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Genetics of type 1 diabetes

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Abstract

Type 1 diabetes (T1D) results from immune-mediated loss of pancreatic beta cells leading to insulin deficiency. It is the most common form of diabetes in children, and its incidence is on the rise. This article reviews the current knowledge on the genetics of T1D. In particular, we discuss the influence of HLA and non-HLA genes on T1D risk and disease progression through the preclinical stages of the disease, and the development of genetic scores that can be applied to disease prediction. Racial/ethnic differences, challenges and future directions in the genetics of T1D are also discussed.

Keywords

Type 1 diabetes; genetics; HLA; etiology; epidemiology

Introduction

Type 1 diabetes (T1D) is the most common form of diabetes in children, as it accounts for approximately 80% of pediatric diabetes cases in the United States.(1) The incidence of T1D is on the rise in the United States and worldwide. (2-4) The SEARCH for Diabetes in Youth study, a population-based study designed to evaluate diabetes in youth in the United States, estimated 21.7 new cases of T1D per year per 100,000 population between 2002 and 2012, (2) and a prevalence of 1.93 cases for every 1,000 children.(5) T1D is most common among non-Hispanic whites (NHW), especially among those of Northern European descent, but it is diagnosed in all races and ethnicities. In fact, a recent report indicated that the rise in T1D incidence in the United States is most pronounced among Hispanics.(2) In contrast, T2D is more common among Hispanic, African-American, American Pacific Islander or American Indian populations than in NHW individuals.(1) There is much variation in T1D incidence in different parts of the world; for example, the incidence of T1D (per 10⁵ children per year) ranges from 0.1 in China and Venezuela to 36.8 in Sardinia and 36.5 in Finland.(6, 7) T1D is

also diagnosed in adult age, with approximately 30% of patients developing symptoms after 18 years of age. Although T1D represents 10% of adult diabetes cases overall, the absolute number of individuals diagnosed with T1D is likely higher among adults than children given the high incidence of diabetes in adults.(8, 9)

The hallmark of T1D is beta-cell loss that leads to insulin deficiency.(10) About 90% of patients develop T1D as the result of the autoimmune destruction of beta-cells (type 1A), as marked by the presence of circulating autoantibodies to islet cell autoantigens. Autoantibody-negative patients are classified as having “idiopathic T1D”, or type 1B, which may include patients with autoimmune diabetes lacking measurable autoantibody responses to common autoantigens (11) as well as patients with rare forms of monogenic diabetes (12, 13), in addition to autoantibody false negatives. Autoantibody-negative T1D may be more common in some non-White racial groups.(14)

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Evidence for the contribution of genetics to type 1 diabetes

The overall risk of T1D in the general population is 0.4%, but it is higher in relatives of patients. For example, siblings of patients have on average a 6-7% lifetime risk; the risk of T1D is 1.3-4% in children of a female patient and 6-9% in children of a male patient.(15, 16) While the risk of T1D in non-identical twins is similar to that of siblings, it exceeds 70% in identical twins with long-term follow-up.(17-19) Additional evidence for the contribution of genetic factors to the etiology of T1D is the occurrence of autoimmune diabetes in association with genetic mutations affecting key genes with immune function.(20) For example, the autoimmune polyglandular syndrome type 1 (APS1) is caused by mutations in the autoimmune regulator (*AIRE*) gene, which is critical for the establishment of immunological self-tolerance.(21, 22) Patients with APS1 have T1D, hypoparathyroidism, Addison's disease, mucocutaneous candidiasis, hepatitis, hypothyroidism, oophoritis and lymphocytic hypophysitis. Mutations in the *FoxP3* gene cause an X-linked syndrome that associates immune dysregulation, polyendocrinopathy and enteropathy (IPEX syndrome). *Foxp3* is a transcription factor that is essential for the development and function of regulatory T cells, which play a critical role in maintaining self-tolerance.(23, 24) Mutations in the *STAT3* gene were associated with the *STAT3* polyautoimmunopathy, a syndrome that includes permanent autoimmune neonatal diabetes, thyroid disease, celiac disease and intrauterine growth retardation.(25) An aberrant, activating mutation in *STAT3* has recently been reported to lead to inhibition of the transcription factor *Isl-1* and in turn decreased insulin expression and synthesis. (26) Although autoimmune diabetes occurring in these settings is generally thought to be different from the more frequent polygenic type, these syndromes highlight how selected genes can critically impact the development of autoimmunity.

Two major approaches have been used to study the genetics of T1D, namely candidate gene association studies and genome-wide linkage analysis studies (GWAS) (reviewed in (27)). Both approaches, although not devoid of challenges (reviewed in (28)), have resulted in an abundance of knowledge about genes and loci that confer risk and protection for T1D.

HLA region

The HLA region on chromosome 6p21 accounts for approximately 50% of the familial aggregation of T1D and its association with T1D has been known for over 40 years.(29)

The strongest association is with HLA DR and DQ. HLA DR and DQ are cell surface receptors that present antigens to T-lymphocytes. Both DR and DQ are alpha-beta heterodimers. The DR alpha chain is encoded by the DRA locus, and the DR beta chain is encoded by DRB loci. Similarly, DQA1 and DQB1 loci encode the alpha and beta chains, respectively, of the DQ molecule. The DR and DQ loci are highly linked to each other and, to a lesser degree, to other HLA loci.

The highest risk haplotypes are those with HLA Class II DR4-DQA1*03:01-DQB1*03:02 (also termed “DR4-DQ8” haplotype), especially the haplotypes carrying the DRB1 alleles *04:05, *04:01 and *04:02.(30) For example, DRB1*04:05 has an OR of 11 and DRB1*04:01 an OR of 8. The second high-risk haplotype is DRB1*03:01-DQA1*05:01-DQB1*02:01 (“DR3-DRQ2” haplotype), which is highly conserved (i.e. in strong linkage disequilibrium) and has an OR of 3.6. It was recently shown that DR3 homozygotes carriers of the HLA-DRB3*02:02 allele were at significantly higher risk of developing T1D than the individuals who were homozygous for the HLA-DRB3*01:01.(31) Up to 90% of people with T1D carry DR4-DQ8 or DR3-DQ2 and about 30% of patients carry both compared to 2% of the general population. The combination of those two haplotypes into the DR4-DQ8/DR3-DQ2 genotype confers the highest risk of T1D, with an average OR of 16.(32-35). Siblings with the high-risk DR3/DR4-DQ8 genotype who shared both haplotypes with their probands have about 85% risk of T1D by the age of 15 years. (36) The larger than additive effect of the HLA DR4 and HLA DR3 haplotypes may result from the formation of HLA-DQ αβ trans-heterodimers from HLA-DQA1*05:01 and HLA-DQB1*03:02 protein chains encoded on different chromosomes. The association between HLA molecules and T1D is thought to result from genetic polymorphisms that encode for different amino acid residues in the peptide-binding pockets of HLA molecules; in turn, this impacts the binding affinity and repertoire of peptides that can be presented to T-cells.(37, 38) Particular amino acid residues at HLA-DQB1 position 57 and HLA-DRB1 position 13 appear important in that they impact antigen-binding properties of that particular combination. There are also protective alleles, such as DQB1*06:02, which is in linkage disequilibrium with DRB1*15:01 (DR2) and DQA1*01:02(39) and others such as DRB1*14:01.(40) Among NHW, DQB1*06:02 is present in about 20% of the general population but only in 1% of children with T1D.(41-43)

Besides DRB1 and DQ alleles, additional genetic factors may contribute to T1D risk. For example, DRB3, DRB4, and DRB5 alleles modify the risk conferred by DRB1 (44). Although the strength of the association is lower than with HLA DR and DQ, HLA-DPB1 and DPA1 are also associated to T1D.(45) However, Class II genes do not completely explain the association between HLA and T1D; HLA Class I genes (A, B and C) also impact T1D risk (31, 46) as well as age of onset, in interaction with Class II genes (DR and DQ). (47) In particular, the alleles with the strongest association with T1D were the protective B*57:01 (OR=0.19) and B*39:06, which confers risk (OR=10.31). (48) HLA class I/peptide antigen complexes play a role in the development of the T-cell repertoire in the thymus and

in antigen-specific T-cell-mediated cytotoxicity.(48) Overall, HLA-DQB1 position 57, HLA-DRB1 position 13 and HLA-DRB1 position 71 explain over 90% of the phenotypic variance from the HLA DRB1-DQA1-DQB1 locus, HLA DPB1 contributes to about 1.5% of the variance explained, HLA-A to 1.5% and HLA-B to 1%.(37)

A reduction in the frequency of high risk HLA types among individuals diagnosed with T1D has been noted over time,(49, 50) in particular among the youngest children.(51) This finding may suggest a shift in the relative contribution of genetics and environmental factors in the etiology of T1D. For example, elevated BMI accelerates progression to T1D (52) and the current elevated prevalence of obesity may be a factor in a growing subset of new cases of T1D.

Non-HLA genes

After the HLA region, the insulin gene (*INS*) has the strongest association with T1D. *INS*, on chromosome 11p15, tagged by -23HphI (rs689) and +1140A/C (rs3842753) SNPs, harbors three major insulin variable number tandem repeats (VNTR) according to the number of repeats. The highest risk is conferred by homozygosity for class I (shortest repeats). These insulin polymorphisms regulate the amount of insulin mRNA in the thymus and are likely to influence the development of immune tolerance to insulin.(53, 54)

Besides the genes identified using candidate gene approaches, GWAS have provided a wealth of knowledge on the genetic basis of T1D, and over 50 loci have been associated with this disease(55) (reviewed in (56)), explaining about 80% of its heritability (57). National and international research networks and studies have contributed to these investigations, which often require large sample sizes, e.g. the Type 1 Diabetes Genetic Consortium (T1DGC), (58) Diabetes and Autoimmunity Study in the Young (DAISY), (59) Diabetes Prevention Trial-1 (DPT-1),(60) TrialNet, (61, 62), BABYDIAB, (63) FinnDiane, (50) Action LADA,(64), Eurodiab,(65) The Environmental Determinants of Diabetes in the Young (TEDDY),(66) Human Biological Data Interchange type 1 diabetes repository (40), Danish study group of Diabetes in Childhood,(67) among others.

The protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) (rs2476601 SNP), on chromosome 1p13, which encodes lymphoid specific phosphatase (LYP), a suppressor of T cell activation, is also associated with T1D.(68) A gain of function LYP variant is associated with suppression of TCR signaling (69, 70) and reportedly promotes the survival of autoreactive T-lymphocytes in the thymus. The *PTPN22* locus has also been associated with effects on the function of effector T-lymphocytes, regulatory T-lymphocytes and B-lymphocytes in the periphery (71, 72). Other genes that modify T1D risk include the cytotoxic T-lymphocyte associated protein (*CTLA-4*) (rs3087243),(73) which is a negative regulator of cytotoxic T cells. It has been recently reported that altered post-transcriptional regulation could mediate the association between *CTLA-4* polymorphisms and T1D.(74) In fact, Abatacept (CTLA4-Ig), which selectively binds to CD80/86, blocks the interaction with CD28 and modulates co-stimulation, and has been shown to transiently halt beta-cell loss in individuals recently diagnosed with T1D.(75) Other loci associated with T1D are the interleukin-2 receptor subunit alpha (*IL2RA*, *CD25*);(76) protein tyrosine phosphatase, non-receptor type 2 (*PTPN2*);(77) interferon-induced helicase (*IFIH1*);(78) the basic leucine

zipper transcription factor 2 (*BACH2*); (79) and ubiquitin-associated and SH3 domain-containing protein A (*UBASH3A*). (80, 81) *IL2RA* variants causing abnormalities in sensitivity to IL2, which is critical to T-regulatory cell function, may alter the balance between T-regulatory cells and T-effector cells and thus increase risk of T1D. (82) *PTPN2* may induce beta-cell apoptosis after interaction with increased local levels of interferon. (83) *IFIH1* encodes melanoma differentiation-associated protein 5 (MDA5), which binds to double stranded RNA viruses and thus mediates the innate immune system's interferon response to certain viruses (reviewed in (84)). *BACH2* regulates proinflammatory cytokine-induced apoptotic pathways in pancreatic beta-cells by crosstalk with *PTPN2*. (85) *UBASH3A* down regulates the NF- κ B signaling pathway upon T-cell receptor stimulation, thus reducing *IL2* gene expression. (86) There is a large overlap among genes associated with autoimmune diseases that explains the frequent co-occurrence of autoimmune disease in individuals and families. For example, the frequency of variants of the *PTPN22* gene is increased in T1D, rheumatoid arthritis, inflammatory bowel disease and juvenile idiopathic arthritis. (87) Of interest, Gli-similar 3 protein (*GLIS3*) gene region has been linked to neonatal diabetes, T1D and type 2 diabetes. (55) This protein has been implicated in the generation of beta cells, *INS* expression and beta-cell apoptosis. (88) Therefore, while many of the genes harbored in loci that have been associated with T1D are related to the immune function, evidence is accumulating that several genes are expressed in beta-cells and may affect beta-cell survival and function, especially in relation to inflammation, environmental stimuli and innate immune responses (reviewed in (56)). It is also possible that genes not directly involved in the immune function contribute to diabetogenesis in a subset of individuals with islet autoimmunity. Genetic variants in the transcription factor 7 like-2 (*TCF7L2*) locus are the strongest genetic factor in T2D. (89) Although this locus is not associated with T1D overall, individuals with T1D with milder autoimmunity, as suggested by the expression of single islet autoantibody and/or absence of high risk HLA types, are more likely to carry the T2D-associated *TCF7L2* genetic variant compared to patients with T1D with stronger autoimmunity. (90, 91)

Genetic scores

One of the current challenges is how to integrate the wealth of knowledge about T1D genetics and apply it meaningfully for diagnosis and risk assessment. For the last 15 years, investigators have proposed various models with various combinations of loci. The DAISY study follows high-risk siblings and the offspring of individuals with T1D, as well as newborns from the general population with high-risk HLA genes (59, 92). In this study, the addition of *PTPN22* and *UBASH3A* SNPs to HLA-DR, DQ genotyping improved T1D risk prediction. In survival analysis, 45% of general population DAISY children with *PTPN22* rs2476601 TT or HLA-DR3/4 and *UBASH3A* rs11203203 AA genotypes developed diabetes by age 15, compared to 3% of children with all other genotypes. (93) The addition of non-HLA markers to HLA-DR3/4, DQ8 did not improve diabetes prediction in DAISY first-degree relatives.

The BABYDIAB study follows children of parents with T1D from birth. In this study, a genetic score developed with 8 non-HLA SNPs (*IFIH1*, *CTLA4*, *PTPN22*, *IL18RAP*, *SH2B3*, *KIAA0350*, *COBL* and *ERBB3*) was predictive of T1D in children with high-risk

HLA genotypes.(94) BABYDIAB investigators developed a second score that used odds ratios to weigh SNPs, and included HLA in addition to nine SNPs in the *PTPN22*, *INS*, *IL2RA*, *ERBB3*, *ORMDL3*, *BACH2*, *IL27*, *GLIS3* and *RNLS* genes. (95) This 10-factor score has recently been tested for prediction of T1D in two DAISY cohorts, namely, first-degree relatives, where it was demonstrated superior to combinations with fewer SNPs, and the general population, where it was not superior to the 3-factor model (96).

Most recently, the Exeter group developed a T1D Genetic Score to identify individuals who became insulin dependent among young adults with diabetes (97) and discriminate T1D from monogenic diabetes. (98) This score was developed studying participants in the Wellcome Trust Case Control Consortium (n=3,887), in which it was highly discriminative of T2D (AUC 0.88). This score was validated in the South West England Cohort, where it predicted insulin deficiency in a group of 20-40 y/o young adults with diabetes (n=223, excluded monogenic and secondary diabetes) (AUC 0.87). The score was developed by taking the first 30 T1D-associated SNPs, ranked and weighed by OR.(97) Using just the first 9 SNPs (i.e. DR3/DR4-DQ8, DR3/DR3, DR4-DQ8/DR4-DQ8, DR4-DQ8/X, DR3/X, HLA-24, HLA-B-57:01, HLADRB1-15, *PTPN22*, *INS*, *IL2RA*, *ERBB3*) returned similar predictive ability. The same T1D genetic risk score, in another study, could discriminate T1D from monogenic diabetes.(97-99) The T1D-GRS was also highly discriminative of monogenic diabetes (MODY or monogenic neonatal diabetes) and T1D.(98).

Genetics and the stages of type 1 diabetes

The onset of T1D symptoms is the clinical manifestation of the disease process that results from the interaction of predisposing genetic factors with environmental exposures, which eventually leads to a T-cell mediated, B-cell facilitated, autoimmune attack on beta-cells. (100, 101) The presence of islet cell autoantibodies is presently the earliest and more robust biomarker of islet autoimmunity.(102) Autoantibody responses to at least two islet antigens define the first stage of T1D (Stage 1); at this point remissions are rare. Stage 2 T1D is defined as the presence of two or more islet autoantibodies and dysglycemia, that is, glucose metabolism abnormalities that do yet not meet diabetes criteria. Stage 3 develops when the established glycemic thresholds for diabetes diagnosed are exceeded.(103) Although remissions after Stage 1 are rare, the risk and rate of progression vary based upon genetics, age at seroconversion, autoantibody titers and body mass index (BMI).(33, 52, 104, 105)

As data on the preclinical stages of T1D accumulates, it has become clear that the influence of genetic factors in T1D varies by disease stage. Prospective studies such as DAISY and TEDDY follow children at increased risk for diabetes since birth and therefore assess the impact of genetic factors during disease progression. In multivariate analyses adjusting for family history and HLA-DR3/4 genotype in DAISY (93, 106), *PTPN22* (rs2476601) and two *UBASH3A* (rs11203203 and rs9976767) SNPs were associated with development of islet autoimmunity, while *INS*, *UBASH3A* and *IFIH1* were significantly associated with progression from islet autoimmunity to diabetes. In TEDDY participants carrying high-risk HLA genotypes, four SNPs achieved significant association to development of islet autoimmunity using time-to-event analysis: rs2476601 in *PTPN22*, rs2292239 in *ERBB3*, rs3184504 in *SH2B3*, and rs1004446 in *INS*.(107) The

Finnish Pediatric Diabetes Register, using transmission analysis, found that the DR3-DQ2/DR4/DQ8 genotype influenced the development of islet autoantibodies, but not subsequent progression to symptomatic (Stage 3) T1D.(35)

The role of race and ethnicity

Most of the current knowledge of T1D genetics originates from studies conducted in NHW populations, in which the highest disease prevalence is observed.(5) However, T1D is still the most frequent type of pediatric diabetes in all other racial and ethnic groups in the United States,(1) with growing importance as the United States demographics shift. As noted earlier, recent data revealed that the rise in T1D is disproportionately affecting Hispanics in the United States.(2) Furthermore, T1D occurs in many non-Caucasian populations in the world.(7) Most studies find racial/ethnic differences in the genetic, immunologic, metabolic and clinical characteristics of T1D (108-114), some of which may impact disparities in management and clinical outcomes (115). The frequency of HLA haplotypes and genotypes classically associated with T1D varies among populations. Importantly, their susceptibility or protective effects on T1D risk vary as well.(116) For example, multiple although not all (109) reports have demonstrated a reduced frequency of DR3 (117-119) but increased frequency of protective allele (DRB1*14:02) in Hispanics compared to NHWs.(119) The SEARCH Study revealed higher frequency of the susceptibility DRB1*04:01 – DQB1*03:02 haplotype in NHWs than Hispanic youth with T1D while DRB1*04:05 – DQB1*03:02 and DRB1*04:07 – DQB1*03:02 were more frequent in Hispanics than NHWs.(111) Interestingly, the DAISY study observed higher frequencies of high-risk or moderate-risk genotypes in Hispanics than NHW among 5,000 newborns from general population in the Denver area.(59) The DR3 and DR7 haplotypes found in African-Americans have only a small difference with the version most common in NHWs, and yet their effects on risk are opposite. For example, the NHW DR7 is DRB1*07:01-DQA1*02:01-DQB1*02:02 and is protective for T1D, while among African-Americans DR7 is most often found as DRB1*07:01-DQA1*03:01-DQB1*02:02 and confers susceptibility. The African DR3 haplotype, DRB1*03:02-DQA1*04:01-DQB1*04:02, is protective while the DRB1*03:01-DQA1*05:01-DQB1*02:01 haplotype, most often found in other races, confers risk (reviewed in (116)). As strategies for T1D diagnosis and prediction rely more heavily on genetics, it will be important to consider racial and ethnic differences in the genetics of T1D.

Conclusions and future directions

Decades of research show that genetics play a key role in the etiology and pathogenesis of T1D. An extensive body of knowledge has accumulated on the genetic factors that influence the development of the disease. However, the genetics of T1D are complex and polygenic, and modulated by imprinting (e.g. *INS* (120)), alternative splicing of islet autoantigen mRNAs (e.g. IA-2)(121), gene-gene interaction, and gene-environment interaction, for example, through epigenetic modifications (87, 122), or mediated by retrovirus(123, 124)). Besides genetic factors that are directly involved in controlling immune response and beta cell function, there is mounting evidence that other pathogenic mechanisms may be involved. For example, as it becomes evident that elevated BMI contributes to the

progression to T1D,(52) the genetics of obesity is emerging as additional factor. Similarly, genes that regulate pathogenic mechanisms of T2D may play a role in subsets of individuals with T1D.(90, 91) Additional complexity lies in racial/ethnic differences, with most of the current knowledge stemming from studies in Caucasian populations, despite the evidence that T1D occurs in all racial/ethnic group and, in the United States, is growing most rapidly among Hispanics.(2)

A critical application of genetics is to improve prediction so that strategies can be designed and implemented to prevent disease in individuals at risk (reviewed in (104, 125)). Furthermore, genetics could play a unique role as time-independent tools for the diagnosis of diabetes in the large and growing number of cases with unclear diagnosis (126, 127), and the prognosis of clinical outcomes in individuals with T1D. Converting our advances in T1D genetics into tools that are applicable to clinical needs is one of the great current challenges that should drive the field. (99)

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Abbreviations

AIRE	Autoimmune regulator
APS1	autoimmune polyglandular syndrome type 1 (APS1)
BACH2	Basic leucine zipper transcription factor 2
BMI	Body mass index
CTLA-4	cytotoxic T-lymphocyte associated protein
DAISY	Diabetes and Autoimmunity in the Young
DPT-1	Diabetes Prevention Trial-1
ERBB3	Erb-b2 receptor tyrosine kinase 3
GLIS	Gli-similar
GWAS	Genome-wide linkage analysis studies
IFH1	Interferon-induced helicase
IL2RA	Interleukin-2 receptor subunit alpha
INS	Insulin (gene)
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)
LYP	Lymphoid specific phosphatase
NHW	non-Hispanic white
PTPN2	Protein tyrosine phosphatase, non-receptor type 2
PTPN22	Protein tyrosine phosphatase, non-receptor type 22
TCF7L2	Transcription factor 7 like-2
TEDDY	The Environmental Determinants of Diabetes in the Young
T1D	Type 1 diabetes
T1DGC	Type 1 Diabetes Genetic Consortium
T2D	Type 2 diabetes
UBASH3A	Ubiquitin-associated and SH3 domain-containing protein A
VNTR	insulin variable number tandem repeats