

## Disease-Specific and Common HLA and Non-HLA Genetic Markers in Susceptibility to Rheumatoid Arthritis, Type 1 Diabetes Mellitus and Multiple Sclerosis

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### Abstract

Autoimmune diseases cause numerous health and social problems throughout the world. The common spectrum of autoimmune diseases affect the majority of tissues within the body, including pancreatic beta cells in type 1 diabetes (T1DM), myelin surrounding nerve axons in Multiple sclerosis (MS) and synovial joint antigens in Rheumatoid Arthritis (RA). The diseases are likely caused by a complex interaction between multiple HLA- and non-HLA related genes and environmental factors. The well documented co-clustering of autoimmune diseases within families and individuals, together with apparent sharing of number risk genes between the diseases suggests at least some common mechanisms of autoimmune development.

**Keywords:** Autoimmune diseases; Rheumatoid arthritis; Diabetes mellitus; Multiple sclerosis

### Introduction

Autoimmune diseases cause numerous health and social problems throughout the world. The common spectrum of autoimmune diseases affect the majority of tissues within the body, including pancreatic beta cells in type 1 diabetes (T1DM), myelin surrounding nerve axons in Multiple sclerosis (MS) and synovial joint antigens in Rheumatoid Arthritis (RA). The diseases are likely caused by a complex interaction between multiple HLA and non-HLA related genes and environmental factors. The well documented co-clustering of autoimmune diseases within families and individuals, together with apparent sharing of number risk genes between the diseases suggests at least some common mechanisms of autoimmune development. The three diseases with possibly different manifestations were chosen for this review, the whole field being very vast. The fact all the three diseases with local rather than general symptoms (joints, pancreatic beta cells, myelin) possess common susceptibility factors stresses the importance of these findings.

Rheumatoid arthritis is one of the most common autoimmune diseases; it is chronic, systemic disease, manifesting as progressive, symmetrical deformation of joints, pain and inflammation. Around 1000 new cases of rheumatoid arthritis are diagnosed in Latvia each year. Both genetic and environmental factors play role in the susceptibility to this disease. Many genetic factors are known to increase risk for developing RA. The main genetic factor, involved in susceptibility and pathogenesis of RA is HLA-DRB1 gene in the Major Histocompatibility complex (MHC) on chromosome 6. The main players in the pathogenesis of RA are cytokines; therefore polymorphisms in the regions that might affect expression of the

cytokine genes are extensively studied in this disease. Also anti-cytokine agents are successfully used as drugs for this disease. Genome-wide association studies have shown around 200 loci, which might be interesting for rheumatoid arthritis. These loci include genes, mainly involved in immune response and antigen presentation, importance of which for RA is already known and extensively studied including the PTPN22 (protein tyrosine phosphatase expressed by the majority of cells belonging to the innate and adaptive immune systems), STAT4 (signal transducer and activators of transcription, nuclear import of STAT4 is linked to its tyrosine phosphorylation), CTLA4 (cytotoxic T lymphocyte antigen-4, a major negative regulatory molecule for T-cell activation), TRAF1/C5 (tumor necrosis factor-receptor associated factor 1/complement component 5), PADI4 (peptidyl-arginine-deiminase type IV), MIF (cytokine which counteracts the immunosuppressive properties of glucocorticoids) and many others [1-5], as well as others genes with yet unknown function. RA patients can be classified in different clinically significant groups according their genomic traits (ACPA (anti-citrullinated-protein-autoantibody) positive versus negative [6]. RA is very heterogeneous disease not only concerning the symptoms, genetic predisposition and antibody status, but also concerning variations in response to different therapeutic approaches. Several genes were found to affect the incidence of side effects and patients response to different drugs such as Methotrexate, these are RFC1 (reduced folate carrier) [7], ABCB1 (the gene which encodes an efflux pump, is an ATP-binding cassette of sub-family B, member 1) [8], and MTHFR (methylene tetrahydrofolate dehydrogenase 1) [9,10] genes. Some genes modify effect of anti TNF therapy: TNFA (tumour necrosis factor alpha) [11], interferon (IFN type 1) gene, promoter polymorphisms of interleukin IL-10 and other genes [12]. Efficiency of Azathioprine therapy depends on TPMT gene, sulfasalazine - on NAT2 gene [13]. The RA susceptibility in Latvian population has been studied already [14], data

on TNFA (rs1800629, rs361525), IL6 (rs1800795), IL18 (rs1946518, rs1946519), IL10 (rs1800894, rs1800871, rs1800895, rs1800872), IRF5 (rs3757385, rs2004640, rs10954213), KLF12 (Krüppel-like factor 12; rs1324913) and PTPN22 (rs2476601) associations with the disease are published.

Diabetes mellitus (DM) and its complications cause numerous health and social problems throughout the world. Number of DM patients constantly increases. Diabetes, characterized by persistent elevation of blood glucose levels (hyperglycaemia), occurs due to inadequate production of insulin (type 1 diabetes; T1DM), or resistance to endogenous insulin usually associated with the metabolic syndrome and obesity (type 2 diabetes; T2D). Despite intensive glycaemic control, individuals with T1DM and T2DM are predisposed to developing vascular complications [15]. DM and its complications are common in Latvia: in 2010 72654 DM patients were registered, 3891 with T1DM and 68217 with T2DM. Kidney malfunction like microalbuminuria was detected in 2737 patients, proteinuria – in 1092, renal failure – in 228, substitution therapy was indicated to 57 patients, kidney grafts were transplanted to 31 patient. Etiologically T1DM is an autoimmune disease both environmental and hereditary factors being important for susceptibility to it. Several studies have demonstrated a fundamental role for the HLA in the susceptibility of, or protection to T1DM. While HLA remains the strongest genetic risk factor, a number of novel gene variants associated with T1DM have been found through genome-wide studies, some of which have been linked to suspected environmental risk factors. However, jointly non-HLA risk alleles described up till now confer only a small additional risk compared to the effect of HLADR, HLADQ. Variants or polymorphisms in UBASH3A (a suppressor of T cell receptor signalling pathway) and PTPN22 (the protein tyrosine phosphatase nonreceptor type 22) were shown as candidates for development of islet autoimmunity and T1DM when controlling for family history and in presence of the HLA-DR3/4-DQB1\*0302 genotype. Polymorphisms in the insulin INS gene predicted development of T1DM. Although the effect of each individual gene is small, the combination of T1DM family history, the HLA-DR3/4-DQB1\*0302 genotype, and the susceptibility variants of PTPN22, UBASH2, and INS were reported to increase 16-fold the risk of islet autoimmunity and 40-fold of T1DM. The IFIH1 (interferon induced with helicase C domain 1, also known as MDA5, or melanoma differentiation-associated gene 5) linkage disequilibrium block on chromosome 2q has also been found to be associated with T1DM in GWAS and increased gene expression is associated with risk of T1DM [16].

Diabetic kidney disease, or diabetic nephropathy (DN), is a major complication of diabetes and the leading cause of end-stage renal disease (ESRD) that requires dialysis treatment or kidney transplantation. In addition to the decrease in the quality of life, DN accounts for a large proportion of the excess mortality associated with T1DM. Meta-analysis of GWAS results revealed an association of ESRD with the rs7583877 in the RNA-binding protein AFF3 gene and a chromosome 15q26 intergenic SNP locating between two growth and development-related RGMA (repulsive guidance molecule a) and MCTP2 (multiple C2-domains with two transmembrane regions 2) genes. Functional data suggest that AFF3 influences renal tubule fibrosis via the transforming growth factor-beta (TGF- $\beta$ 1) pathway. The strongest association with DN as a primary phenotype was seen for an intronic SNP in the receptor tyrosine kinase ERBB4 gene [17].

It should be mentioned that some genetic predisposition factors apparently are not spotted in GWAS studies, although sufficient

association is revealed in studies with individual genes. DNA damage by endogenous free radicals and further ineffective repair of these lesions is considered to be one of the etiological factors of DM [18,19]. Oxidative stress and abnormal production of nitric oxide are of the main causes of increased DNA breakage in DM leading to development of its complications. Thus polymorphism of genes responsible for the free radical production and scavenging appear to be of special interest. Endothelial nitric oxide synthase (eNOS) polymorphisms have been reported to be strongly associated with DN risk, there are also reports on association of some alleles of inducible NO synthase (iNOS) gene with DM complications [20]. Increased DNA breakage due to oxidative stress determines importance of DNA repair genes (base excision repair gene MUTYH, X-ray repair cross complementing group 1 XRCC1 and 8-Oxoguanine-DNA glycosylase hOGG1) in resistance or susceptibility to DM [21,22].

Multiple sclerosis (MS) is most common, clinically extremely heterogeneous, chronic inflammatory disease of the CNS affecting about 2.5 million people around the world (2500 of them in the Latvia), presumably young adults, with onset usually at the second to fourth decade of life and, similarly to other autoimmune diseases, women being affected 3-4 times more frequent than men [23]. Pathologically, there are perivenular infiltrates of Cd4+ and CD8+ T cells in the CNS white matter and meninges with demyelinating lesions and loss of axons in both white and grey matter [24]. List of different MS subtypes includes the relapsing-remitting (RR), secondary progressive (SP0 and primary progressive (PP), and within each subtype there is also considerable individual variation in disease course [25].

The cause of MS is not clear. Disease develops in genetically susceptible individuals with the contributions of environmental factors, such as infection, sunlight exposure, and vitamin D deficiency [26]. There are also marked changes in systemic immune function with loss of regulatory T cell (Treg) function and increases in myelin-reactive CD4+ T cells [27-29].

Unbiased genome-wide association scans have identified susceptibility loci in regions containing genes with immune, co-stimulatory, signal transduction functions and vitamin D related, including, for example, the CD6, CD25, CD40, CD58, HLA-A, HLA-B, HLA-DRB1, IL2RA, IL7R, IL12A, IRF8, the Janus kinase (JAK)/signal transducer and activator of transcription STAT3, gene of the receptor for tumour necrosis factor- $\alpha$  TNFRSF1A, CYP27B1 (1 $\alpha$ -hydroxylase - an enzyme, which converts vitamin D to its active form) and other genes [30-34]. Osteopontin OPN gene may be involved in MS development and especially, progression and cytokines may be suggested as therapeutic target to counteract MS progression [35].

According to the ICSNPathway analysis (Identify candidate Causal SNPs and Pathway analysis) applied to the MS GWAS dataset [36], 9 HLA and 7 non-HLA candidate SNPs and 5 and 10 candidate causal pathways respectively are mostly susceptible to MS including risk HLA loci: rs1802127 (MSH5), rs9277471 (HLA-DPB1), rs8084 and rs7192 (HLA-DRA), rs2072895 and rs2735059 (HLA-F), rs915669, rs915668 and rs1063320 (HLA-G); and risk non-HLA loci: rs5896 (F2, prothrombin), rs8181979 (SHC1; (Src homology 2 domain containing transforming protein 1), rs9297605 (TAF2, RNA polymerase II), rs669 (A2 M; M-type phospholipase A2 receptor), rs2228043 (IL6ST; interleukin 6 signal transducer), rs1061622 (TNFRSF1B), rs1801516 (ATM). The most strongly associated pathways were the rs1802127 to MSH5 to meiotic recombination and meiotic cell cycle and rs5896 to

F2 to the transcriptional activation DNA-binding protein B from mRNA [37].

Evidence underlines the importance of microRNAs (miRNAs) such as miR326, miR-323, miR-223, miR-23a, miR-15b and others in the MS pathogenesis [38,39]. It was shown [39] that rs1044165 (miR-223) likely acts as MS protective factor, while rs3745453 (miR-23a) seems to be a risk factor for MS. Extracellular miRNAs appear to be taken in consideration as a new source for both biomarker and risk factor identification and therapeutic drug discovery.

### The RA, T1DM and MS common elements of genetic architecture

Well documented co-clustering of autoimmune diseases within families and individuals are in good agreement with apparent sharing of a number of risk genes and polymorphic loci between particular diseases. A whole genome linkage scan by microsatellite markers provided significant evidence of linkage between the T1DM and MS [40]. At least the IL7R-CAPSL(interleukin 7 and calcyphosine-like protein ) CD226, IL2RA, HLA Class I, HLA Class II, CLEC16A, RGS1 (regulator of G protein signaling ), ZMIZ1 (zinc finger, MIZ-type containing 1), TNFSF14 (tumor necrosis factor (ligand) superfamily, member 14) , SOXB (SRY (sex determining region Y)-box 3), CLECL1

and NFKB1 genes are susceptible to both the T1DM and MS. RA and MS share the susceptibility to variations in VCAM1 (vascular cell adhesion molecule 1), IL22RA2, PVT1, CLECL1 and CD37 [32,41,42]. Despite large number of genes reported to be associated with each given disease, some polymorphic loci appear to be common for several diseases. These are, for example, the rs2104286 of the IL2RA sharing by MS and T1DM [43] and the rs10466829 of the CLECL1 sharing by RA, T1DM and MS [32]. The proteasomal PSMA6/PSMC6/PSMA3 gene cluster on Chromosome 14 [44] also appears to be a good candidate for association with several autoimmune diseases. Besides formerly revealed association of several polymorphisms in the cluster with Graves' disease [45] and juvenile idiopathic arthritis [46,47] our recent findings indicate associations with T1DM [48] and MS [49]. Childhood asthma [50] and childhood obesity [51,52], pathologies with a pronounced autoimmune and immunological component are also associated with some genetic variations in this cluster.

Functions of some non-HLA genes associated with autoimmune diseases are listed in Table 1. Several genes are involved in signaling pathways in T-lymphocytes (PTPN22, STAT 4, CTLA-4, PADI4, MIF, PADI4), apoptosis (TRAF1/C5, TNFSF14), calcium and G-protein-dependent signalling pathways (CLEC16A, CAPSL, RGS1) and other pathways.

No.	Abbreviated gene name	Full gene name	Function of the protein	Associated diseases
1.	PTPN22	Protein tyrosine phosphate	An inhibitor of T-cell activation, contributes to signaling cascades (TLR, TCR, BCR pathways) initiated in immune cells, including B cells and cells of the innate immune system.	RA, systemic lupus erythematosus (SLE), T1DM, Hashimoto disease (HD), Graves'disease (GD), vitiligo [53]
2.	STAT 4	Signal transducer and activators of transcription 4	Part of the JAK-STAT signalling pathway, expressed only spermatozoa, myeloid cells, and T lymphocytes. STAT 4 is activated by tyrosine phosphorylation in response to interleukin-12 (IL-12) treatment of T cells, involved in T helper cell function.	RA, SLE, Sjögren's syndrome, juvenile idiopathic arthritis (JIA), GD, myasthenia gravis [54,55]
3.	CTLA-4	Cytotoxic T-lymphocyte antigen-4	Cell surface molecule involved in the regulation of signaling pathways affecting T-cell responses. Activation results in decreased T-lymphocyte activity and regulates the immune response.	RA, SLE, T1DM, Addison's disease (AD), Vitiligo, MS, HD [56,57]
4.	TRAF1/C5	Tumor necrosis factor-receptor associated factor 1/complement component 5 locus	The TNF receptor associated factor 1 (TRAF1) is an adaptor protein, it TNF family members, to downstream signaling networks. TRAF1 is implicated in cell growth, proliferation, apoptosis, bone turnover, cytokine activation.	RA [58]
5.	PADI4	Peptidyl-arginine-deiminase type IV	The PADI4 enzyme is expressed in T and B cells, neutrophils, eosinophils, monocytes. It mediates the citrullination of histones(conversion of arginine residues to citrulline). Target for autoantibodies in RA.	RA [58,59]
6.	MIF	Macrophage migration inhibitory factor	A T cell derived cytokine, inhibits the random migration of macrophages in vitro and promotes macrophage accumulation during delayed-type hypersensitivity reactions.	T1DM, RA [60]
7.	UBASH3A	Ubiquitin associated and SH3 domain containing A	Belongs to T-cell ubiquitin ligand (TULA) family, facilitates growth factor withdrawal-induced apoptosis in T cells. An active phosphatase capable of dephosphorylating	T1DM [61,62]

			multiple tyrosine-phosphorylated proteins, suppressor of T cell receptor signalling pathway.	
8.	STAT3	Signal transducer and activator of transcription 3 (acute-phase response factor)	STAT 3 protein is activated through phosphorylation by the receptor associated kinases in response to various cytokines and growth factors including IFNs, EGF, IL5, IL6, HGF, LIF and BMP2. Then it forms homo- or heterodimers that translocate to the cell nucleus where it act as transcription activator of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis.	MS [30]
9.	CLEC16A	C-type lectin domain family 16, member A	A transmembrane calcium- dependent (C-type) lectin-like receptor	MS, RA, T1DM [42]
10.	CAPSL	calcyphosine-like protein	calcium sensor and calcium signal modulator.	T1DM [32]
11.	RGS1	Regulator of G protein signaling	Regulator of G protein signaling	T1DM, MS [32]
12.	ZMIZ1	zinc finger, MIZ- type containing 1	A member of the PIAS (protein inhibitor of activated STAT) family of proteins. The encoded protein regulates the activity of various transcription factors, including the androgen receptor, Smad3/4, and p53. The encoded protein may also play a role in sumoylation.	T1DM, MS [32]
13.	TNFSF14	tumor necrosis factor (ligand) superfamily, member 14	A member of the tumor necrosis factor (TNF) ligand family. Functions as a costimulatory factor for the activation of lymphoid cells, stimulates the proliferation of T cells, and trigger apoptosis of various tumor cells.	T1DM, MS [32]
14.	VCAM1	vascular cell adhesion molecule 1	A cell surface sialoglycoprotein expressed by cytokine-activated endothelium, mediates leukocyte-endothelial cell adhesion and signal transduction.	T1DM, RA [32]
15.	SOXB	SRY (sex determining region Y)-box 3	Member of SOX (SRY-related HMG-box) family of transcription factors involved in the regulation of embryonic development and in the determination of the cell fate.	T1DM, MS [32]
16.		Pvt1 oncogene (non-protein coding)	Oncogene, associated with several types of cancer and renal diseases.	T1DM, RA [32,41,42]

**Table 1:** Non HLA genetic markers of autoimmune diseases.

Coexistence of autoimmune diseases has been recently reviewed and statistically evaluated suggesting association of diseases and their common origin [63]. However the problem is only in the beginning of experimental evaluation and has to be very topical in genomic studies in nearest future.

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