

Review Article

Genetics of Type 1 Diabetes Mellitus

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ABSTRACT

Type 1 diabetes is an autoimmune disease in which the patient's immune system destroys the insulin-secreting β -cells of the pancreas. A majority of cases is thought to occur as a result of gene-environment interaction. About 18 regions of the genome have been linked with influencing type 1 diabetes risk. These regions, each of which may contain several genes, have been labeled IDDM1 to IDDM18. The most well-studied is IDDM1, which contains the HLA (Human Leukocyte Antigens) genes that encode immune response proteins. Variation

in HLA genes is an important genetic risk factor, but they alone do not account for the disease as other genes are involved. Other important loci associated with type 1 diabetes with much smaller effect than HLA, include the insulin variable number of tandem repeats, PTPN22 (Protein Tyrosine Phosphatase non-receptor type 22), and CTLA-4 (Cytotoxic T-Lymphocyte Antigen-4).

This review will focus on genetic factors associated with type 1 diabetes mellitus.

KEYWORDS: cytotoxic T-Lymphocyte antigen-4, insulin gene, protein tyrosine phosphatase non-receptor type 22, type 1 diabetes mellitus

INTRODUCTION

Type 1 diabetes (T1D) is a multi-factorial autoimmune disease characterized by insulin deficiency, due to the T-cell mediated destruction of pancreatic β -cells^[1,2]. The disease accounts for about 10% of all cases of diabetes^[3]. There is a marked geographic variation in incidence, with an annual incidence of more than 40 per 100,000 children in Finland to less than two per 100,000 in Japan^[4,5]. The incidence of T1D in Kuwait was 20.1 per 1000,000 children between 0-14 years. The incidence among boys at 21.1 per 100,000 was slightly higher than that among girls at 19.0 per 100,000^[6]. In addition, there is compelling evidence of a temporal increase in the incidence of T1D, with countries such as Finland experiencing more than a doubling in incidence over the past four decades^[7]. The current global increase in incidence of 3% per year is well reported^[3,8]. This rapid rise strongly suggests that the action of the environment on susceptibility genes contributes to the evolving epidemiology of T1D^[3]. The general population has a 1 in 300 risk of developing T1D, whereas a first-degree relative with T1D has a 1 in 2 lifetime risk^[9,10]. Prevalence of T1D in Kuwait was 269.9 per 100,000. There was no significant difference in prevalence between male and female. T1D was more prevalent in the age group 10 - 13 years and lowest in the age group 6 -

9 years^[11]. Monozygotic twins have a concordance rate of 30 to 50%, whereas dizygotic twins have a concordance rate of 6 to 10%^[10]. Eighty-five percent of cases of T1D occur in individuals with no family history of the disease. Differences in risk also depend on which parent has diabetes. Children of mothers who have T1D have only a 2% risk of developing T1D, whereas children of fathers who have T1D have a 7% risk^[10]. In disorders following a mendelian pattern of autosomal dominant or recessive transmission, the pattern of inheritance of the disease phenotype is usually obvious. It is much more difficult in diabetes to confidently define the reported linkage susceptibility genes, since the mode of inheritance of the genes causing these complex disorders is unknown^[12].

Among the genetic determinants of susceptibility, with more than 18 putative loci identified to date, a region in chromosome 6p21 (IDDM1) containing the major histocompatibility complex (MHC) is the only one consistently associated with T1D in genome-wide screenings^[2]. Candidate gene studies also identified the insulin gene (INS) on chromosome 11 as the second most important genetic susceptibility factor, contributing 10% of genetic susceptibility to T1D^[13]. Over the last decade, whole genome screens have indicated that there are at least 15 other loci associated with T1D,

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and of those, other two genes intimately associated with T-cell activation have been identified recently^[3,14-16]. An allele of the gene for a negative regulator of T-cell activation, cytotoxic T-Lymphocyte antigen 4 (CTLA-4), found on chromosome 2q33, is considered to be the third susceptibility locus for T1D and has been associated with increased levels of CTLA-4^[17] and the frequency of regulatory T-cells^[18]. A variant of Protein tyrosine phosphatase non receptor type 22 (PTPN 22), the gene encoding LYP (Lymphoid tyrosine phosphatase), also a suppressor of T-cell activation, has been deemed the fourth susceptibility factor^[3,19,20].

To date, no single gene is either necessary or sufficient to predict the development of T1D. Although T1D is likely a polygenic disorder, epidemiological pattern of T1D, including seasonal and temporal changes in incidence, suggest that environmental factors are involved^[21], with the exception of possible role for viruses, infant nutrition, obesity and lack of exercise. The environmental factors that initiate or precipitate the onset of T1D have not been established^[21]. Studying the genetics of T1D will allow us to better define this disease, to improve our ability to identify individuals at risk, and to predict the risk of associated disorders^[9]. To the best of our knowledge, no genetic study was done in Kuwait to detect the common gene for T1D.

Pathophysiology

T1D is the most severe type of diabetes, requiring insulin injections on a life long basis^[22]. The majority of cases result from proven autoimmune-mediated cell destruction (Type 1a); approximately 10 to 20% of cases are antibody-negative and are termed idiopathic (Type 1b)^[23]. A decline in insulin secretion is demonstrated for up to 12 years before the onset of clinical disease. Inflammation of the pancreatic islets (insulinitis) involves CD4⁺ and CD8⁺ lymphocytes, B-lymphocytes, and macrophages^[24,25].

Two mechanisms of onset for T1D are proposed. The first mechanism suggests that environmental factors trigger the autoimmune process, most often in childhood before 10 years of age^[24]. Although the diagnosis of T1D is usually preceded by only a few weeks of known symptoms, in fact clinical disease becomes evident only after a long prodromal period characterized by the gradual destruction of pancreatic beta cells^[23]. The second mechanism suggests that a superantigen reaction results in rapid destruction of pancreatic beta cells within a few weeks to a month, leading to the onset of clinical disease^[26].

HLA genes in predisposition to T1D:

The best evidence for a genetic component in the susceptibility to T1D comes from studies of the HLA genes in both population and families as well as from animal models^[27]. It has been estimated that HLA (IDDM1) provides up to 40 - 50% of the familial clustering of T1D^[28,29]. The HLA region is a cluster of genes located within MHC on short arm of chromosome 6 (6p21.3)^[21,27].

The HLA Classes:

Within the HLA region, they are grouped into three classes.

Class I genes: (HLA - A, HLA -B and HLA-C) encode class I HLA antigens, located on the surface of all nucleated cells^[30].

Class II genes: (HLA -DR, HLA-DQ and HLA-DP) produce class II HLA antigens that are found exclusively on B-lymphocytes, macrophages, epithelial cells of the islets of Langerhans, and activated T-lymphocytes. Their expression on other cells may be induced by cytokines such as α -interferon and INF- γ ^[30,31].

Class III genes: code for complement components (C2, properdin factor B, C4A and C4B), 21-hydroxylase and products involved in T-cell-mediated inflammation, such as TNF-A and TNF-B, and acute phase protein^[31].

The HLA class II Region:

Statistically is the strongest genetic association with T1D conferred by HLA class II gene alleles^[27]. HLA class II molecule, particularly DR and DQ, account for approximately 40% out of the genetic risk for T1D development^[12,32]. As the HLA region displays a significant degree for linkage disequilibrium, it has been very difficult to study the effect of individual HLA-DQ or DR genes separately^[27].

Spectrum of diabetes risk HLA haplotypes:

Several loci within or near HLA complex appear to modulate diabetic risk and add further complexity to the analysis of T1D^[33]. Individual with the highest risk for T1D express both predisposing haplotypes: DQA1*0501-DQB1*0201 (DQ2), which is almost always inherited with DRB1*0301 (DR3) and DQA1*0301-DQB1*0302 (DQ8), inherited with DRB1*0401 or DRB1*0402 (DR4)^[34-37]. These individuals have been referred to as DR3/DR4 or DQ2/DQ8 heterozygotes. So, a great majority of patients carry the HLA -DR3 or DR4 class II antigens and approximately 30% of patients are DR3/DR4 heterozygotes^[33]. The DR3/DR4 genotype confers the highest diabetic risk with a synergistic mode of action, followed by DR4 and DR3 homozygosity, respectively^[38]. Based

on DNA sequencing, the HLA-DQ locus was found to be the most strongly associated with diabetes susceptibility^[33]. The precise mechanism through which HLA-DQ determines disease susceptibility is still not clear^[39]. This locus encodes for several variants of the HLA-DQ molecule, a heterodimer consisting of two glycoprotein chains (and) involved in immune recognition and antigen presentation to CD4 T-cells^[33]. In Caucasians, the HLA-DQ heterodimers (the -chains are labeled DQA1 and the -chains DQB1) encoded by DQA1*0301, DQB1*0302 and DQA1*0501, DQB1*0201 alleles have the strongest association with diabetes^[31,33]. These alleles are in linkage disequilibrium with the HLA-DR4 and DR3 alleles^[40].

It has also been noted that DQB1*0302 differs from DQB1*0301 at position 57, where it lacks an aspartic acid residue^[33]. The DQB1*0201 allele also lacks aspartic acid at position 57, and it has been proposed that this residue may be involved in the molecular mechanism underlying T1D-encoded susceptibility^[40,41]. In fact, the amino acid residue at position 57 of the DQ- chain appears to be critical for peptide binding and recognition^[42]. Other residues of the DQ- chain may influence peptide binding and diabetes susceptibility, and in particular the combined variation of residues at position 57 and 70 seem to more strongly correlate with diabetes risk^[43,44]. An arginine residue at position 52 of the DQ- chain also correlates with diabetes susceptibility^[45]. However, some DQB1 including DQB1*0302/DQB1*0201 (DR7), DQB1*0201(DR3)/DQB1*0201(DR3) and DQB1*0201(DR3)/DQB1*0201 (DR7) are low risk^[31].

Certain haplotypes of class II HLA genes exert a protective action against the development of diabetes. HLA -alleles have also been associated with protection from T1D, the haplotype DQA1*0102/DQB1*0602/DRB1*1501 being known to confer protection. Evidence suggest that such protection may be mostly encoded by the DQB1*0602 allele and even the first degree relatives with islet cell antibodies have a low diabetic risk if they carry DQB1*0602. However, this protective effect is not absolute^[12,34,46,47].

Other loci in the class II region have been associated with T1D besides HLA-DQ and DR^[27]. HLA-DPB1*0101, DPB1*0301, and DPB1*0202 were reported to be positively and DPB1*0402 negatively associated^[48-50].

To summarize, some HLA haplotypes are associated with high, moderate or low risk of developing T1D whereas some even confer protection against T1D (Table 1).

The HLA class I Region:-

A number of observations indicate that class II genes cannot explain all of HLA association with

Table 1: HLA haplotypes and type 1 diabetes

High Risk Haplotypes			
DR 3	DQA1*0501	DQB1*0201	DRB1*0301
DR 4	DQA1*0301	DQB1*0302	DRB1*0401
DR 4	DQA1*0301	DQB1*0302	DRB1*0405
Predisposing Haplotypes			
DR2	DQA1*0102	DQB1*0502	DRB1*1601
DR4	DQA1*0301	DQB1*0302	DRB1*0402
DR4	DQA1*0301	DQB1*0302	DRB1*0404
Protective Haplotypes			
DR2	DQA1*0102	DQB1*0602	DRB1*1501
DR6	DQA1*0101	DQB1*0503	DRB1*1401
DR7	DQA1*0201	DQB1*0303	DRB1*0701

T1D^[33]. There is evidence that several alleles at the class I HLA B and C loci may influence susceptibility as well as the age of onset^[51] and the rate of -cells destruction^[52]. In addition, the class I chain -related MIC-A and MIC-B genes located between the HLA-B and TNF genes may also effect T1D susceptibility^[33].

The HLA class III Region:

The TNF (Tumour Necrosis Factor) gene is a strong candidate from class III, since this gene polymorphisms may affect the production of TNF- , a potent cytokine, thus affecting the immune response potential^[33]. It has been reported that TNF polymorphisms are associated with age of onset and influence the inflammatory process leading to the destruction and pancreatic -cell and development of T1D^[53].

Apart from determining T1D risk, HLA genes can also modulate clinical features of the disease, such as age of onset or outcome of active cellular autoimmunity^[54]. Thus, the combination of the DR3 and DR4 haplotypes not only predisposes strongly to T1D but also accelerated disease onset^[54]. Conversely, the rare individuals contracting T1D despite the presence of the protective DQB1*0602 allele generally show a very late onset of disease^[55].

In conclusion, the HLA associations with T1D are complex, with many haplotypes influencing disease risk^[56].

IDDM2: The Insulin Gene:

Insulin is composed of two distinct polypeptide chains, chain A and chain B, which are linked by disulfide bonds. Many proteins that contain subunits, such as hemoglobin, are the products of several genes. However, insulin is the product of one gene, INS^[57]. The research done by Nakayama *et al* has strongly shown that insulin is a primary autoantigen in the beginning stages of diabetes. Also, supporting this evidence is the presence of insulin antibodies in the blood of prediabetic and diabetic patients^[58].

The insulin gene is the second well established susceptibility locus in T1D on chromosome 11p

15.5^[12,30]. It contributes about 10% toward T1D susceptibility^[59].

The variable number of tandem repeats (VNTRs):

The risk area of this locus is localized to a region flanking the insulin gene that contain a short sequence of DNA that is repeated many times^[16,60]. Because the repeated sequences follow one behind the other (in tandem) and because the number of repeats varies between individuals, this phenomenon is called VNTRs^[57]. The VNTRs polymorphism is categorized into classes I to III.

- **Class I** has alleles that range from 26 to 63 repeat units^[30].

- **Class II** has alleles that average around 80 repeat units^[57].

- **Class III** has alleles ranging from 141 to 209 repeat units^[54].

Occurrence rate of VNTR I in the Caucasoïd population is approximately 70%, and that of VNTR III 30%. VNTR II occurs very rarely^[12].

The class of VNTR is associated with susceptibility to T1D. Short class I alleles are associated with a higher risk of developing T1D, whereas the longer class III alleles are protective^[57,61]. The presence of at least one class III allele is associated with a three-fold reduction in the risk of T1D^[57,61]. The mechanism by which the insulin VNTR polymorphism influence the risk of T1D is unclear^[56].

HLA and insulin regions account for almost 60 - 70% of the familial aggregation of T1D. In some population, the combined effects of HLA and insulin contribute less than 50% of familial increased diabetic risk. Therefore, several genome-wide linkage studies have been conducted to identify candidate regions that may contain unidentified susceptibility genes^[12,62].

Cytotoxic T-Lymphocyte Antigen - 4 (CTLA- 4):

CTLA- 4 is expressed when the T-cell has been activated after antigen presentation. Because it is only expressed in activated T-cells, and because it down regulates the function of T-cells, it is likely that CTLA- 4 has a role in guarding against autoimmunity^[57,63]. Loss of this gene may result in activated T-cells attacking self antigens. Indeed, genetic variants of CTLA- 4 have been linked with autoimmune disorders^[57]. CTLA- 4 gene is localized on the long arm of chromosome 2 (2q 33) and this genetic region, IDDM 12, was previously found to be associated with predisposition to T1D^[17,63]. Some evidence has also been produced to suggest that CTLA- 4 polymorphisms may influence gene expression. Three polymorphisms are currently known in CTLA- 4, including a A/G SNP in exon 1, a C/T SNP in the first intron and a microsatellite repeat in the 3' untranslated region^[54]. CTLA- 4

expressed on the cell surface of activated T-cells is responsible for the attenuation of immune response by binding to ligands CD80 or CD86 expressed on the surface of antigen presenting cells^[12,64]. The CTLA-4-CD80/CD86 interaction decreases synthesis of IL2 or may induce apoptosis in previously activated cells^[12,64].

Protein tyrosine phosphatase non-receptor type 22 (PTPN 22):

The fourth established human T1D susceptibility locus is PTPN22. It encodes a lymphoid protein tyrosine kinase (LYP) that is important in negative control of T-cell activation and in T-cell development^[12,20]. A single nucleotide polymorphism at nucleotide 1858 in PTPN22 was associated with T1D^[12,20]. Bottini and co-workers evaluated a functional polymorphism in LYP gene in two series of patients with T1D^[33]. This polymorphism is the most potent after IDDM1 and IDDM2. The LYP gene, also termed PTPN22, is a lymphoid tyrosine phosphatase located on chromosome 1 P13^[33]. It is of interest that PTPN22 has an effect similar in magnitude to the insulin gene polymorphism. Similar to CTLA-4, PTPN22 is a T1D susceptibility locus that is shared by several organ specific and systemic autoimmune diseases^[65].

Interleukin (IL):

It is well recognized that IL-2 has paradoxical functions in T-cell homeostasis, acting as a potent T-cell growth factor during the initiation of immune responses and having a crucial function in the termination of T-cell responses and maintenance of self tolerance^[12]. The latter function has been proposed to be due to a requirement for IL-2 signaling for the development and function of regulatory T-cell, although IL-2 signaling is not required for their development in the thymus. Its level might affect disease susceptibility via the mechanisms that maintain immune homeostasis^[66]. It has been proved that although the levels of CD4+ CD25+ regulatory T-cells had been normal in patients with T1D, their ability to suppress T-cell proliferation was markedly reduced compared with control subjects^[66]. From this point of view it is a very interesting evidence that the region containing the gene IL-2RA encoding the alpha chain of the IL-2 receptor (CD25) on chromosome 10p15-p14 could be the fifth susceptibility locus for T1D^[67].

IL-6 is a cytokine that has been implicated in a number of immune mediated diseases^[66]. There is a polymorphism at position 174 of the promoter region of the IL-6 gene that may alter the expression

Table 2: Susceptibility loci for type 1 diabetes

Locus	Chromosome	Candidate Genes
IDDM1	6p21.3	HLADR/DQ
IDDM2	11p15.5	INSULIN (INS) VNTR
PTPN22	1p13	PTPN22 (LYP)
SUMO4	6q25 (IDDM5)	SUMO4
IDDM3	15q26	-
IDDM4	11q13	LRP5, FADD
IDDM5	6q25	MnSOD, SUMO4
IDDM6	18q12-q21	JK(Kidd), ZNF236, BCL2
IDDM7	2q31-33	NEUROD
IDDM8	6q25-27	-
IDDM9	3q21-25	-
IDDM10	10p11-q11	GAD2
IDDM11	14q24-q31	ENSA, SEL-1L
IDDM12	2q33	CTLA-4, CD28
IDDM13	2q34	
IDDM15	6q21	
IDDM16	14 q 32	
IDDM17	10q25	
IDDM18	5q31.1 - 33.1	IL12B

of the gene^[68]. IL-6 gene may contribute to the genetic susceptibility for T1D^[68].

IDDM 3 - IDDM 18: (Table 2)

IDDM 3 - IDDM 18, with the exception of IDDM 17, have all been discovered by linkage studies using affected sib-pair families, either in whole or partial genome scans. For most of these regions positional candidate genes have been further analyzed^[27].

IDDM3 was originally reported to be located near the D15 S107 marker on chromosome 15q 26 and so far no diabetes susceptibility genes have been identified on IDDM3 locus^[27].

IDDM4 is a region on chromosome 11q13 and one of its genes which might be involved in T1D genetic predisposition that can be coding for FADD, a molecule involved in the apoptosis process^[69].

The region of chromosome 6q25 that contains the IDDM5 locus includes the Mn-superoxide dismutase (Mn SOD) genes^[33]. MnSOD metabolizes harmful oxygen free radicals and converts them into less reactive and less harmful molecules^[57]. Polymorphism affecting the function of MnSOD could render β -cells more susceptible to free oxygen radicals damage^[33]. However, this region may contain a susceptibility gene that is common to more autoimmune diseases^[70].

Several candidate diabetes susceptibility genes have been identified in the IDDM6 locus. They include a gene associated with colorectal cancer that may be linked to autoimmune disease, a gene that encodes a zinc finger DNA binding domain (ZNF 236) that may be linked with diabetic kidney disease, and a molecule that opposes apoptosis (bCl-2)^[3,57].

Within the IDDM7 locus on chromosome 2q 32 are several candidate diabetes risk genes^[71]. One is NEUROD 1, a transcription factor regulating the expression of the insulin gene and playing an important role in the development of pancreatic β -cells^[33].

IDDM8 is found on chromosome 6 q 25 - q 27. At present there is no known candidate gene in the 6q 25 - q27 region^[33]. IDDM9 has not yet been approved^[56].

Another susceptibility locus may exist on chromosome 10p11 - q11, and has been termed IDDM10^[72]. The gene GAD2 is closely linked to the region of chromosome 10. Glutamic acid decarboxylase (GAD) catalyzes formation of the neurotransmitter GABA. Targeting of this enzyme by autoantibodies has been implicated in the pathogenesis of T1D^[57,73,74]. However, several studies have failed to demonstrate evidence of linkage of GAD2 to T1D^[27].

IDDM11 appears to lie on chromosome 14q 24.3 - q31^[33]. Two candidate genes have been recently mapped to this chromosomal region. The ENSA gene encodes alpha-endosulfine, an endogenous regulator of β -cells K(ATP) channels^[75]. The recombinant alpha-endosulfine has been shown to inhibit sulfonylurea urea binding to β -cells membrane, to reduced K (ATP) channel currents and to stimulate insulin secretion^[75]. The SEL-1L gene codes for a negative regulator which is required for differentiation and maturation of cells as well as cell-cell interactions during development^[33]. SEL-1L is abundantly expressed only in the pancreas, and recently shown to be critical for the development of the pancreas and β -cells^[76].

Several IDDM13 candidate genes have yet to be associated with T1D^[27]. IDDM14 has not yet been approved^[57]. The IDDM 15 locus has been linked with T1D and mutations near this region are associated with a rare form of diabetes called transient neonatal diabetes^[77].

One of the candidate genes in the IDDM 16 locus is the immunoglobulin heavy chain. Immunoglobulins (antibodies) have a central role in the immune response against foreign antigens and in error can also attack self antigens, resulting in autoimmune disease^[57].

IDDM 17 maps to the long arm of chromosome 10(10q 25). It was discovered to be linked to T1D, but the candidate gene is not yet known^[33].

IDDM 18 was identified and mapped to chromosome 5q 31.1 - q33.1, close to the gene for the P40 subunit of the IL12 gene, IL 12B^[78,79]. IL-12 P40 production influence T-cell responses, and may therefore be important in T1D susceptibility^[80].

Other Susceptibility Loci:

A number of additional chromosomal regions demonstrating some evidence of linkage to T1D have been identified^[27].

The effect of gender and HLA genotype complicate studies of the contribution of genes on the X-chromosome to T1D susceptibility^[81].

There is also increasing evidence of the key role of Vitamin D levels in T1D susceptibility^[82-84]. Vitamin D has important immunomodulatory properties^[85] and depletion or relative resistance may play a part in the aetiology of T1D, possibly through effects on insulin secretion^[86].

Several studies point to the involvement of TNF in T1D, although the contribution of TNF- and TNF- to autoimmune disease in general and to diabetes in particular is not well established^[87].

Researchers in Houston (2004) identified a new gene mutation. The gene called SUMO-4 contributes a portion of the risk of this form of diabetes. SUMO-4 plays a role in regulating the immune system. When mutated, the gene functions abnormally, prolonging the inflammatory response. This finding gives scientists a clue about the autoimmune cause of diabetes^[88].

At the very end, there is also a report on association between CD4 SNP promoter polymorphism and T1D^[89].

Environmental Triggers for T1D:

Studies in most populations confirm an increase in the incidence of T1D, particularly among young children^[3]. Some studies however have shown convincingly that the increases among young children are occurring because of a shift to lower age at onset rather than an overall increase in incidence in all age groups^[3]. These changes are too rapid to be caused by alterations in the genetic background and are likely the result of environmental changes^[3]. The temporal increase in the incidence of T1D is almost certainly due to environmental factors. Moreover, it was noted that the incidence of diabetes has seasonal variation with an increase in children presenting with T1D in the fall of autumn and winter suggesting that viral infections might precipitate the disease^[5,12,90].

To date, 14 different viruses including picornaviruses, rotaviruses, herpesvirus, mumps, rubella and retroviruses, have been reported to be associated with the development of T1D in human and animals models^[91]. Viruses may be involved in the pathogenesis of T1D in at least two distinct ways: by inducing beta cell -specific autoimmunity, with or without infection of the beta cells (e.g. Kilham rat virus) and by cytolytic infection and destruction of the beta cells (i.e. encephalomyocarditis virus in mice)^[91]. Coxsackie viruses

have been of particular interest because of a homology between the virus and the target antigen glumatic acid decarboxylase 65 (GAD 65). Both negative and positive studies have been reported^[92,93].

Nutritional factors were suggested to induce immunopathological process. Antibodies to milk protein and T-cells responses to these protein were reported to be increased amongst children with T1D^[12]. Gerstein's extensive meta-analysis demonstrated a weak but statistically significant association between T1D and a shortened period of breast-feeding^[10,94].

Overall, the search for environmental factors contributing to the development of diabetes has been relatively disappointing. With the exception of congenital rubella infection, none have been confirmed. Prospective studies will perhaps bring more light to the problem^[12].

CONCLUSION

Genes play an important role in the development of T1D. The list of known and rarely occurring candidate genes associated with T1D is very long and consistently increasing, pointing to the extreme genetic heterogeneity of the disease. Theoretically, there are as many potential candidate genes as hormones, receptors, enzymes etc. included in the blood glucose regulation and related metabolic processes. To date, more than 250 candidate genes have been investigated, and results have shown a very high variability in gene association with T1D^[31].

Researchers have not yet identified all the gene mutations that put a person at risk for T1D. Even if they did know all of the mutations, researchers find that people with low risk genes (DR2, DR5, long VNTR) can still develop T1D. So a genetic test might identify people as negative who eventually go on to develop diabetes. Even if a genetic test reveals that a person is at high risk, doctors have no course of action for preventing diabetes. Instead, the test may simply add stress to the family.

Genetic studies have revealed not only different candidate genes for the development of T1D in different population, but also gene variability within the same population. Thus, the evidence for the involvement of several genes rather than a single gene in the genesis of T1D appears to dim the prospects for possible use of gene therapy in the near future^[31].

The combination of susceptibility genes and environmental factors may initiate a disease process that is associated with a formation of an autoimmune response to the insulin-producing cells. This autoimmune reaction is reflected by the presence of antibodies against prominent antigens in the pancreatic -cells^[22].

In summary, the identification and description of autoantibodies in T1D has allowed us to gain remarkable insight into the natural history of this disease. In combination with a growing understanding of genetic susceptibility, we are currently able to predict accurately which patient will develop T1D^[11]. As efforts continue to help researchers understand the etioimmunopathogenesis of T1D, many questions still remain as to the role for cellular immunity and issues related to which specific environmental triggers induce or regulate the autoimmunity related to T1D^[10].

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