

Brief Communication

Understanding type 1 diabetes through genetics: Advances and prospects

Nikhil Tandon

Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

The largest contribution of type 1 diabetes mellitus (T1DM) from a single locus comes from several genes located in the major histocompatibility complex on chromosome 6p21. Because DQB1 is the best single genetic marker for T1DM, it is the gene most often used to identify individuals with a high risk of developing disease. As per the data collected from the All India Institute of Medical Sciences, among the human leukocyte antigen (HLA)-DRB1 genes, HLA-DR3 showed strongest association with the disease; however, unlike Caucasians and other populations, DR4 was not significantly increased in these patients. HLA-DR10, 11, 13, and 15 showed a negative association with the disease as they were reduced in these patients. In India, the relative risk of developing T1DM is higher with the DR3-DQ2 haplotypes as compared to DR4-DQ8 haplotypes. Studies have shown that in North India, the relative risk for T1DM is comparatively higher (>30) with the DQ2/DQ8 genotype, but is relatively lower (approximately 18) for the DQ2/DQ2 genotype. In addition, the three sets of HLA-B-DR3 haplotypes, mainly B58-DR3, B50-DR3, and B8-DR3 have shown to have modulated susceptibility for T1DM in India and worldwide. New interventions that will be tested in the future will be conducted through T1DM TrialNet, a collaborative network of clinical centers and experts in diabetes and immunology. These studies will identify unaffected first-degree relatives with beta cell autoantibodies who will be eligible for new interventions.

Key words: Genes, genetics, type 1 diabetes mellitus

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is considered as the second most common chronic childhood disease. The only disease with a higher prevalence in children is asthma. It has a significant impact on daily existence in mobility and on mortality. The peak age at onset of T1DM is around the time of puberty, and generally occurs earlier in girls than in boys. Although T1DM is generally diagnosed in children and young adults, it can occur at any age.

The incidence of T1DM is increasing around the world at a rate of about 3%/year, reasons for which are currently

unknown. Countries with the highest incidence include Finland, Sardinia, and the Scandinavian countries. Those with the lowest incidence are found in Asia. In addition, Native - Americans and some population in Latin America have an extremely low incidence of the disease. The dramatic difference in T1DM incidence worldwide is, in all likelihood, related to variations in the prevalence of genetic and environmental risk factors for the disease.

ENVIRONMENT AND TYPE 1 DIABETES

There are several epidemiologic patterns that suggest that environmental factors are important in the etiology of T1DM. For example, the diagnosis of T1DM is more common during the winter compared to summer. This parallels the seasonal patterns observed for infectious diseases, which have been suggested as risk factors. In addition, when children from countries with a low rate of incidence of T1DM migrate to countries with a high rate of incidence of T1DM, their risk also increases and becomes similar to that of the host country. This difference

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Corresponding Author: Dr. Nikhil Tandon, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, Ansari Nagar East, Gautam Nagar, New Delhi - 110 029, India. E-mail: nikhil_tandon@hotmail.com

is much less dramatic for individuals who migrate during their adult years, indicating that the childhood exposures are probably most diabetogenic.

Studies that have compared children with T1DM to unrelated nondiabetic children (i.e., case-control studies) have shown that several environmental risk factors are important in the etiology of T1DM. These include infant/childhood diet. For example, breastfeeding appears to be protective, and early exposure to cow's milk increases T1DM risk. A number of viral infections have also been associated with T1DM. These include those that occur in utero during pregnancy, as well as those that typically occur during childhood (e.g. *Enteroviruses*). Because the peak onset of T1DM is at puberty, it is thought that changing levels of hormones may also precipitate the disease. Finally, stress has been suggested as a risk factor for T1DM.

The role of improved hygiene in the etiology of T1DM is also currently being explored. It has been hypothesized that delayed exposure to microorganisms, due to improvements in standard of living, hinders the development of the immune system, such that it is more likely to respond inappropriately when introduced to such agents at older (compared to younger) ages.

This explanation is consistent with recent reports indicating that factors such as day care attendance, sharing a bedroom with a sibling and contact with pets are protective against T1DM. Further studies are needed to determine if improved hygiene can explain the temporal increases in the incidence of T1DM worldwide.

There is also evidence that T1DM is, in part, a genetic disorder. Identical twins (i.e., monozygous twins) are more likely to have T1DM than nonidentical twins (i.e., dizygous twins). But concordance rates in identical twins are <50%, supporting the hypothesis that environmental factors are also important in the development of T1DM.

GENETICS AND TYPE 1 DIABETES

Siblings of an individual with T1DM are about 15 times more likely to develop T1DM than individuals in the general population. This translates to a cumulative risk of approximately 6% till 30–35 years; however, the risk also increases in the presence of susceptibility genes.

In the era before the Genome-Wide Association Studies (GWAS) came up (1976–2006), genes namely human leukocyte antigen (HLA), insulin (INS), cytotoxic T-lymphocyte antigen-4 (CTLA-4), protein

tyrosine phosphatase, nonreceptor type 22 (PTPN22), interleukin (IL) 2 receptor, alpha and interferon-induced helicase were considered as T1DM associated genes. Post-GWAS studies, there are additional genes which have been identified; amongst them the key ones belong mainly to the IL and protein tyrosine phosphatase families.

THE DQ GENE

The largest contribution of T1DM from a single locus comes from several genes located in the major histocompatibility complex (MHC) on chromosome 6p21. Because DQB1 is the best single genetic marker for T1DM, it is the gene most often used to identify individuals with a high risk of developing disease. However, risk estimates based on DQB1 alone are less precise than those based on the combination of alleles at both the DQA1 and DQB1 loci. These combinations are called haplotypes, and reflect the specific alleles on each of the two chromosomes. Thus, DQB1 and DQA1 typing provide more accurate risk estimates than those based on DQB1 alone.

The two DQA1-DQB1 haplotypes that are most strongly associated with T1DM are DQA1*0501-DQB1*0201 and DQA1*0301-DQB1*0302. That is, chromosomes with DQB1*0201 and DQA1*0501 confer a higher risk for T1DM than chromosomes with DQB1*0201 but some other DQA1 allele (not *0501). Similarly, chromosomes with DQB1*0302 and DQA1*0301 confer a higher risk for T1DM than chromosomes with DQB1*0302 and another DQA1 allele (not *0301).

Studies have shown that Caucasians with two high-risk haplotypes (DQA1-DQB1) have a 16-fold higher T1DM risk than an individual who has no high-risk haplotypes; whereas the risk is only about 4 times higher in those with one high-risk haplotype. This also means that Caucasians with two high-risk haplotypes are 4 times more likely to develop T1DM than those with one high-risk haplotype. Similarly, African Americans with two high-risk haplotypes (DQA1-DQB1) have a 45-fold higher T1DM risk than their normal counterparts; whereas, Asians with two high-risk haplotypes (DQA1-DQB1) have 11-fold higher T1DM risk than their normal counterparts.

A similar study illustrated the absolute risk (or actual likelihood) of developing T1DM depending on the number of high-risk haplotypes an individual carries. It was found that Caucasians and African Americans with two high-risk haplotypes have about a 3% chance of developing the disease before 30 years of age. The risk for Asians with two high-risk haplotype is much lower (<1%).

RISK STRATIFICATION

However, in families where there is already one person with T1DM, the risk to unaffected relatives is much higher than that for the general population. For example, in Caucasian families, siblings of an individual with T1DM are about 15 times more likely to develop the disease than a person from the general population (i.e. without a family history of the disease).

Furthermore, it has been observed that the T1DM risk for a sibling who has the same two HLA haplotypes as their T1DM sibling is quite high (about 25%). If they share one or zero HLA haplotypes with their affected sibling, their risk is much lower, about 8% and 1%, respectively. The fact that the risk for individuals who have no shared HLA haplotype is still increased compared to that for the general population suggests that genes other than those in the HLA region must also increase susceptibility for the disease.

Type 1 diabetes mellitus risk can be stratified into different categories (low risk, intermediate risk and high risk) according to the number of affected first-degree relatives (FDRs) and HLA genotype. In individuals with no affected FDRs, the T1DM risk is 0.4%, whereas in those individuals with no affected FDRs but having HLA protective genes, the risk falls even further to 0.01%. In individuals with one affected FDR, the T1DM risk is 0.3%, despite having HLA protective genes. Under intermediate risk category, the T1DM risk is relatively high that is, 5% in individuals with one affected FDR and HLA risk genes, whereas under high-risk category, the T1DM is around 10–20% in individuals with one affected FDR and HLA high-risk genes and rises to 20–25% in individuals with multiple affected FDRs.

INDIAN DATA

As per the data collected from the All India Institute of Medical Sciences, among the HLA-DRB1 genes, HLA-DR3 showed strongest association with the disease; however unlike Caucasians and other populations, DR4 was not significantly increased in these patients. HLA-DR10, 11, 13, and 15 showed a negative association with the disease.

In India, the relative risk of developing T1DM is higher with the DR3-DQ2 haplotypes as compared to DR4-DQ8 haplotypes. Studies have shown that in North India, the relative risk for T1DM is comparatively higher (>30) with the DQ2/DQ8 genotype, but is relatively lower (approximately 18) for the DQ2/DQ2 genotype. In addition, the three sets of HLA-B-DR3 haplotypes, mainly

B58-DR3, B50-DR3, and B8-DR3 have shown to have modulated susceptibility for T1DM in India and worldwide.

A survey done on the worldwide incidence (per 100,000/year) of T1DM and the main disease-susceptibility HLA alleles/haplotypes revealed that there are three sets of disease conferring B-DR haplotypes in the Indian population: B8-DR3 similar to that observed in Caucasians, B58-DR3 as occurs in the Chinese and B50-DR3 which occurs exclusively among Indians as a “unique haplotype.” It was also found that B18-DR3 also acts as the susceptibility haplotype, in addition to B8-DR3 and B-DR4, among Spanish population.

In recent years, a number of studies have screened the entire human genome in families with more than one T1DM individual to identify regions, other than the HLA region, that also contain T1DM susceptibility genes. Although it is thought that many genes contribute to T1DM susceptibility, it is now known that these genes all have a smaller influence on T1DM compared to those in the HLA region. As a result, the HLA region has been designated as IDDM1.

OTHER GENES

The next strongest locus involved in genetic susceptibility to T1DM is IDDM2 on the short arm of chromosome 11. This locus encodes the INS gene. Additional information about the INS gene (and other genes) can be found by searching the Online Mendelian Inheritance in Man (OMIM) database on the National Center for Biotechnology Information website (www.ncbi.nlm.nih.gov). The OMIM number for the INS gene is 176730. The 5' regulatory region of INS contains a variable number of tandem repeat (VNTR) locus that has been associated with T1DM. There are three classes of VNTR alleles: Class I (26–63 repeats), class II (~80 repeats), and class III (141–209 repeats). A person who carries two class I alleles has about a two-fold increased risk of developing T1DM as compared to those who carry no class I VNTRs. Class III alleles seem to provide dominant protection against developing T1DM. Class II alleles are virtually nonexistent in Caucasian populations and have no effect on T1DM risk.

Various polymorphisms in CTLA-4 gene in the 5'UTR, 3'UTR regulatory regions of chromosome and exon 1 have been studied extensively in T1DM. CTLA-4 is a strong candidate gene for autoimmune diseases because it encodes a T-cell receptor that plays a role in controlling T-cell apoptosis (programmed cell death) and is a negative regulator of T-cell activation.

The CTLA-4 gene region on chromosome 2q33 has also been associated with T1DM. The locus that includes the CTLA-4 gene has been termed IDDM12. The OMIM number for the CTLA-4 gene is 123890.^[1]

Specifically, an A49G polymorphism within the first exon of the CTLA-4 gene was found to be associated with development T1DM, especially in homozygous condition. This polymorphism appears to increase T1DM risk in multiple population, including Italian, Spanish, French, Mexican-American, and Korean population.

Protein tyrosine phosphatase, nonreceptor type 22 (lymphoid), also known as PTPN22, is a protein that in humans is encoded by the PTPN22 gene. It is a lymphoid specific tyrosine phosphatase (LYP) and is present at the chromosome 1p13. The OMIM number for this is 600716. It encodes an LPY that is important in negative T-cell activation and development, and increases the relative risk of T1DM by nearly 80% due to C858T polymorphism (Arg620Trp). PTPN22 may also alter binding of LYP to cytoplasmic tyrosine kinase, which regulates the T-cell receptor signaling kinases.

In addition to HLA class I and class II alleles, the single nucleotide polymorphisms and microsatellites in the central MHC region have also been studied. These include factor B, tumor necrosis factor (TNF), lymphotoxin-alpha, Hsp70, and copy numbers of C4A and C4B genes. Allele A at -308 position of TNF α gene, which is a high producer allele has shown a positive association with the disease, however -238A was negatively associated. A total of 13 alleles have been encountered for TNF α microsatellite in this study. Of these TNF α 2, α 5 and α 13 were shown to be raised in T1DM patients. Fragment analysis of the MICA microsatellite has revealed the presence of 5 alleles in the North Indian population. MIC-A5.1 has been shown to be associated with T1DM.^[2] This is quite in contrast to Caucasians who show the association with A5 and A5.1.

In a similar study, the effect of MICA5.1 on disease development was studied. The patients were analyzed in a way to find the individual effect of DR3 and MICA5.1 on T1DM. It was found that DR3 positive MICA5.1 positive and DR3+MICA5.1 negative individuals have similar relative risk suggesting that MICA5.1 has no independent association with T1DM.^[3]

POTENTIAL FOR CURE: ONGOING STUDIES

Although a cure for T1DM is currently unavailable, several large international investigations have been designed to evaluate a number of primary and secondary disease

interventions. Two are targeted toward unaffected FDRs in families with an individual with T1DM. One is targeted to the general population of Finland. To determine if individuals are eligible, genetic testing for DQB1 is performed.

For the trial to reduce Type 1 Diabetes in Genetically At-risk (TRIGR) and the Diabetes Prediction and Prevention Project (DIPP), genetic testing is performed as part of newborn screening. Infants who carry high-risk DQB1 alleles are eligible to participate.

For TRIGR, newborns are randomized to receive either a regular cow's milk formula or one with hydrolyzed proteins, which is thought to be protective. This study is being conducted in Europe and North America. For DIPP, newborns with high-risk DQB1 alleles from the general Finnish population are followed up until they develop beta cell antibodies. When this occurs, they are randomized to an intervention based on nasal INS.

New interventions that will be tested in the future will be conducted through T1DM TrialNet, a collaborative network of clinical centers and experts in diabetes and immunology. These studies will identify unaffected FDRs with beta cell autoantibodies who will be eligible for new interventions. Those who carry the protective DQB1*0602 gene, however, are generally excluded.

In addition to the intervention trials, there are also three natural history studies for T1DM that are ongoing in the US. These include Diabetes Autoimmunity in the Young in Colorado, Prospective Assessment in Newborn of Diabetes Autoimmunity in Florida, and the Diabetes Evaluation in Washington-IT. All are based on newborn genetic screening in the general population, and, therefore, concerns have been raised about proper informed consent. Similar concerns have been raised for the DIPP study in Finland, which is also screening the general population.

SUMMARY

Type 1 diabetes mellitus cannot be prevented or managed. There are ethical concerns regarding genetic testing for T1DM, especially in children. Educational programs are however needed for parents who consent to have their children involved in such studies because risk estimation is dependent on genes/autoantibodies used for assessment.

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