will continue to help delineate triggers of diseases and identify functional variants and cellular mechanisms, which can contribute to the development of new therapies.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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