# Genetic and Epigenetic Aspects of T1DM

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Type 1 diabetes mellitus (T1DM) is a polygenic multifactorial disease based on immune-mediated or idiopathic destruction of pancreatic β-cells resulting in absolute insulin deficiency. T1DM is the most common form of diabetes in children and adolescents worldwide.

Keywords: type 1 diabetes mellitus ; HLA ; genes ; genetics ; epigenetics

## 1. Introduction

Type 1 diabetes mellitus (T1DM) is a polygenic multifactorial disease based on immune-mediated or idiopathic destruction of pancreatic β-cells resulting in absolute insulin deficiency [1]. T1DM is the most common form of diabetes in children and adolescents worldwide [2]. In Russia, according to the federal register, as of 1 January 2023, the number of patients with diabetes mellitus registered at the dispensary was 4,962,762 people (3.31% of the population of the Russian Federation). Among them, the proportion of patients with T1DM was 5.58% (277.1 thousand), with T2DM was 92.33% (4.58 million), and with other types of diabetes was 2.08% (103 thousand) [3]. Slowly progressing T1DM in adults (late-onset autoimmune diabetes of adults (LADA)), which typically manifests itself after the age of 25 years, occurs with an incidence of from 6 to 50% in different populations. Neonatal diabetes mellitus (NDM), which manifests itself during the first 6 months of a child's life, develops on average in 0.001% of newborns. T1DM, LADA [4], and NDM have common and specific molecular genetic markers; their identification is currently underway. The investigation of the abovementioned diabetes forms is one of the actively developing areas in fundamental diabetology [5].

In T1DM, the β-cells of the Langerhans islets in the pancreas are destroyed, which causes hyperglycemia, ketoacidosis, and a number of other concomitant disorders in the body's homeostasis. The progress of T1DM is usually divided into three main stages. The first stage begins with the initiation of autoimmunity to β-cells and is attested by the availability of two or more islet autoantibodies with concomitant normoglycemia. The second stage is characterized by the presence of autoimmunity to β-cells and dysglycemia; this stage is presymptomatic. The third stage is the beginning of the disease itself with a complete dependence on insulin therapy [6]. Now it is recognized that the loss of β-cells may progress slowly; some people do not develop diabetes until many years after the appearance of autoantibodies. Nevertheless, in individuals of older age or in certain adults, the destruction of β-cells can begin rapidly, in contrast to a special form of slow-onset autoimmune diabetes named latent autoimmune diabetes of adults (LADA). In other words, in the common autoimmune etiology of T1DM, the rates of disease progression differ and the mechanisms underlying these differences are unknown.

T1DM has a significant hereditary risk, estimated to range from 40% to 60% based on family and twin studies; approximately 50% of this heritability is thought to be attributable to the major histocompatibility complex (HLA) region [7] [8].

More than 40 years have passed since the associations of *HLA* genes with T1DM were first identified, and over this time period, researchers found that the contribution of these genes largely depends on a number of other regulatory genes and genome regions, in which the nucleotide sequence alterations play a key role in the risk of developing T1DM [5].

The National Center for Biotechnology Information (NCBI) database contains more than 20 thousand papers devoted to the investigation of genetic factors that are involved in the pathogenesis of T1DM. In addition to the genes of the major histocompatibility complex, scientific interest is focused on investigating the significance of a number of other genes such as *INS* (insulin), *PTPN22* (tyrosine phosphatase), *IFIH1* (RIG-I-like receptor), *SH2B3* (adapter protein), *CD226* (immunoglobulin superfamily protein), *TYK2* (tyrosine kinase 2), *FUT2* (galactoside-2-alpha-L-fucosyltransferase 2), *SIRPG* (signal-regulatory protein gamma), *CTLA4* (immunoglobulin superfamily protein), *CTSH* (cathepsin H), *CTLA4* (cytotoxic T-lymphocyte glycoprotein), and *UBASH3A* (ubiquitin-associated protein A containing the SH3 domain) [9].

There is evidence of augmentation in the T1DM risk through the mechanisms of genomic imprinting with the participation of the INS gene [10] and the alternative splicing of islet cell autoantigen IA-2 mRNA [11], as well as through gene–gene and gene–environment interactions stipulated by epigenetic modifications [12][13] or retrovirus-mediated changes in different cells involved in pancreatic β-cell functioning [14][15]. The most relevant areas are related to the replication of genome-wide association studies (GWAS), the analysis of rare single nucleotide polymorphic variants (SNPs) identified outside the *HLA* genes, and the investigation of epigenetic patterns in β-cells.

On the basis of the currently identified genetic predictors of T1DM, a number of mathematical models have been generated that are used as tools for predicting the risk of developing the disease. It is worth noting that all predictors included in models should have high predictive value. However, due to the lack of knowledge about the contribution of some rare genetic risk variants of *T1DM*, such as *SH2B3*, *CD226*, and *CTLA4*, prognostic models involve only the gene variants, whose changes are highly reliably associated with the mechanisms of development of islet autoimmunity and accompanied with the dysregulation of antigen-presenting cells, activation of T cell signaling, and regulation of T1 interferon levels and cytokine signaling [16]. Models are constantly improving due to the emergence of new genetic and epigenetic data.

## 2. Major Histocompatibility Complex (HLA) Locus: Population Aspects

The HLA system area is one of the most complex and polymorphic regions in the human genome and consists of more than 200 genes located within chromosome 6, p-arm at 21.3. The structure of these genes determines the individual profile and affinity of T cell receptors, which affect the functioning of the immune system. There are three classes of *HLA* genes, namely I, II, and III, differing in their functions. HLA class I molecules, in the form of transmembrane glycoproteins, are found on the surface of all nucleated cells. *HLA* genes class II are located in B lymphocytes, macrophages, dendritic cells, Langerhans islet cells, and thymic epithelial cells. The HLA class III region encodes some molecules important in inflammation including complement components C2, C4, and factor B; tumor necrosis factor (TNF)-alpha; lymphotoxin; and three heat shock proteins [17].

Genetic predisposition to the risk of developing T1DM is determined by HLA class II [18][19]. The region of HLA class II genes has a complex structure; it contains three loci, named *DR*, *DQ*, and *DP*; each of them includes a variable number of α- and β-chain genes. The *HLA-DRB* is the most polymorphic locus, which, in turn, consists of the *HLA-DRB1* gene and may also include the following genes, with dependence on the 13 gene haplotypes: *DRB3*, *HLA-DRB4*, *HLA-DRB5* and pseudogenes *HLA-DRB2*, *HLA-DRB6*, *HLA-DRB7*, *HLA-DRB8*, and *HLA-DRB9* [20].

The following three genes are of the greatest importance in clinical practice: *DRB1*, containing more than 400 allelic variants; *DQA1*, consisting of 25 allelic variants; and *DQB1*, which has 57 allelic variants. There are pronounced population differences in the frequency and spectrum of *HLA* haplotypes between world populations, as well as between European populations living in different regions of Europe. For example, in most European populations, the most common *HLA* haplotype is *A*01-B*08*; among the Finns, that is *A*03-B*35*; in populations of southeastern Europe, that is *A*02-B*51* [21].

Most *HLA* risk haplotypes have been identified in cohort studies of European ancestry, and thus they may differ somewhat from those in populations of Asian and African ancestry. In particular, a comparative analysis by Harrison et al., 2020, revealed that the *DR3-DR3* variant in Indians was more significantly associated with T1DM compared to Europeans (odds ratio OR = 148.8 versus OR = 16.9 in Europeans); and, on the contrary, *DR4-DR4* was not associated with a high T1DM risk in Indians [22].

The results of next-generation sequencing (NGS) based on DNA sampling of T1DM patients from the Laboratory of Diabetes and Inflammation (JDRF/Wellcome Trust) and control sampling from the British Cohort of 1958 Births showed that patients with the alleles *DRB1*03:01* and *DRB3*02:02* were at an independent risk of developing T1DM compared with carriers of the allele *DRB3*01:01* [23]. Haplotypes *DRB1*03:01-DRB3*02:02* have a high risk of developing T1DM (OR = 25.5, 95% CI 3.43–189.2) [23]. Another study of people of European ancestry was performed by the scientific group of Zhao, 2016. Herein, patients participated in the nationwide study “Swedish Better Diabetes Diagnosis” and were aged from 9 months to 18 years. Researchers found that among 25 alleles of the *HLA-DRB1* genes, only 4 were associated with T1DM. They were presented by *DRB1*03:01:01*, *DRB1*04:01:01*, *DRB1*04:04:01* and *DRB1*04:05:01*. Moreover, for the *DRB4* gene, a variant *DRB4*01:03:01* was associated with T1DM, while for the variant *DRB4*01:01:01*, no association was identified [24].

Some *HLA-DQA1* variants, such as *DQA1*02:01*, which is protective for T1DM in European populations [5][25], are among the most common alleles in Brazilian cohorts [26]. Gomes et al., 2023, found that the risk of T1DM developing in Brazilians may be determined by risk haplotypes, which are typical to European populations; but, if the subjects were of African origin, the same risk variants had a protective effect [27].

Ethnic ancestry history affects patterns of genetic drift and selection around the world, exerting the risk of developing multifactorial diseases. Allele frequencies, including those in genomic regions, which influence the risk of T1DM, are generated by evolutionary history [28]. In particular, it is well known that genetic diversity is predominant in African populations, but due to the emphasis of modern DNA testing on *HLA* risk haplotypes specific to European populations, there is a high potential for the misidentification of T1DM risk in populations of non-European ancestry. For example, the *HLA-DRB1*04:03* genotype, which is quite common among East Asians and Hispano-Americans, is protective and counteracts the high-risk alleles *HLA-DQ8* and *HLA-DQ2* attributable to Europeans. Haplotypes *HLA-DR-DQ*, which occur at low frequency in Europeans, are associated with the risk of T1DM in populations from Africa and the Middle East [28].

Such differences raise the question of whether population-specific genetic associations, if they are secondary to environmental factors, may depend on the geographical location of peoples. Data indicate that the frequency of *HLA* alleles and haplotypes in European populations was generated by strong selection pressures, including the medieval bubonic plague epidemic as one of the most significant factors. In modern European populations, the *HLA-DRB1*13* variant is revealed more than twice as often, while the *HLA-B* alleles encoding isoleucine at position *80 (I-80+)*, and *HLA C*06:02* and *HLA-DPB1* alleles, encoding histidine at position 9, are found twice as rarely when compared to people from burials of the chronological period of the plague epidemic. Thus, significant shifts in *HLA* allele frequencies may indicate natural selection on resistance to a specific pathogen [29].

Modern research notes that over the past 50 years, the frequency distribution of HLA genotypes associated with T1DM has been significantly changed [30][31], which may indicate a shift in the processes of evolutionary selection and an increase in environmental pressure contributing to higher penetrance of the disease [32].

Thus, the investigation of genetic diversity among the different peoples of the world in terms of the prevalence of certain HLA haplotypes is of paramount importance for assessing the risk of developing T1DM.

## 3. Candidate Gene Research

The candidate gene approach allowed the identification of several genes whose changes were associated with T1DM. In particular, Bottini et al., 2004, found that the rs2476601 polymorphism in the *PTPN22* gene, encoding the lymphoid protein tyrosine phosphatase (LYP), was associated with T1DM in non-Hispanic North American Europeans; the rs2476601 polymorphism impairs the LYP–CSK complex formation, whose biological function is to inhibit T cell activation [33]. This polymorphic variant was investigated by Russian researchers as well. Ivanova et al., 2013 conducted a search on associations of the rs2476601 polymorphism with T1DM in Bashkirs, Yakuts, Buryats, Udmurts, and Russians and found that the 1858T variant of the *PTPN22* gene was associated with T1DM in the Udmurt, Russian, and Bashkir populations, while no such pattern was found in the Yakuts and Buryats [34].

Gene mapping has shown that *CTLA-4*, as well as its adjoining genes, may be involved in susceptibility to T1DM [35]. Kavvoura et al., 2005, using the MEDLINE and EMBASE databases, which contain genotyping information for 5637 people with T1DM and 6759 healthy control people, identified the A49G mutation of the *CTLA-4* gene in individuals with T1DM. Although the G allele is more common in Asian populations compared to Europeans, the risk effect associated with the presence of the G allele proved to be independent of race and ethnicity [36].

In 2007, Lowe et al., 2007, based on resequencing of the interleukin 2 alpha receptor gene *IL2RA*, identified an association between two independent groups of SNPs covering regions of 14 and 40 kilobase pairs, including intron 1 of the *IL2RA* gene and the 5′-regions of the *IL2RA* and *RBM17* genes in individuals with T1DM. Among them, rs11594656 was associated with lower circulating levels of *IL-2RA* ($p = 6.28 \times 10^{-28}$). The authors suggested that a genetically determined low immune response predisposes to T1DM [37].

Thus, multi-year research into candidate T1DM genes made it possible to identify several significant loci of the examined genes, which were reproduced by several researcher groups.

## 4. Multicenter and Genome-Wide Association Studies (GWAS)

Genome-wide association studies (GWAS), as well as a number of large multicenter studies, have significantly expanded knowledge about the genetic basis of T1DM; they have identified about 70 highly significant risk single nucleotide polymorphisms (SNPs) that are not localized in *HLA* genes.

Over the past 15 years, such work has been carried out by large national and international collaborations, including the Type 1 Diabetes Genetics Consortium (T1DGC) [37][38], The Environmental Determinants of Diabetes in the Young (TEDDY) [39], Diabetes Autoimmunity Study in the Young (DAISY) [40], Diabetes in the Newborn Study (BABYDIAB) [41], Wellcome Trust Case Control Consortium (WTCCC) [42], Diabetes Prevention of Type 1 (DPT-1) [5], “International TrialNet Research Network” [43][44], “Finnish Diabetic Nephropathy Study” (FinnDiane) [31], “Multinational European Project on Latent Autoimmune Diabetes in Adults” (Action LADA) [45], “Multicentre Clinical study of the Vienna Eurodiab Center” [46], etc. These studies resulted in the accumulation of an enormous amount of diverse data, much of which remain to be validated, since the ethnic component and involving different age groups might bring about rather contradictory results.

In particular, the WTCCC has identified relatively few new T1DM risk markers. Among them are the following gene variants: *ERBB3* (epidermal growth factor receptor), *SH2B3* (adapter protein), and *CLEC16A* (tyrosine phosphatase) [42]. A genome-wide association study and further meta-analysis by Barrett et al., 2009, based on a sampling of 7514 cases of T1DM and a control group of 9045 healthy individuals showed an association of more than 40 SNPs ($p < 10^{-6}$) with type 1 diabetes. After excluding loci previously associated with T1DM, the other 27 loci were further examined in an independent sampling of 4267 cases of T1DM, 4463 healthy control individuals, and 2319 siblings. In GWAS replication, more than 15 loci retained a statistically significant association with T1DM ($p < 0.01$; overall $p < 5 \times 10^{-8}$). The most significant SNPs are localized in the interleukin genes *IL10*, *IL19*, *IL20*, and *IL27*, as well as in the transcription factor *GLIS3* gene and the cytokine *CD69* gene [47]. Mutations in the *GLIS3* gene were identified in children from three different consanguineous families with neonatal diabetes, concomitant congenital hypothyroidism, and other clinical complications [48]. The 12p13.31 region contains a number of immunoregulatory genes, including *CD69*, which is induced by T cell activation and functions in the egress of cells from the thymus; they belong to members of the family of the calcium-dependent (C-type) lectin (CLEC) domain with immune functions. The authors concluded that the relative risks for non-HLA loci were reduced in carriers of risky *HLA* haplotypes, which confirms the polygenic and genetically heterogenic structure of T1DM [49].

Despite the fact that most polymorphic variants associated with T1DM are localized in non-coding regions, it is the coding regions of DNA that are of significant interest, since they not only affect gene expression in the pancreas but also significantly change the structure of signaling proteins in immune-competent cells. Onengut-Gumuscu et al., 2015, identified coding variants associated with T1DM in seven genes including *PTPN22* (tyrosine phosphatase, previously identified in a candidate gene study), *IFIH1* (receptor of RIG-I-like receptor group), *SH2B3* (adapter protein), *CD226*, *TYK2* (Tyrosine kinase 2), *FUT2* (Galactoside-2-alpha-L-fucosyltransferase 2), and *SIRPG* (Signal regulatory protein gamma) [50].

In addition, SNPs were identified, which overlap potential enhancers next to the genes *CTLA4* (Cytotoxic T-lymphocyte glycoprotein), *CTSH* (Cathepsin H), and *UBASH3A* (Ubiquitin-associated protein A containing the SH3 domain) [50]. The authors emphasized that most markers located in enhancer sequences actively affected gene expression in thymus cells and T and B cells, as well as CD34+ stem cells. According to their preliminary inferences, enhancer–promoter interactions can now be analyzed in these cell types to determine which genes and regulatory sequences are causative, namely, determining the first links in the pathogenesis of type 1 diabetes.

It is worth noting that the rs2476601 loci of the *PTPN22* gene and rs11203203 of the *UBASH3A* gene are associated with the emergence of autoimmunity to pancreatic β-cells, while polymorphic variants of the *INS*, *UBASH3A*, and *IFIH1* genes are associated with the transition from an autoimmune reaction against pancreatic β-cells to the development of clinical diabetes. Similar results were obtained in participants in the TEDDY study, where carriers of high-risk *HLA* haplotypes and four risk polymorphic variants including rs2476601 in *PTPN22*, rs2292239 in *ERBB3*, rs3184504 in *SH2B3*, and rs1004446 in *INS* exhibited a significant association with the development of an autoimmune reaction to β-cells of pancreatic gland islets [51]. The Finnish Childhood Diabetes Registry revealed that the *DR3-DQ2/DR4/DQ8* genotype affected the production of islet β-cell autoantibodies but not the subsequent development of T1DM [52].

Genome-wide association studies and their meta-analysis, as well as their replication and bioinformatics processing, have highlighted an enormous number of previously unknown DNA markers, which confirmed the complex heterogeneous and polygenic structure of T1DM. Currently, it is a relevant issue to assess the contribution of the enormous number of

variants with a small risk effect (odds ratio (OR)), located throughout the genome, in the heterogeneity of the disease and clinical outcomes of T1DM.

## 5. The Polygenic Risk Score in Individuals with Type 1 Diabetes Mellitus

One of the promising methods of bioinformatics analysis, which helps to assess the hereditarily determined risk of multifactorial diseases, is the polygenic risk score (PRS), which implies calculating an individual susceptibility coefficient to a specific phenotype of disease on the basis of the analysis of a large number of polymorphic variants. An obvious application of PRS in the diagnosis of T1DM is assessing the risk contribution of the complex combined effects of *HLA* risk haplotypes jointly with other DNA markers. The assessment is performed on the basis of a polygenic score, which is calculated using a weighted sum of individual risk alleles significantly associated with the trait [53].

Winkler et al., 2014, using multivariate logistic regression of data (sampling N = 5781) from the Type 1 Diabetes Genetics Consortium (T1DGC), found that the additional inclusion in the model of 40 SNPs of genes, which are not located in the *HLA* locus, significantly improved the prediction of T1DM, compared with models that include only *HLA* alleles and haplotypes. On the basis of the method of including and excluding genetic predictors, the authors selected a model with optimal predictive value which involved the following genes: *HLA*, *PTPN22*, *INS*, *IL2RA*, *ERBB3*, *ORMDL3*, *BACH2*, *IL27*, *GLIS3,* and *RNLS* (AUC = 0.86, 95% CI 0.84–0.88) [54].

In light of the results described above, DNA screening for identifying groups with a high risk of T1DM has become important. Screening for T1DM using a variety of diagnostic tests at multiple time points during the first years of a person's life is feasible but quite expensive. This problem could be solved with DNA analysis, which does not depend on age and environmental factors and does not change over time, so the introduction of PRS disease prediction models in newborn screening could identify individuals at high risk for broader monitoring and prevention of severe consequences of T1DM.

## 6. Functional Role of DNA Risk Loci Related to Developing T1DM in Signaling Pathway Changes

Once DNA loci have been identified, the next step should be directed to the investigation of their role in the functional and molecular alterations in cell signaling pathways that bring about T1DM development. In the study by Shapiro et al., 2021, the researchers suggested that the dysfunction of FUT2 (galactoside-2-alpha-L-fucosyltransferase 2), due to gene mutation, leads to a lack of secretion of the ABO blood group antigen through the intestinal mucosa. That, in turn, may cause an impairment in the immune barrier of intestinal epithelial cells, which results in increased susceptibility to certain viral infections, as well as in changes in the composition of the microbiome and microbial metabolites, especially short-chain fatty acids. The expression of the ABO antigen in the intestinal mucosa affects the binding of exogenous pathogens and commensal microbiota. The fecal microbiota of individuals with the rs601338*A/A variant was found to contain, on average, fewer probiotic bifidobacteria, which are capable of producing immunoregulatory short-chain fatty acids and promoting intestinal barrier integrity, which is critical for preventing commensal-induced autoimmunity [55]. The rs601338 risk allele is associated with a sharp deterioration in the first phase of insulin response in children with multiple autoantibodies at T1DM [55]. This fact could explain the relationship between patient age and secretory status at the time of diagnosis. Examinations indicated that therapy, positively affecting FUT2, was likely to be required at an early age for patients with a specific genotype [56][57].

In the context of the pathogenesis of T1DM, TYK2 (a member of the JAK family) enhances antigen presentation by stimulating the expression of *HLA* gene class I and promotes the expression of the chemokine CXCL10, which causes the activation of T cells and their recruitment toward the pancreatic islets, thereby increasing the risk of developing the autoimmune process [58]. Moreover, this effect may be significantly complicated by the biological activity of Cathepsin H (CTSH). Shapiro et al., 2021, made a number of assumptions regarding the importance of this molecule. The fact is that CTSH is a lysosomal proteinase, which plays a role in protein recycling, prohormone processing, and HLA II antigen presentation, as well as it may antagonize CXCL10.

Even as CTSH is expressed ubiquitously, its representation is most pronounced in type II lung alveolar cells during the maturation of surfactant protein [59]. Allele C of the rs2289702 locus in exon 1 of the *CTSH* gene turned out to be protective at T1DM; it can affect the cleavage of cathepsin to its active form and its delivery to lysosomes [60]. The T allele of this locus is associated with the prevention of an early onset of T1DM, especially in patients younger than seven years [61]. One possible explanation for this finding is that decreased *CTSH* gene expression may reduce the N-terminal cleavage of Toll-like receptor 3 (TLR3), impairing TLR3 functionality and dropping TI-IFN expression in response to viral infections in early childhood [61]. However, insight into the mechanism of the relationship between *CTSH* expression and

the risk of developing T1DM gets further complicated by the report of *CTSH* overexpression, which induces intrinsic β-cell protection from cytokine-mediated damage and the stimulation of insulin production [62]. Functional examinations support the relevancy of continuing investigations of CTSH modulation as a potential means of preventing T1DM with specific attention to the off-target effects of targeted therapy toward this protein expression in the treatment of T1DM.

The polymorphic variant rs2476601 in exon 14 of the *PTPN22* gene leads to the replacement of arginine with tryptophan at position 620 and is one of the loci most significantly associated with T1DM, being second in importance only to the *HLA* and *INS* variants. The gene encodes non-receptor lymphoid tyrosine phosphatase type 22 (LYP), which is responsible for dephosphorylation of signaling proteins. LYP is one of the most powerful inhibitors of T cell activation. The substitution affects the interaction between the LYP proline-rich motif and CSK tyrosine kinase, causing the impairment of signal transduction modulation. The study indicates that the mutation is associated with the synthesis of autoantibodies to insulin, which manifests itself more rapidly in children carrying high-risk *HLA* haplotypes or in first-degree relatives with type 1 diabetes [63]. Nevertheless, the role of rs2476601 in enhancing T cell activity remains controversial, since there is uncertainty in understanding how this variant affects the functional activity of tyrosine phosphatase [64]. However, it is reliably known that the rs2476601 polymorphism impairs the interaction between LCK and LYP, which is accompanied by a decrease in LYP phosphorylation and, ultimately, contributes to the inhibition of gain in the function of T cell activation [65]. It is believed that a gain in LYP activity may be a predisposition to autoimmunity through the decreased activation of regulatory T cells, which are required to suppress autoreactivity [66]. When regarding a potential complete loss of tyrosine phosphatase activity, it implies impairment of the signaling apparatus of T cell receptors, which, in turn, leads to the less effective dephosphorylation of signaling proteins and increased activation of effector T cells [67].

T cell ubiquitin-1 ligand UBASH3A reduces T cell receptor signaling. Currently, most T1DM-associated variants of the *UBASH3A* gene are intronic. Meanwhile, it is known that UBASH3A regulates the NF-κB signaling pathway through a ubiquitin-dependent mechanism and that the risk alleles rs11203203 and rs80054410, associated with T1DM, increase the expression of the *UBASH3A* gene in primary human CD4+ T cells upon the stimulation of T cell receptors, which results in reducing NF-κB signaling through the IκB kinase complex and diminishing *IL2* gene expression [68]. Suomi et al., 2023, published a summary of the results of transcriptomic profiling of whole blood samples from patients with T1DM as part of the INNODIA study. They found that the expression of some genes and the activity levels of signaling pathways involved in innate immunity were reduced during the first year after diagnosis. A significant change in gene expression was associated with positive ZnT8A autoantibody status [69].

On the other hand, *SIRPG*, *STXBP1*, and *UBASH3A* genes had an inverse correlation with positive ZnT8A autoantibody status. SNPs, associated with T1DM, near the *SIRPG* gene have been shown to modulate disease risk by controlling the alternative splicing of the gene. It encodes syntaxin binding protein 1, which regulates the docking and fusion of vesicles with the plasma membrane during exocytosis. STXBP1 is important for the cytotoxic activity of CD8+ T cells and NK cells. The *UBASH3A* genetic variant is associated with the development of T1DM in children from the DAISY and BABYDIAB cohorts. Type 1 diabetes-associated variants of the human *UBASH3A* gene caused higher levels of gene expression and decreased NF-κB signaling and *IL2* expression in CD4+ T cells [69].

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