THE MOLECULAR GENETICS OF TYPE 1 DIABETES

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Abstract

Type 1 diabetes mellitus (T1D) is a T cell-mediated autoimmune disease that cause destruction of pancreatic islet β- cells. Susceptibility to T1D is determined by interaction between several genetic loci and environmental factors. Alleles at the human leukocyte antigen (HLA) locus explain up to 50% of the familial clustering of T1D, but other loci are also contributed to T1D and there is a universal trial to understand their role in this complex disease. In addition, there is a consensus among epidemiologists that the worldwide incidence rate of type 1 diabetes has been rising in recent decades. The cause of this rise is unknown, but epidemiological studies suggest the involvement of environmental factors, and viral infections in particular.

Finding new loci and the pathways in which the destruction of β-cells happen, can lead to possible diagnostic and therapeutic applications of these genetic findings. Also, determining the environmental factors causing T1D is useful, because we can eliminate them and trying to prevent the disease in susceptible individuals by this knowledge.

Keywords: *Diabetes, polygenic disease, Insulin gene, Interleukin*

Introduction

Diabetes is a disease caused by the body's incapacity to either produce insulin (Type 1 Diabetes, T1D) or make use of it properly (Type 2 Diabetes, T2D). Much attention is being given to obesity-related T2D, partly because of the threats posed by the current epidemic of T2D, which may have a serious impact on the provision and costs of health care. T1D may only account for 5–10% of all diabetes cases, but it remains a serious, lifelong disease [1].

T1D is a polygenic multistage T cell-mediated autoimmune disease that causes specific destruction of pancreatic islet β cells_ cells (80–90%) or of their functional impairment_ by means of interactions between genes and environmental factors, resulting in dysfunctional glucose homeostasis and the requirement for exogenous insulin. The rate of β cell destruction varies from patient to patient, but the progression of the autoimmune process is generally slow and may take several years before the onset of the disease. Hence, T1D usually presents during

childhood or adolescence, although it may develop much later in life. The variation in age at onset could be indicative of disease heterogeneity, with different mechanisms leading to β cell destruction in childhood onset versus adult onset diabetes. The disease occurs worldwide, usually develops at a younger age, although it may develop at any age [2,3,4,5,6,7,8]. T1D is affecting approximately 0.4% of European populations and strongly clustered in families [9].

T1D incidence varies widely between countries, within countries and ethnic groups. The reason(s) for the observed variations in T1D incidence is unclear, but differences in diet, lifestyle, and/or genetics may be involved [2,8]. Studies confirm that this increase is occurring worldwide, by an average of 3% per year mainly in very young children. Diabetes was uncommon in the 19th century, and rates were relatively low until the mid-1950s [2].

T1D as a polygenic disease

As a polygenic disease T1D has both environmental and genetic determinants. Epidemiological evidence supports the role of environmental factors in the development of human T1D. Environmental factors include viral infections; dietary factors in early infancy, vaccination, climatic influences, toxins, and stress [8].

The genetic factors of susceptibility to T1D are better understood than the environmental risk factors [8]. T1D has a strong genetic component. First degree relatives have a higher risk for T1D than the general population, and siblings have a higher risk than offspring [7]. The importance of genetic background in diabetes predisposition suggests that potentially lethal allelic variants of certain genes have been retained, either because they have historically conferred a strong selective advantage or because they are in linkage disequilibrium (LD) with advantageous alleles [10].

Data from twin studies demonstrating large differences in the risk for disease development between monozygotic and dizygotic twins. A study reported probandwise concordance rates of 42.9% for monozygotic twins and 7.4% for dizygotic twins, and suggesting that 88% of phenotypic variance in T1D is due to additive genetic effects and 12% is due to environmental factors [2]. Additionally, the best-studied example of incomplete penetrance is T1D and it was performed by twin studies. About 6% of sibs of a patient are concordant for T1D. Because about 16% of MHC-identical sibs of a patient also have T1D, this is strong evidence for a susceptibility gene within the MHC. We can refer to the probandwise concordance rate in monozygotic twins as intrinsic penetrance, whereas we refer to penetrance observed in other relatives of a patient or among unrelated persons as apparent penetrance [11].

Until recently, all the genes that were identified to be associated with T1D susceptibility originated from candidate gene studies. Only few of these associations were confirmed over all studies performed (for example *HLA, INS, PTPN22*), whereas others were only replicated in some studies, or not at all [12].

More direct evidence is seen in the strong association between several genetic variants and T1D. Genetic studies have significantly advanced our knowledge of genetic susceptibility factors for T1D, making it one of the most studied complex genetic diseases to date [1]. Because of environmental factors and the existence of several susceptibility polymorphisms with partial effect, genetic study of polygenic diabetes mellitus, both T1D and T2D, is difficult.

We will review susceptibility genes which play important role in T1D development and its progression.

The Major Histocompatibility Complex

The *HLA* complex (or Major Histocompatibility Complex (*MHC*)) was the first genetic region found to be associated with T1D (the *IDDM1* locus) in 1974 by Nerup *et al.* followed by Cudworth and Woodrow. The *HLA* complex locates on chromosome 6p21 and extends over 4 Mb and contains at least 128 genes, of which the majority is involved in immunity. The *HLA* complex is divided into three main regions: classes I(*A*, *B* and *C*), II(*DP*, *DQ* and *DR*) and III [1,13].

HLA-DR/DQ—The class II loci *HLA-DRB1* and *HLA-DQB1* in the *MHC* are known to be associated with T1D risk based on functional, structural and genetic evidence and are present in 90% of patients who develop T1D. It was proposed that *HLA-DQB1* is the main diabetogenic gene in *HLA*. However, the focus returned to *HLA-DRB1* when allelic forms of *HLA-DRB1* were found to influence the risk of *DQB1* susceptibility alleles. Many studies have investigated the risk of *HLA-DRB1– DQB1* haplotypes in different populations and showed that several haplotypes are associated with a spectrum of different disease risks, ranging from strong susceptibility to almost complete protection [13,1,14].

Risk of diabetes is influenced by both *DRB1**04 variants and *DQ* alleles on *DR4* haplotypes. Thus there is a hierarchy of *DRB1**04 haplotypes, while *DRB1**0403 is protective. Similarly, for *DRB1**0401, variation of *DQB1* influences risk, as haplotypes with *DQB1**0302 are highly susceptible, while those with *DQB1**0301 are modestly protective. The influence of *DRB1**04-DQ haplotypes on diabetes risk is complex and influenced by genotype, as the proportion of *DQB1**0301 is greater in *DR1/4* patients (13.1%) than in *DR3/4* (0.7%) patients and, additionally within these genotypes, there is a different distribution of *DRB1**0401 alleles [14].

However, there are protective *DR-DQ* haplotypes. The most common is the DR2 (*DRB1**1501) bearing haplotype. The *DR2* haplotype is dominantly protective (20% of general population individuals have DQB1*0602 but it is present in only 1% of T1D patients) [14]. It is known that *DR-DQ* does not explain all of the T1D linkage to *HLA* but, because of LD, it has been difficult to determine remained, weaker components [13].

Although these studies support a direct role for the *DR* and *DQ* molecules in disease pathogenesis, they did not explain how the molecules influence disease risk. The prevailing hypothesis is that predisposing alleles bind autoantigenic epitopes less efficiently, and this results in incomplete development of T cell self-tolerance, either in the thymus or in the periphery(loss-of-function scenario) [13].

HLA-DP—*HLA-DPB1* alleles have been reported to be associated with T1D, but are not generally recognized as major contributors to T1D. Several groups have reported a negative association of *DPB1**0402 with T1D. On average, the relative risk for *DPB1**0402 overall from studies is 0.56. *DPB1**0301 and *DPB1**0202 have been reported to be predisposing to T1D [14].

Class I— *HLA* class I genes are primarily involved in the innate immune system. The initial association with T1D was detected with allelic forms of *HLA* class I genes that encode for *HLA*-

B8 and *-B15* molecules. However, it was soon recognized that this association was an indirect signal due to the strong LD in the *HLA* region, and that the strongest association was observed with the *HLA-DR* class II genes [1]. Also, a study of large cohorts by regression analysis has detected smaller effects from the class I *HLA* molecules *A* and *B* [13].

HLA-A is associated with T1D independent of *DR/DQ*. A24 is associated with a younger age of onset, A30 (typically on the *DR3-B18- A30* haplotype) is higher risk, and *A1* (typically on the *DR3-B8-A1* haplotype) is lower risk than other *DR3* haplotypes. *HLA-B* and *HLA-C* alleles are also associated with T1D independent of *DR/DQ*. *HLA-B18, B39, B44, C3, C8* and *C16* are associated with T1D and with age of onset after adjustment for LD with *DR/DQ* [13]

Extended Haplotypes — The *DR3-B8-A1* haplotype is extremely conserved [≥99% identity of single nucleotide polymorphisms (SNPs)]. The *DR3-B8-A1* haplotype is the most common extended haplotype, as it is present in 9% of Caucasian *MHC* control haplotypes and 18% of case *MHC* haplotypes from individuals with T1D [14].

MHCIII — Some of the MHC class III (central region) genes may also be involved in conferring risk to T1D. This region encodes molecules with a variety of functions, and in general, the central region genes are associated secondarily to the disease associated DR and DQ alleles through strong LD [7]. One recent article reports that slightly more than half of Caucasian MHC haplotypes (based on complement alleles, *HLA-B* and *HLA-DR/DQ* typing) are fixed from *HLA-DR/DQ* to *HLA-B*. Extreme variability in the MHC class III region has been identified using SNP typing [14].

The genes of, for example, tumour necrosis factor (*TNF*) and *BAT2* gene lies within the class III region of the *MHC*. The frequency of *BAT2.9* allele has been reported to be significantly increased in T1D particularly patients with younger age of disease onset. On the contrary, the frequency of *BAT2.12* allele has been found to be significantly decreased in these patients as compared with the control subjects. This suggests that the *BAT2* microsatellite polymorphism is associated with age-at-onset of T1D and possibly with the inflammatory process of pancreatic β cell destruction during the development of T1D. However, this association is not independent of *TNFα*, as the *BAT2.9* allele is found to be strongly associated with *TNFα9* in the young-onset T1D patients [7].

MIC-A — A distinct family of MHC genes designated MHC class I chain-related genes (*MIC*) has been identified within the class III region. The MIC family consists of three pseudogenes *MIC-C, MIC-D* and *MIC-E* and two functional genes namely *MIC-A* and *MIC-B*. Sequence analysis of the *MIC-A* gene has revealed a trinucleotide repeat (GCT) microsatellite polymorphism within the transmembrane region. So far, five alleles of exon 5 of the *MIC-A* gene, each consisting of 4, 5, 6 and 9 repetitions of GCT and five repetitions of GCT with an additional nucleotide insertion (GGCT), have been identified. These alleles have been named A4, A5, A6, A9 and A5.1 (7). *MIC-A* is reported to be associated with T1D when the *DR/DQ* genotype is fixed (within *DR3/4* siblings and offspring) [13].

Many studies have shown an association of *MIC-A* alleles with T1D in families from the USA, Korea, Latvia, China and Japan. In these families transmission of *MIC-A* allele 5 and 5.1 from parent to the offspring was found to be significantly more frequent than expected suggesting a

positive association of *MIC-A5* and A5.1 with T1D. Among Asian patients, *MIC*-A6 and A9 were found to be negatively associated with the disease [7].

Insulin gene variable number of tandem repeats

Because of its central role in glucose homeostasis [15], the second (10% percent of the cases[8]) most important genetic susceptibility locus), in Caucasians, was the INS gene. Moreover, the region surrounding INS on chromosome 11p15 has been consistently linked to T1D for more than two decades. Several studies have shown a strong association of the variable number of tandem repeat (VNTR) polymorphism in the insulin gene with T1D [13,7,1,16,14]. This region was mapped to a variable number of tandem repeats (VNTR) situated 596 bp upstream of the insulin gene (INS) on chromosome 11p15.5 and exerts its biological effect by regulating INS gene transcription in *cis* [13]. These polymorphisms regulate the expression of two downstream genes: the insulin and the insulin-like growth factor 2 (IGF2) [7].

Based on the number of tandem repeats of 14-15 bp sequences, these VNTR alleles are grouped into three classes: class I alleles (20-63 repeats), class II alleles (64-139 repeats) and class III alleles (140-210 repeats). The short class I alleles are generally predisposing, especially in homozygous state, they confer more than two fold relative risk for T1D whereas class III alleles are associated with dominant protection[7]. Class III alleles are associated with 20% lower INS mRNA than class I in the pancreas but two- to threefold higher in the thymus[13]. Class I alleles are found in nearly 80% of Caucasian chromosomes, class III alleles occur less common (nearly 20%) whereas class II alleles are most infrequent [7].

Lymphoid tyrosine phosphatase

A third susceptibility gene associated with T1D has been identified and is directly related to T cell activation. This gene, *PTPN22*, maps to chromosome 1p13 and encodes the lymphoid tyrosine phosphatase protein also referred to as 'Lyp' which is recently shown to be consistently associated to several autoimmune diseases, including T1D. It belongs to the family of protein tyrosine phosphatases, which are regulators of the immune response [13,1]. Lyp inhibits T cell receptor (TCR) signal transduction by dephosphorylating three kinases important for TCR signaling. Lyp also downregulates T cell activation by interacting with a suppressor of kinases known as C-terminal Src tyrosine kinase (Csk). The SNP associated with T1D is a change at residue 1858 from C to T, which results in an arginine to tryptophan substitution at position 620 of the Lyp protein (R620W) [13]. This association was later replicated in numerous studies in Caucasian populations. However, the *PTPN22*-R620W association was not replicated with T1D in Asian populations [17].The C1858T variant in the coding region of *PTPN22* was first demonstrated to be associated to T1D in two different populations [1]. Functionally, *PTPN22* is a good candidate gene for T1D susceptibility, because protein tyrosine phosphatases play important roles in TCR signaling. Targeted disruption of Pep (PEST domain-enriched tyrosine phosphatase) results in increased numbers of memory T cells that could accentuate any autoimmune phenomena. One hypothesis was that the 620W allele would result in a loss of TCR inhibition and T cell hyper responsiveness, but recent studies have shown that it has an enhanced inhibitory effect on TCR signaling. A recent study using lymphocytes from subjects homozygous for 620W confirmed that it results in a increased inhibition of TCR signaling by Lyp. The authors of the study conclude that the presence of this variant not only alters the function and character of the T cell compartment but also has a direct impact on β-cell function [13].

T-lymphocyte-associated antigen 4

Candidate gene studies also have identified *CTLA4* (cytotoxic T-lymphocyte-associated antigen 4) along with *CD28* and *ICOS* genes are located on chromosome 2q31-35 in humans. Within this 23 centimorgan (CM) interval, the 2q33 region (referred as IDDM12) is associated with autoimmune diseases. On the basis of a large study, the association of *CTLA4* with T1D was generally confirmed [17]. The *CTLA4* gene is a good candidate for T1D because it is a negative regulator of T-cell activation [13,7]. *CTLA4* is expressed by CD4+ and CD8+ T cells and *CTLA4* down-regulates T-cell proliferation and cytokine production. It is thought that the *CTLA4* function is critical for regulating peripheral selftolerance and prevention of autoimmunity so it been considered as a candidate gene for T1D. The largest genetic study to date maps the effect to the 3´ flanking region to a SNP whose function is still undefined. However, an effect from the 5´end of the gene could not be ruled out. Possible candidates for this 5´ effect include the A49G substitution in exon 1, which results in the substitution of an alanine for a threonine in the signal sequence of *CTLA4*, and the C318T polymorphism in the promoter region. The A49G polymorphism is the only polymorphism that changes the primary amino acid sequence of *CTLA4*[13].

Interleukin-2 receptor α gene

have identified A novel T1D locus have been identified by genetic association studies, mapping to the interleukin (IL)-2-receptor α gene (*IL2RA*) on chromosome 10p15.1. The *IL2RA* gene is composed of eight exons and encodes the α chain of the IL-2 receptor complex (also known as CD25). *IL2RA* is central to immune regulation as an important modulator of immunity. *IL2RA* expression on regulatory T cells is essential for their function in suppressing T cell immune responses and autoimmune disease. These functions made this gene an suitable candidate for T1D, suggesting a potential role of *IL2RA* in the pathogenesis of T1D, probably involving regulatory T cells[13].

There is no amino acid polymorphism at *IL2RA*. By rigorous resequencing and fine mapping, the association recently was mapped to a relatively rare (frequency 0.06) protective allele at the -10 388 C/A polymorphism (dbSNP rs41295061) in the 5´ flanking region. There also is evidence of a second effect at the same locus that might also modulate expression[13].

The mechanism by which the SNPs contribute to diabetes risk is currently unknown, and may be complex given two associated SNPs in the same locus, neither of which alters the coding sequence [14].

Interferon-induced helicase

The interferon-induced helicase (*IFIH1*)(also known as the melanoma differentiation-associated 5 (*MDA5*), or Helicard) encodes an RNA helicase involved in the innate immune response to viral infection and this gene is a likely target of virus-driven selective pressure [18]. Its transcripts have widespread expression in lymphoid and other tissues, suggesting that it could have a role in many autoimmune conditions. This gene is located on chromosome 2q24. The *IFIH1* gene is thought to play a role in protecting the host from viral infection by sensing viral nucleic acid in the cytoplasm and triggering a cellular antiviral and apoptotic response. Many studies reported

associations between viral infection and T1D susceptibility [19,4], which reinforces the *IFIH1* gene as a good functional candidate for T1D. The most associated marker in *IFIH1* was defined as the SNP rs1990760, which encodes an alanine to threonine amino acid change at codon 946. Given the specificity of different helicases for double-stranded RNA viruses, knowledge from this genetic locus is likely to help narrow down the types of pathogens potentially involved in triggering T1D [13].

CYP27B1

CYP27B1 (cytochrome p450, subfamily 27, polypeptide 1) encodes vitamin D1α-hydroxylase and it is responsible for the final step in the production of vitamin D. It is mapped on chromosome 12q13.1-q13.3. It was examined as a candidate gene because of the importance of vitamin D in regulating immune function. Two SNPs in perfect LD (–1260C > A and +2838T > C) were found to be associated with T1D. The gene has no common amino acid polymorphism or splicing variants; therefore, the mechanism probably involves effects on transcription. Epidemiological evidence that vitamin D supplementation might prevent T1D gives this finding a particular significance [13].

CLEC16A

One locus identified by two studies using different technologies on different populations, maps on chromosome 16p13.2 containing a single gene. This gene is *CLEC16A* (C-type lectin domain family 16 gene A, formerly KIAA0350), which is expressed almost exclusively in immune cells and encodes a predicted protein sequence with a C-type lectin domain. Its expression in B lymphocytes and DCs, both specialized APCs, as well as in NKT cells is particularly interesting because C-type lectins are known to play important functional roles in antigen uptake and presentation by both b cells and DCs. In DCs C-type lectins are involved in the internalization of antigen for processing and presentation through recognition of their carbohydrate moieties. More importantly, NKG2A, NKG2C and NKG2D are C-type lectin-like molecules expressed at the surface of NKTs and interact with specific *MHC* class I molecules as part of the recognition of self by these important cells that bridge innate with adaptive immunity . In addition to the lectin domain, *CLEC16A* also has a sequence with similarity to an ITAM (immunoreceptor tyrosine-based activation motif), characteristic of proteins associated with activation, survival and differentiation of haemopoetic-derived cells, which might be another clue as to its function. None of the associated SNPs change amino acids, and preliminary results show no evidence of effect on mRNA levels. Therefore the functional mechanism of this locus remains to be determined. It is also possible that the T1D association is not actually due to *CLEC16A* but to variants affecting two other genes that marginally overlap the associated LD block. These are LOC729954, a theoretically predicted gene that has not been studied, and DEXI (dexmethasone induced), which is upregulated in emphysema [13].

Phosphotyrosine-protein phosphatase, non-receptor 2

Another of the novel loci from the GWA studies also maps to a specific gene on 18q11, PTPN2. (phosphotyrosineprotein phosphatase, non-receptor 2, also known as TC-PTP or PTP-S2)[13]. It is currently unknown whether the SNPs identified in the *PTPN2* gene will lead to a gain or a loss of function of the protein [20]. Given the importance of tyrosine phosphorylation in lymphocyte

activation, elucidation of the role of this little-studied gene in T1D pathogenesis might result in interesting pathophysiological insights and potentially novel therapies by specific inhibitors [13].
It was recently shown that the phosphatase *PTPN2* is expressed in human islets that its expression is regulated by the proinflammatory cytokines IL-1 β, IFN-γ, and TNF-α in these cells. *PTPN2* was first identified in humans as a T-cell PTP with two spliced variants, namely TC45 and TC48[21]. Because of its modulatory role in a wide variety of signaling pathways, perturbations in PTPN2 expression are associated with several autoimmune disorders including T1D [20].

Small ubiquitin-like modifier 4 (SUMO4)

SUMO4 was tested as a positional candidate gene for the *IDDM5* locus on chromosome 6q25. Association of the non-synonymous SNP (M55V) associated with T1D has been published and replicated in Asian populations, but not in most studies performed in Caucasian populations [17]. The polymorphism M55V, causing an amino acid change in the evolutionarily conserved met55 residue has been shown to activate the nuclear factor kappaB (NF-kappaB), hence the suspected role of SUMO4 in the pathogenicity of T1D[8].

Othe novel loci

Genome-wide association studies identified an additional novel locus on 12q24 was also replicated and maps to a LD block that also contains numerous genes. Fine mapping and functional studies will be needed to identify the gene responsible in these two loci [13].
More detailed studies suggest 12q13/*ERBB3* [22], 12q13.1/*VDR*, 2q43/*NFKB* [23,24,25]are good candidate for T1D. Also, an imprinting region on chromosome 14q32.2 be concerned as a susceptibility region [26].

In studies by aim of finding common genes in T1D and other autoimmune diseases, some loci were observed to be important. For example 5p13/*IL7R* and 18q22/*CD226,* have been implicated in T1D and multiple sclerosis [27,28]. It has already been reported that the 12q24/*SH2B3* locus is shared between T1D and celiac disease, and possibly loci 4q27/*IL2-IL21* and 3p21/*CCR3*. In addition, there is some evidence for association of the established T1D loci, 2q33/*CTLA4* and 1p13/ *PTPN22,* in celiac disease [9].

The International Hap Map consortium also aids Genetic studies. The major impetus for this effort is the genome can be parsed into blocks of linkage disequilibrium (averaging 11-22 Kb in size) within which the vast majority of common sequence variants are correlated with each other. Further, the alleles at variants within these blocks fall into a few simple patterns or haplotype. Because there are only a few haplotypes, genotyping a few, well-chosen single nucleotide polymorphism (SNP_s) can accurately indicate which haplotype are present. These SNP_s are called haplotype SNP_s or ht SNP_s. A majority goal of the Hap Map consortium is to identify a set of ht SNP_s that will allow much of the common variation in the genome to be interrogated efficiently for association with disease. Thus, genome-wide association studies will not require typing all 10 million common variants but rather a few hundred thousand $htSNP_s$ that capture most of the common variation for any particular gene[8].

CONCLUSION

T1D(T1D) is a chronic autoimmune disease with a strong inflammatory component. Islet inflammation (insulitis) probably takes place in the context of a 'dialog' between invading immune cells and the target β-cells. This dialog is partially mediated by cytokines and chemokines released by both β-cells and immune cells and by immunogenic signals delivered by dying β-cells. This leads to induction and amplification or, in some cases, resolution of insulitis. The evolution of islet inflammation, and its potential progression to clinical diabetes, probably depends on the interplay between the patient's genetic background and environmental triggers, such as viral infections and/or dietetic components [29].

It has long been known that the likelihood of a person developing T1D is higher the more closely related he or she is to a person with the disease, such that first-degree relatives of cases are at an estimated 15 times greater risk of T1D than a randomly selected member of the general population [30]. Thus, determining the susceptibility loci is an important aim to diagnose of T1D in patient's relatives in early stage of disease progression.
Also, future therapies based on the knowledge of the genetics and molecular mechanisms of genetic susceptibility of T1D. This knowledge opens the possibility for the search of new therapies [9].

Identification of genetic-based pathways for complex diseases, such as T1D, provides the initial framework for investigations of environmental influences on a given genetic background (26).
Another aim is to determine the interaction between genes and environmental factors, for example understanding the role of vitamin D in prevention of T1D and finding the molecules involved in the pathway and important in T1D can lead to prevention of the disease, simply by using vitamin D supplementation or drugs that interfere in an specific pathway. And the role of viruses in T1D is important because by prevention of viral disease in people with susceptible genes for progression of the disease even by using antybody against the viral particles, we can prevent T1D.

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