**PATHOGENESIS OF TYPE 1 DIABETES**

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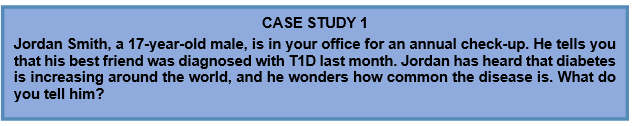
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**ABSTRACT**

Type 1A diabetes (T1D) represents an autoimmune disorder that can affect individuals from within a year of birth until age 60. A number of genes strongly influence the development of disease, including genes found within the human lymphocyte antigen (HLA) complex. The role of non-HLA genes is being defined in recent studies, and we are beginning to identify pathways that lead to autoimmunity and eventually pancreatic islet cell destruction. Although genes can predispose one to type 1A diabetes, environmental factors may also play a significant role in the pathogenesis. These as-yet-undefined factors appear to have accelerated the onset and markedly increased the frequency of disease in many populations around the world over the last 30 years. The development of ever more sophisticated immunoassays to detect antibodies directed against pancreatic antigens have helped define the autoimmune nature of the disorder, but as importantly have also provided an opportunity to identify those individuals with prediabetes and to stratify their risk of developing overt hyperglycemia. Immunologic assays as well as intervention trials are allowing us to learn more about the immune pathways that are disordered and offer hope for future therapeutic approaches to prevent and reverse type 1A diabetes.

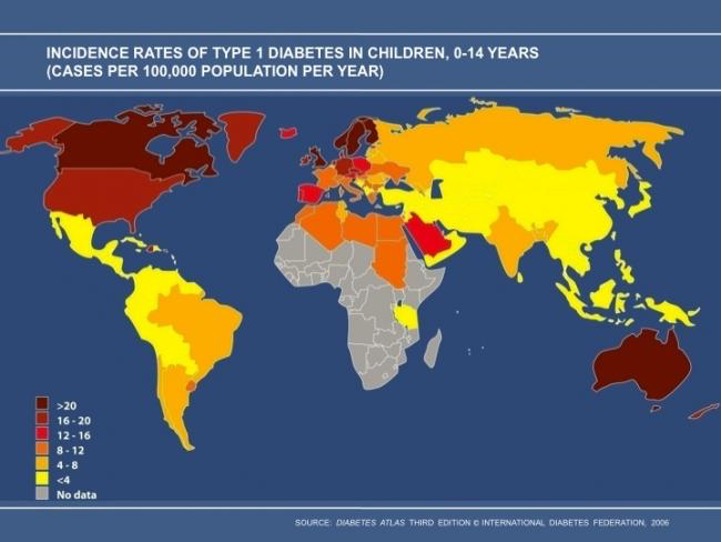
**INTRODUCTION**

In the U.S. alone, more than one million people are living with type 1 diabetes (TID) and approximately 80 people per day, or 30,000 individuals per year, are newly diagnosed (1, 2). Recent epidemiological studies demonstrate that the global T1D incidence is increasing at a rate of approximately 3-4% per year, notably among younger children (3, 4). Despite improvements in insulins, insulin delivery methods, and home glucose monitoring, the vast majority of those with T1D do not achieve recommended levels of glycemic control.  This is particularly true in childhood and adolescence, where a recent U.S. study reported mean HbA1c values exceeding 9.5%, and a high frequency of both DKA and severe hypoglycemia (5). In addition to the increased risk of morbidity and mortality, TID places significant emotional and financial burdens on individuals, families, and society. These realities highlight the need for both better TID therapies and the continued push towards the prevention of TID. In recent decades, research efforts have described the natural history of type 1 diabetes and expanded the ability to identify individuals at risk for the disease even before clinical onset, via the recognition of genetic markers or TID-specific autoantibodies. The increasing ability to identify the at-risk population affords researchers the opportunity to intervene at progressively earlier stages in the disease.  With the understanding that established islet autoimmunity, confirmed by the presence of multiple T1D autoantibodies, inevitably leads to clinical TID, investigative efforts are shifting towards the prevention or modification of autoimmunity.  Furthermore, with the mounting evidence that any amount of residual C-peptide improves long term clinical outcomes in TID, some therapies aim to preserve remaining beta cell function in those with clinical disease. In this chapter, we review the epidemiology of TID and the genetic and environmental risk factors for T1D.

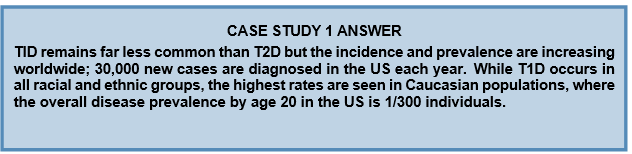


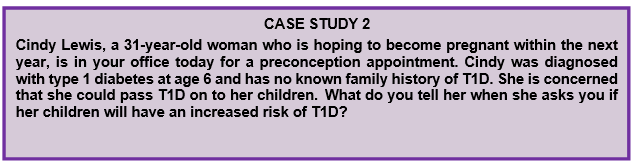
**EPIDEMIOLOGY OF DIABETES**

T1D, or autoimmune diabetes, represents 5-10% of diabetes, and like autoimmunity in general, TID is increasing worldwide. The increase likely is attributable to environmental factors or epigenetic changes, as genetic changes don’t occur rapidly enough to explain such a dramatic increase. The SEARCH for Diabetes in Youth Study is a multicenter observational study investigating trends in incidence and prevalence of diabetes in American youth < age 20.  SEARCH data suggests that the prevalence of TID among non-Hispanic white youth is ~1/300 in the US by age 20 years (6). Between 2002 and 2009, the incidence of TID among non-Hispanic white youth < age 20 years increased by an average of 2.7% per year (7). Similarly, the EURODIAB study evaluated TID incidence trends in 17 European countries from 1989-2003 in youth < age 15 years, and found an average annual incidence increase of 3.9%. This trend predicts a 70% increase in TID prevalence between 2005-2020 among European youth < 15 years old (8) with the peak of diagnosis between ages 10-14 (9). While incidence and prevalence are well documented in children, TID occurs in adults as well, at a frequency that is less certain; estimates are that 25-50% of all TID cases are diagnosed in adulthood. The uncertainty likely is due to a less dramatic clinical presentation than is typically seen in children who present with TID. The incidence of TID varies tremendously by geographic location, with higher rates generally seen in countries located farther from the equator. Worldwide incidence data was reported in 2000 by the DIAMOND project (10), a WHO-sponsored effort to address the public health implications of TID. The incidence of TID between 1990 and 1994 in 50 countries is shown in Figure 1. Between 1990 and 1994, the incidence of TID in individuals aged 0-14 years in both Finland and Sardinia was 37/100,000 individuals, whereas the incidence in both China and Venezuela was 0.1/100,000 individuals, a 350-fold difference. The increased incidence coupled with reduced early mortality has contributed to the increasing prevalence of disease.



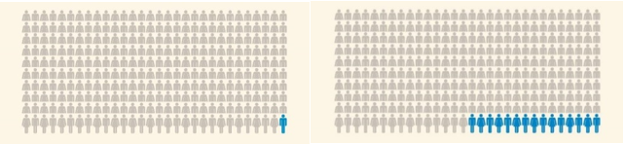
**Figure 1. Worldwide incidence of TID 1990-1994, used with permission from International Diabetes Federation.**





**WHAT IS THE RISK OF TYPE 1 DIABETES?**

As is true for Cindy, 85% of individuals who develop TID have no family history of TID; nonetheless, a family history of the disease does increase an individual’s relative risk.  The prevalence of TID in the US non-Hispanic white population by age 20 is ~0.3%, as compared with ~5% of those with a relative with TID, a 15-fold increase in relative risk.   This relative risk is depicted in Figure 2.

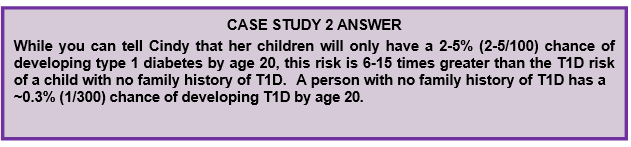


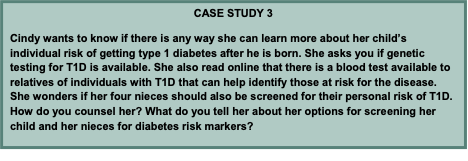
**Figure 2. Among 300 people without a family member with diabetes, 1 will have TID. Among 300 people with a family member with diabetes, 15 will have TID.**

The risk of TID among family members varies depending on who the affected family member is, as shown in Table 1.

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| **Table 1. Prevalence of TID in Individuals with a Family History of TID** | | |
| **Relative with TID** | **Prevalence at age 20** | **Reference** |
| Mother | 2% | (11, 12) |
| Father | 6% | (11, 12) |
| Non-twin sibling | 6% | (13) |
| Dizygotic (fraternal) twin | 10% | (13, 14) |
| Monozygotic (identical) twin | >50% | (15) |

The heritability pattern suggests that both genes and environment contribute to risk.  Curiously, the risk of TID in offspring is higher if the father has TID (~6%) as compared to if the mother has TID (~2%) (11, 12). Moreover, the risk to a dizygotic twin is slightly higher (~10%) than is the risk to a non-twin sibling with similar HLA risk genes (~6%) (13, 14) suggesting that the intrauterine environment and/or similar early life exposures may be important. Lastly, the risk to a monozygotic twin is upwards of ~50%; surprisingly the second twin’s diagnosis may occur many decades after the index twin, highlighting the complexities of gene and environmental interactions that underlie the disease (15).

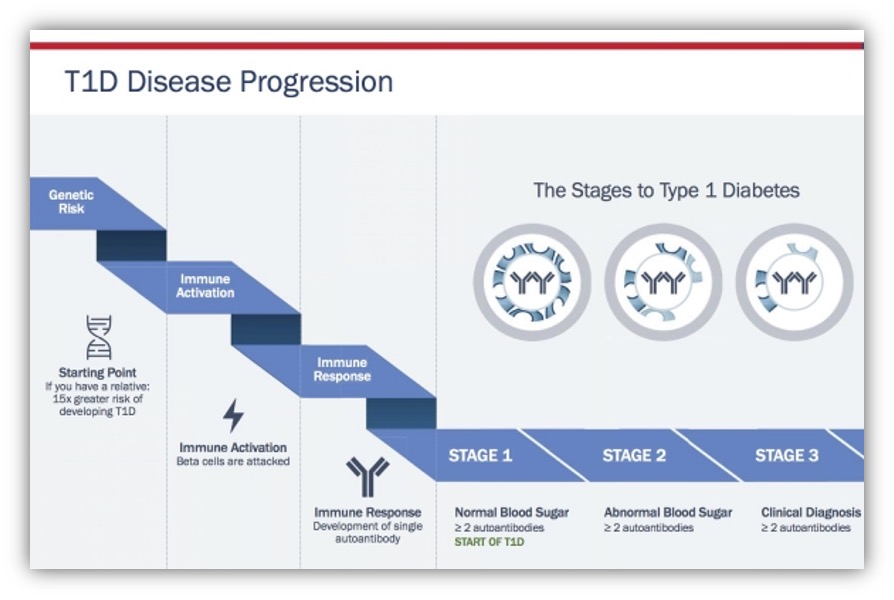




**THE NATURAL HISTORY TYPE 1 DIABETES**

It is now understood that TID is an immune-mediated disease that begins in the setting of genetic predisposition and then progresses along a predictable path: early islet autoimmunity (one autoantibody), established islet autoimmunity (two or more autoantibodies), abnormal glucose tolerance, clinical TID with some remaining beta cell function, and finally, little or no remaining beta cell function. This understanding comes from decades of effort by multiple investigators and from participation by thousands of patients with TID and their family members.  George Eisenbarth’s description of TID as a chronic autoimmune disease, manifested by autoimmunity and a gradual linear fall in beta cell function until there is insufficient beta cell mass to suppress symptomatic hyperglycemia, has served for decades as the TID natural history paradigm (16). The “Eisenbarth” model has undergone refinements in recent years; namely, although autoimmunity and beta cell dysfunction do appear prior to diagnosis, these changes are often step-wise and non-linear.  Furthermore, beta cell destruction may not be absolute.  Nonetheless, the paradigm is largely correct and serves as the underlying rationale for TID trials.

The long pre-symptomatic natural history of TID presents an opportunity to intervene earlier than is done currently. Diabetes-specific autoantibodies can appear many years before clinical diagnosis and may reliably be used to predict disease progression. In 2015, JDRF, the Endocrine Society, and the American Diabetes Association proposed a new TID staging system which underscores that TID begins with islet autoimmunity rather than with symptomatic hyperglycemia (17). Stage 1 TID is defined as the presence of 2 or more autoantibodies with normoglycemia; stage 2 TID is 2 or more autoantibodies, impaired glucose tolerance, and no symptoms; stage 3 TID is clinical disease. The staging system is depicted in figure 3.



**Figure 3. New staging classification of Type 1 diabetes. Stages of Type 1 Diabetes. Adapted from internet image. https://beyondtype1.org/clinical-trials-and-the-type-1-diabetes-cure/final-trialnet-stages-of-diabetes-graph-2/ Used with permission.**

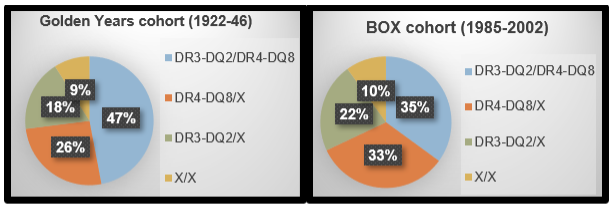
**HOW TO DETERMINE RISK OF TID**

Risk of TID may be determined by the identification of autoantibodies, usually in those identified as having genetic risk through HLA testing or by family history. Autoantibodies are detectable years before the onset of clinical TID.

**Determining Risk: Genes**

With the knowledge that TID runs in families and with advances in technology, investigators have described the genetic risk of TID.  TID risk is strongly linked to HLA class II DR3 and DR4 haplotypes, with the highest risk in those with the DR3/DR4 genotype.  The importance of HLA genes to TID risk highlights the role of the adaptive immune system in the development of autoimmunity.  Newer studies have discovered multiple other genes that also contribute to TID risk (18). They are largely genes known also to impact immune function; however, their contribution is dwarfed by the impact of HLA genes. Interestingly, recent work suggests that HLA genes primarily contribute to development of autoantibodies, while non-HLA genes and environmental factors may be more important in the progression from autoantibodies to clinically overt disease (19, 20). The description of non-HLA risk genes (such as the genes for insulin, a major TID autoantigen) highlights other potential pathways to disease and potential therapies.

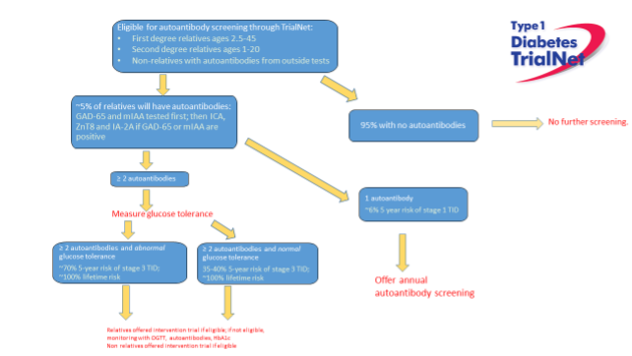
Although the contribution of HLA class II risk genes overwhelms the contribution of non-HLA risk genes, the HLA contribution may be decreasing as the overall incidence of TID increases.  This suggests that in a population with non-HLA genetic susceptibility, the environment may have become more conducive to the development of TID. This was reported in a 2004 Lancet article by Gillespie, et al., in which the investigators compared the frequency of HLA class II haplotypes in a UK cohort of 194 individuals diagnosed with TID between 1922-1946 (the Golden Years cohort) to a cohort of 582 individuals diagnosed between 1985-2002 (the BOX cohort) (21). In this comparison, shown in Figure 4, 47% of individuals in the Golden Years cohort were positive for the highest risk genotype DR3-DQ2/DR4-DQ8, compared to 35% of individuals in the BOX cohort.



**Figure 4. Decreased contribution of high-risk HLA haplotypes over time. HLA class II haplotypes in Golden Years and BOX cohorts, adapted from Gillespie et.al Lancet 2004 (21).**

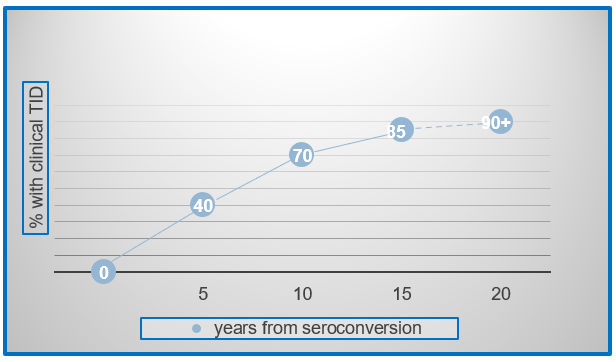
**Determining Risk: Family History And Islet Cell Autoantibodies**

Natural history studies of relatives such as Diabetes Prevention Trial (DPT-1) and Diabetes TrialNet Pathway to Prevention have helped define the risk of TID in those with a family history of TID.  Since 2000, Diabetes TrialNet has screened over 200,000 relatives of people with TID, aiming to enroll at-risk individuals in prevention trials.  Among relatives of people with TID, ~5% will have at least one of five islet autoantibodies (22). TrialNet screens for islet cell antibodies (ICA), autoantibodies to insulin (IAA or mIAA), antibodies to a tyrosine phosphatase (IA-2; previously ICA512), antibodies to glutamic acid decarboxylase (GAD), and antibodies to a zinc transporter (ZnT8).  With each additional autoantibody, the risk of TID increases predictably. Unsurprisingly, those with islet autoimmunity and abnormal glucose tolerance are at an even further increased risk of symptomatic T1D. The TrialNet strategy to identify islet autoimmunity among relatives of individuals with TID is shown in Figure 5. There are many other screening efforts ongoing outside of TrialNet. (23-25)



**Figure 5. Diabetes TrialNet process for identifying relatives with islet autoimmunity.**

Natural history studies have shown not only that islet autoimmunity predicts TID risk, but also that islet autoantibodies usually appear early in life; 64% of babies destined to develop T1D before puberty will have antibodies by age 2 and 95% by age 5 (26). Furthermore, the data from both prospective birth cohort studies (27) and cross-sectional studies (28-31) is remarkably consistent and suggests that the risk of progression from established autoimmunity to clinical TID is in the range of 40% after 5 years, 70% after 10 years, and 85% after 15 years. This risk over time is depicted in Figure 6. The key understanding from natural history studies is that essentially all individuals with confirmed islet autoimmunity will eventually develop clinical T1D at a rate of 11% per year.



**Figure 6. Established islet autoimmunity inevitably progresses to clinical T1D. Extrapolated data from multiple studies in genetically at-risk individuals; Ziegler et al. JAMA 2013; DPT-1 Study Group Diabetes 1997; Sosenko et al. Diabetes Care 2014; Mahon et al. Pediatric Diabetes 2009.**

Identifying individuals with islet autoimmunity has two potential benefits; namely, the opportunity to monitor closely for disease progression, conferring a reduced risk of morbidity and mortality at the time of TID diagnosis, and the identification of individuals who are eligible for prevention trials.  It is perhaps underappreciated that there is potentially a direct clinical benefit to identifying those with islet autoimmunity.  Individuals with islet autoimmunity followed regularly until clinical diagnosis present with lower HbA1c and experience less DKA than those diagnosed in the community (Table 2) (32-36). For this reason, since 2009, the ADA has recommended that all individuals with a relative with T1D be counseled about the opportunity to be screened for diabetes autoantibodies in the context of a clinical research trial (37).

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| **Table 2.**  **Individuals Diagnosed with T1D While Enrolled in a Clinical Trial have Less Morbidity at the Time of Diagnosis. (32-36)** | | | | |
| **STUDY** | **HbA1c at time of TID diagnosis** | | **% with DKA at time of TID diagnosis** | |
|  | **Enrolled in study** | **Usual care** | **Enrolled in study** | **Usual care** |
| SEARCH |  |  |  | 25.5% |
| BABYDIAB | 8.6% | 11.0% | 3.3% | 29.1% |
| DPT-1 | 6.4% |  | 3.7% |  |
| DAISY | 7.2% | 10.9% | < 4% |  |
| TEDDY < age 5 |  |  | 13.1% |  |
| SEARCH < age 5 |  |  |  | 36.4% |
| BABYDIAB < age 5 |  |  |  | 32.3% |

**STRATEGIES TO BRING SCREENING FOR RISK TO CLINICAL PRACTICE**

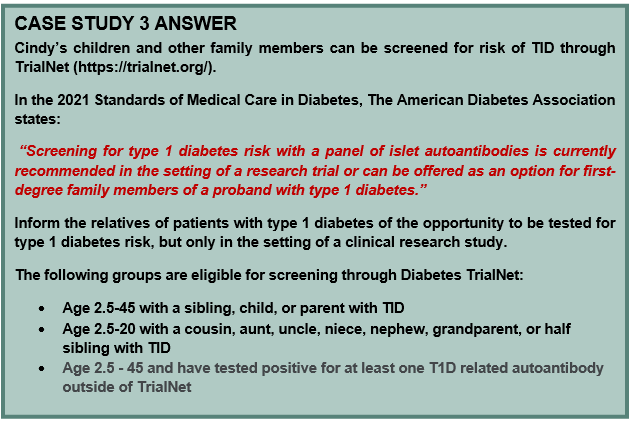
Screening relatives does identify a population of those at risk for clinical T1D; however, at least 85% who get T1D have no relatives with disease.  Thus, to truly prevent all T1D, testing of the general population would have to occur. This could be done with current technology by testing all babies for genetic (HLA) risk at birth and then following with antibody testing. The Population Level Estimate of type 1 Diabetes risk Genes in children (PLEDGE) study enrolls newborns from the general population and offers one-time genetic testing and follow-up autoantibody testing at 2 and 4 years of age (38). The study aims to demonstrate feasibility and to develop evidence to support eventual inclusion of a T1D screening program in standard primary care.

Other studies, such as The Environmental Determinants of Diabetes in the Young (TEDDY) study, the Diabetes Autoimmunity Study in the Young (DAISY), and the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) are exploring similar methodologies to screen and monitor for risk (24, 39, 40).  However, with an increasing number of individuals developing T1D even without the high-risk HLA types, such approaches may still miss some destined to develop disease.

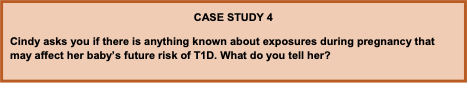
An alternative risk detection strategy for those without a family history may be to perform point-of-care antibody testing in a routine pediatric visit.  Since almost all who will develop diabetes before puberty will have antibodies by age 5; such testing could be done at age 4-5 and perhaps once again in the teenage years.  This method will still miss those who develop T1D before this age, but would likely be a cost-effective approach to finding those at risk.  If these at-risk subjects are monitored regularly until development of clinical disease they would benefit from reduced morbidity at time of diagnosis even if a prevention therapy were not yet available.

There are many ongoing projects aimed at screening members of the general population for diabetes autoantibodies even without prior HLA testing (23, 25, 41, 42).

As risk-screening programs employ varying assays and recruit from different populations, interpretation and translation of results is unclear. It is not yet known whether those found to be autoantibody positive through one program will experience the same rates of T1D progression and/or benefit from the same therapies as individuals who have participated in other screening and intervention efforts.



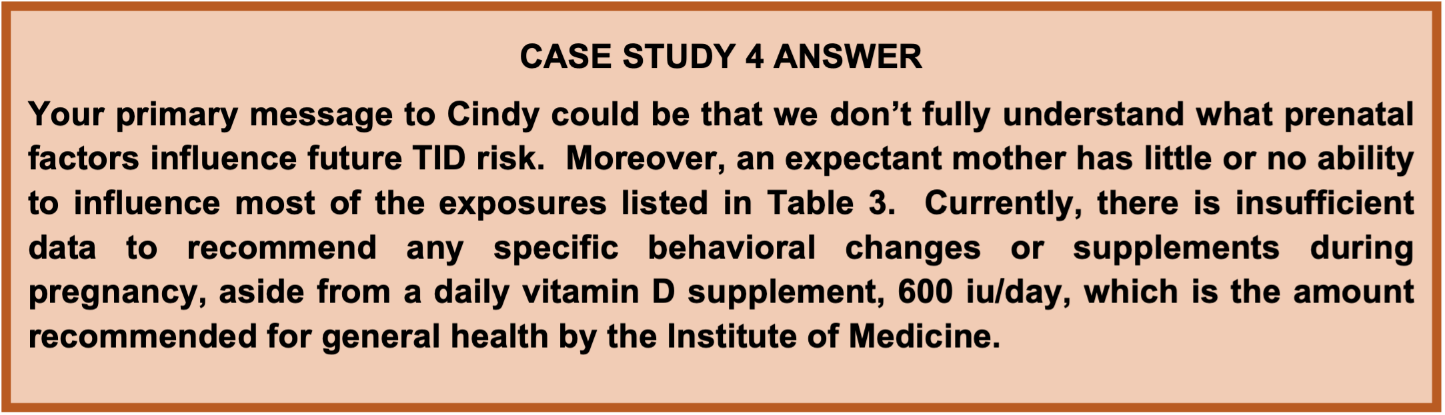
**Source: (37).**



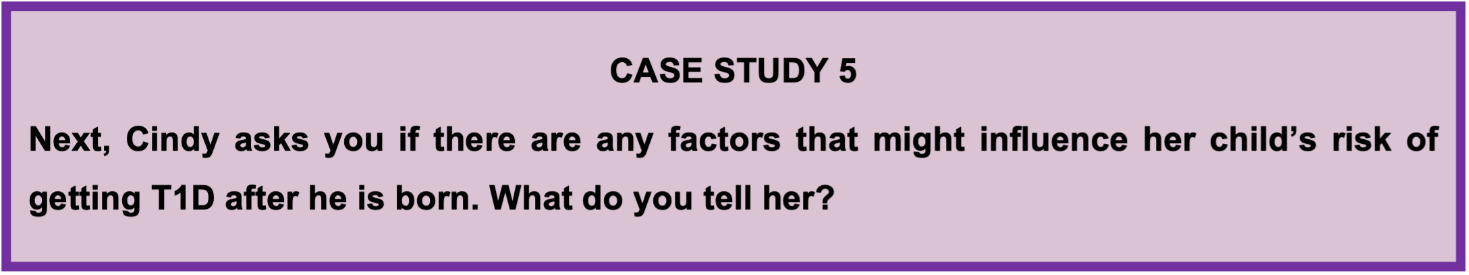
**PRENATAL INFLUENCES**

The prenatal environment can have profound effects on the developing fetus. With the recognition that antibodies often develop early in life and that essentially all those with established islet autoimmunity (two or more autoantibodies) will eventually develop TID, investigators have looked to the prenatal period to search for factors that could contribute to disease development in utero.  As shown in Table 3, decades of observational studies have yielded inconsistent results.  Yet this remains an important area of investigation and one that may lead to primary prevention strategies for T1D. The Environmental Determinants of Islet Autoimmunity (ENDIA) study is an ongoing prospective birth cohort study in Australia that enrolled infants and unborn infants of first degree relatives with T1D. Biologic samples including blood, stool, and saliva will be collected longitudinally for investigation of factors including viral exposures during pregnancy and early childhood, maternal and fetal microbiome, delivery method, maternal and early infant nutrition, pregnancy and early childhood body weight, and both innate and adaptive immune function. In 2018, the ENDIA study completed target enrollment of ~1500 subjects, who will be followed regularly until the development of islet autoimmunity (43).

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| **Table 3.  Potential Prenatal Influences on TID Ris**k | | |
| **Pre-natal or intrauterine exposure** | **Relative risk to offspring** | **Reference** |
| Maternal age | Inconsistent data | (44-46) |
| Birth weight > 2 SD above norm (~4000g) | Inconsistent data | (47-51) |
| Birth weight < 2 SD below norm (~2500g) | Inconsistent data | (49-51) |
| Birth order: second and later born | Inconsistent data | (46, 52, 53) |
| Birth interval < 3 years | Inconsistent data | (46, 54) |
| Caesarean delivery | Inconsistent data | (51, 55, 56) |
| Pre-eclampsia | Inconsistent data | (51, 57) |
| Pre-term delivery (<37 weeks gestation) | Inconsistent data | (51, 58) |
| Maternal vitamin D supplementation | Inconsistent data | (59-62) |
| Maternal antibiotic use | No association | (53, 63) |
| maternal BMI/pregnancy weight gain | No association | (51, 64) |
| Maternal omega 3 fatty acid supplementation | No association | (60, 65, 66) |



**Source: (67).**



Investigators also have studied the early childhood period for clues to the causes of islet autoimmunity and TID; these have included both observational studies and randomized clinical trials. Such influences might be divided into early nutritional exposures and early microbial/infectious exposures, both of which can affect development of the normal immune system.

The inconsistent findings relating to environmental factors reported from observational studies and clinical trials led to the design and implementation of a large international comprehensive evaluation of genetically at-risk babies using cutting edge technologies to study genetics, genomics (gene function), metabolomics, and the microbiome. The Environmental Determinants of Diabetes in the Young (TEDDY) is an international prospective birth cohort study that recruited almost 8,000 babies at increased risk for TID (based on HLA and family history) from Finland, Germany, Sweden, and the US from 2004-2010.  Information on environmental exposures such as diet (including breastfeeding history), infections, vaccinations, and psychosocial stressors will be collected. Participants will be followed until the age of 15 for the development of islet autoimmunity or TID. The wealth of data from this study will provide a foundation for future randomized clinical trials (24). One interesting finding reported in December 2019 is that there are subtle differences in the gut microbiome—such as, persistent stool enterovirus B species--in children who develop islet autoimmunity compared to children who do not develop autoimmunity (68).

**EARLY NUTRITIONAL EXPOSURES**

**Breastfeeding**

The hypothesis that human breastmilk may protect against future TID development was presented as early as 1984 (69). Since then, there have been several prospective cohort studies to suggest that breastmilk lowers the risk of islet autoimmunity and TID, including the German BABYDIAB/BABYDIET study (70), the Colorado-based DAISY study (71), and the Norwegian MIDIA study (72), but others show no effect (73).  Although the data on whether breastmilk is protective against TID isn’t clear, it certainly isn’t harmful.  Given the well-established general benefits of breastfeeding, patients may safely be advised to follow the American Academy of Pediatrics’ guidelines related to infant feeding. The mechanism by which breastmilk may lower the risk of TID is uncertain, but one theory suggests that breastmilk has positive effects on the infant microbiome. The microbiome is discussed in greater detail below.

**Cow’s Milk And Bovine Insulin Exposure**

In contrast to considering breastfeeding as potentially beneficial in protecting against autoimmunity, it was hypothesized that early introduction of cow’s milk or cow protein might accelerate disease.  This concept was tested in the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) which asked whether weaning to hydrolyzed casein (which is free of bovine proteins including insulin) formula (n=1081) instead of regular cow’s milk formula (n=1078) in genetically at-risk infants could prevent or delay TID.  Though the TRIGR pilot study was suggestive of benefit, no benefit was seen in the fully powered study (74) (75). Similarly, The Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes of (FINDIA) suggested that weaning to hydrolyzed cow’s milk formula was not effective in reducing the appearance of autoantibodies, though they did report that a patented cow’s milk formula specifically removing bovine insulin appeared to be beneficial in this pilot study (76).  While additional studies may be informative, current data does not support that weaning to hydrolyzed cow’s milk formula is protective against islet autoimmunity.

**Gluten Exposure**

Both BABYDIAB (77) and DAISY (78) were observational studies that suggested an association between introduction of gluten and islet autoimmunity.  However, these studies had different results as to the timing of gluten introduction. Similarly, no effect was found in the BABYDIET study; a randomized controlled trial that asked whether delayed introduction of gluten to 6 vs 12 months would affect the risk of diabetes autoimmunity (79, 80).

**Vitamin D And/Or Omega 3 Fatty Acids**

Vitamin D is an important component of a normal immune response; moreover, the higher incidence of TID in northern climates suggests that vitamin D deficiency could contribute to autoimmunity and TID.  However, data from observational studies is mixed on whether vitamin D and/or omega 3 supplementation is beneficial or not (60, 81-86). A pilot randomized trial of omega 3 supplementation to pregnant mothers and infants failed to demonstrate a profound immunologic effect of treatment (87). With routine vitamin D supplementation recommended for infants (88), it is unlikely that a fully powered randomized trial would be feasible to assess the impact on autoimmunity.

**MICROBIAL EXPOSURES**

**The Hygiene Hypothesis**

Parallel to the rising incidence of TID and other autoimmune diseases, there has been a worldwide trend towards urbanization, increased standard of living, smaller family sizes, less crowded living conditions, safer water and food supplies, less cohabitation with animals, wide use of antibiotics, childhood vaccination, etc.  While these trends are generally considered improvements in human existence, the so-called “hygiene hypothesis,” proposed by Strachan in 1989 (89) suggests a possible downside; that is, that early microbial exposures might have a protective effect via the early education of the immune system and the development of normal tolerance to self-antigens. Data cited in support of the hygiene hypothesis comes from comparisons between eastern Finland and Russian Karelia (Figure 7) (90-92).



**Figure 7. Border between Finland and Russian Karelia, with a 6-fold difference in the incidence of TID, from "Karelia today”. The countries share a common border and ancestry and thus have similar geography, climate, vitamin D levels, and prevalence of HLA risk haplotypes. However, Finland has 6-fold higher incidence of TID. This markedly higher rate of TID is accompanied by a much lower rate of infectious disease. In Finland as compared to Karelia 2% vs 24% had hepatitis A; 5% vs 24% had toxoplasma gondii; and 5% vs. 73% for helicobacter pylori. There is an ongoing study aiming to better understand the mechanisms that may underlie these differences.**

**The Microbiome**

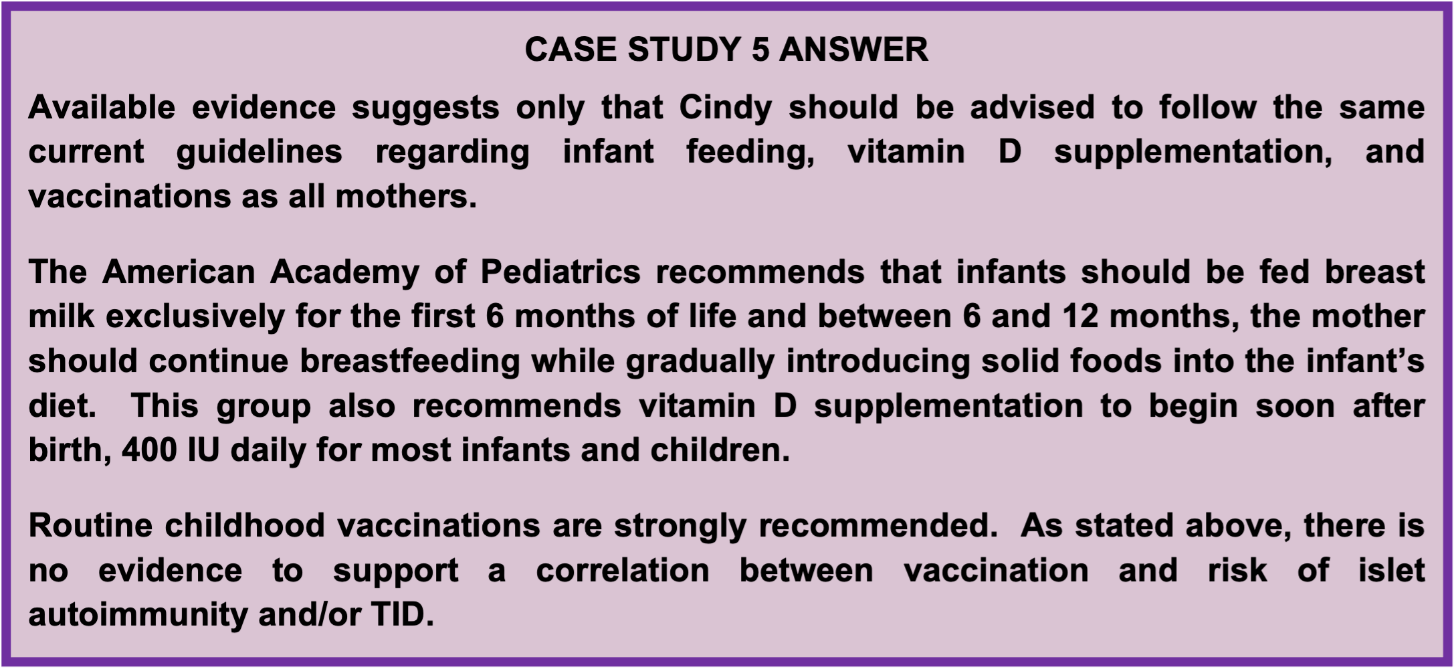
Another possible interface between microbial exposure and human disease is through the microbiome; that is the gut flora established within the first 3 years of life (93).  It has been hypothesized that perturbations in normal early microbiome development might pre-dispose to disease whether through direct modulation of innate immunity or via alteration of intestinal permeability and the downstream effects on adaptive immunity. Interestingly, it appears that the gut microbiome is less diverse and less “protective” in individuals with islet autoimmunity or recent onset TID (94-96).  Whether this difference is cause, effect, or correlation isn’t known. Nonetheless, multiple factors might affect the early intestinal microbiome, some of which also have been shown to correlate with risk of islet autoimmunity and TID.  For example, breastfeeding can alter the intestinal microbiome of the infant by increasing the number and diversity of beneficial microbiota (97, 98). As previously discussed, multiple prospective observational studies suggest that breastfeeding protects against future development of islet autoimmunity and TID, but there’s no evidence to connect this directly to the infant microbiome.

**Viral Infections**

A viral etiology for initiation of autoimmunity is an attractive idea; a beta cell trophic virus could contribute to disease by directly killing beta cells, by leading to a chronic infection which triggers an immune response, or by molecular mimicry in which self-antigens are erroneously recognized as viral epitopes targeted for destruction.  Notably, these possible mechanisms would not necessarily point to a particular virus; any virus widespread in a population could theoretically lead to autoimmunity in genetically susceptible individuals if encountered at a vulnerable time in immune system or beta cell development.  With the notable exception of congenital rubella which is associated with type 1 diabetes (99), other data relating viruses to initiation of autoimmunity is less conclusive.  While some studies have reported viral “footprints” in islets from individuals who have died from TID, these have not been consistently confirmed.  Similarly, many studies have focused on enteroviruses, including coxsackie B, due to observations suggesting seasonal variation in antibody development that is reminiscent of the timing of such infections (100) (101), yet this remains controversial.  Aside from a viral role in the initiation of autoimmunity, others have proposed that acute viral infections may impact the transition from islet autoimmunity to clinical TID due to increased insulin demand during infections.  Patients commonly report an acute viral illness preceding the diagnosis of TID, and the clinical onset of TID more commonly presents in the fall and winter months in both the northern and southern hemispheres (102); but this does not imply a causal relationship.

**Vaccinations**

In recent decades, an increasing number of parents in Western countries have declined routine childhood vaccination of their children, which has created a situation with significant personal and public health consequences.  Multiple high-quality studies have thoroughly investigated vaccinations and TID, and none have found any association with islet autoimmunity or TID (103-107)



**Sources: (88, 103-108).**

**FUTURE CONSIDERATIONS**

Despite advances in glucose monitoring and insulin delivery, the daily psychological and financial burden of disease on individuals, their families, and society together with the persistence of complications and reduced life span demand a paradigm shift.

As of 2021, we know much about the natural history of disease. We know that antibodies can develop early in life and that essentially all of those with established islet autoimmunity will develop clinically overt disease. We also know that identifying these individuals is of significant clinical benefit. Those with islet autoimmunity followed carefully until diagnosis have markedly less morbidity at the time of diagnosis and lower HbA1c values. Family members of T1D probands should be made aware of their disease risk and should be offered autoantibody screening and enrollment in monitoring trials. Correspondingly, patients with TID should be informed of the opportunity to have their relatives screened for TID risk in the setting of a clinical research study.

While the interaction of humans with their environment must contribute to disease; how this occurs is still being elucidated. It is likely that there are many different paths by which individual gene/environment interactions result in T1D; suggesting that dissecting this heterogeneity will provide better insights and therapies.

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**ADDITIONAL INFORMATION** (From prior chapter by Aaron W. Michels, MD and Peter Gottlieb, MD)

**INTRODUCTION**

Type 1 diabetes mellitus is defined as immune mediated diabetes mellitus ([1-6](https://www.endotext.org/chapter/pathogenesis-of-diabetes/pathogenesis-of-type-1a-diabetes/#_ENREF_1)). It can become manifest with hyperglycemia presenting in the first days of life or in adults over the age of 60. Current estimates indicate that immune mediated diabetes represents approximately 5 to 10% of the diabetes developing in adults and that approximately as many individuals develop this form of diabetes as adults as do children ([7-9](https://www.endotext.org/chapter/pathogenesis-of-diabetes/pathogenesis-of-type-1a-diabetes/#_ENREF_7)). In the United States the great majority (>90%) of Caucasian children developing diabetes have type 1 diabetes; whereas, approximately 50% of African American and Hispanic American children developing diabetes lack the autoantibody and immunogenetic markers of typical type 1 diabetes ([10-12](https://www.endotext.org/chapter/pathogenesis-of-diabetes/pathogenesis-of-type-1a-diabetes/#_ENREF_10)). Most of these latter children appear to have variants of type 2 diabetes with a small number having specific characteristic genetic syndromes (e.g. MODY: Maturity Onset Diabetes of Youth) with identified mutations of genes such as glucokinase and HNF (Hepatic Nuclear Factors) ([13](https://www.endotext.org/chapter/pathogenesis-of-diabetes/pathogenesis-of-type-1a-diabetes/#_ENREF_13)). In addition, studies of the pathology of the pancreas of Hispanic and African American children who lack islet autoantibodies show that all islets have some beta cells, but in decreased numbers ([11](https://www.endotext.org/chapter/pathogenesis-of-diabetes/pathogenesis-of-type-1a-diabetes/#_ENREF_11)). In contrast, in the pancreas of patients with type 1 diabetes, there is lobular loss of beta cells (termed pseudoatrophic islets) ([11](https://www.endotext.org/chapter/pathogenesis-of-diabetes/pathogenesis-of-type-1a-diabetes/#_ENREF_11)).

When an individual presents with type 1 diabetes it indicates that they and their relatives have an increased risk of having or developing a series of autoimmune disorders (12). Celiac disease, hypothyroidism, hyperthyroidism, Addison's disease, and pernicious anemia are some of the most prominent associated diseases. For example, approximately 1/20 patients with type 1 diabetes have celiac disease (14,15). Most of these patients are asymptomatic and the disorder is only discovered if anti-transglutaminase autoantibodies are measured and individuals with positive antibodies biopsied. In that the therapy for celiac disease, namely gluten avoidance, is highly effective, and we routinely screen all type 1 diabetic patients. We also screen for thyroid disease, which has an incidence of approximately 20% in type 1 diabetes, with yearly TSH measurements and for Addison's disease (21-hydroxylase autoantibodies) (16).

**GENETIC SUSCEPTIBILITY**

Type 1 diabetes is itself heterogeneous, with several forms of immune mediated diabetes with known genetic causes as parts of autoimmune syndromes (thus likely to be classified as other Specific Forms of Diabetes). In particular, patients develop immune mediated diabetes when they have mutations of the AIRE (Autoimmune Regulator) gene (21). Mutations of the AIRE gene result in Autoimmune Polyendocrine Syndrome Type I (23,24). Most forms of type 1 diabetes are polygenic in etiology, and polymorphisms of genes within the major histocompatibility complex (HLA genes) play a major role in determining disease susceptibility (27,28).

The alleles of different HLA genes (e.g., DRB1 and DQB1) are non-randomly associated with each other, such that with DRB1\*0401 one usually finds one of three DQ alleles (e.g., DQB1\*0301, DQB1\*0302, DQB1\*0303) rather than any one of more than forty different DQB molecules. Such non-random association of alleles of different genes on the same chromosome is termed linkage disequilibrium. The histocompatibility complex is divided into three regions, class II, class III and class I. The most important determinants of type 1 diabetes are the HLA DQ and DR alleles. These molecules on the surface of antigen presenting cells (e.g., macrophages) bind and present short peptides that are recognized by T cell receptors of T lymphocytes (27,35,36). They are termed immune response genes in that the specific amino acid sequence of these molecules determines which peptides will be bound and to a large extent determine which peptides an individual will respond to. Each different amino acid sequence is given a number. For the DQ molecules both its alpha and beta chain gene are polymorphic, and thus to specify a DQ molecule one must specify both chains. For DR molecules only the DRB chain is polymorphic and thus only this chain is specified. Each number after the star indicates a specific amino acid sequence of the HLA allele and the letters and first number the gene (e.g., DRB1\*0401, DR B chain gene number 1, allele 0401).

There is a tremendous spectrum of diabetes risk associated with different DR and DQ genotypes (37-39) (Figure 6). For Caucasians with type 1 diabetes the most common diabetes-associated haplotypes are DR3 and DR4. More than 90% of patients with type 1A diabetes have one or both of these alleles versus approximately 40% of the general U.S. population. With the finer sequence information that is now available, DR4 haplotypes are subdivided based on specific variants of DRB1 and DQB1. The highest risk DR4 haplotypes have DRB1\*0401, DRB1\*0402, DRB1\*0405, while DRB1\*0403 is moderately protective. The highest risk DR4 haplotypes have DQB1\*0302, with DQB1\*0301 and DQB1\*0303 of lower risk. Thus, both DR and DQ alleles contribute to diabetes risk. DR3 haplotypes are almost always conserved with DRB1\*03 combined with DQA1\*0501, DQB1\*0201 (40). The highest risk genotype has both DR4/DR3 DQB1\*0302/DQB1\*0201. This genotype occurs in 2.4% of newborns in Denver, Colorado, and between 30 and 50% of children developing type 1 diabetes. Approximately 50% of children developing type 1 diabetes early (i.e., less than age 5) are DR3/4 heterozygotes versus 30% of young adults presenting with type 1A diabetes.

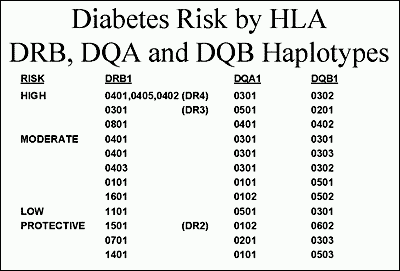


Figure 6. Hierarchy of diabetes risk with examples of haplotypes that lead to diabetes susceptibility, are neutral, or protective. Modified from teaching slides www.barbaradaviscenter.org

There are three HLA molecules that provide dominant protection. The most common is DQB1\*0602 that occurs in approximately 20% of U.S. individuals (41-43). Protection is not absolute, but less than 1% of children with type 1 diabetes have this molecule. DQA1\*0201 with DQB1\*0303 and DRB1\*1401 also provide dramatic protection, rarely being found in patients with type 1 diabetes and rarely transmitted from a parent with the alleles to their diabetic offspring (38,39). It is noteworthy that both DR and DQ alleles can protect. The specific mechanism underlying both susceptibility and protection are not fully understood. One attractive hypothesis is that protective alleles when expressed within the thymus lead to deletion of T cells with receptors that recognize a critical islet peptide (44). With deletion of such T cells, the risk of diabetes would be reduced. In addition, it is likely that high-risk HLA alleles present specific peptides of target islet molecules to T lymphocytes (28).

Multiple additional loci (Figure 7) have been implicated with estimates that approximately 50% of the familial aggregation of type 1 diabetes is attributable to the HLA region, perhaps 10% to the insulin locus, with all other loci contributing much less, though in aggregate their contribution is important. In the Cox analysis (Figure 7) of approximately 700 sibling pairs the only significant LOD score was for a locus on chromosome 16q that was not given an iddm designation with earlier genome screens. Several areas implicated in the past had suggestive scores, but there is overlap with the families from which the original evidence was generated. It is likely that contributing loci may differ between populations contributing to the initial difficulty of replicating putative loci in different studies (56,57). More than 40 genetic loci contributing to diabetes risk have been implicated (Figure 7). Polymorphisms of the insulin gene are well established as contributing to risk. A repeat sequence upstream (5') of the insulin gene termed a Variable nucleotide tandem repeat or VNTR, is divided into three general repeat sizes with the longest set of repeats associated with protection from diabetes (46-48). This set of alleles is also associated with greater thymic production of insulin messenger RNA (49), leading to the hypothesis that greater thymic message and presumably greater proinsulin production dampens anti-insulin autoimmunity (49-51). A functional polymorphism of the LYP gene (Lymphocyte Specific Phosphatase; PTPN22- Protein Tyrosine Phosphatase) has been associated with type 1 diabetes, rheumatoid arthritis, and lupus erythematosus (52-54). The R620W missense mutation (tryptophan replacing arginine) disrupts the binding of the phosphatase to the molecule Csk and this blocks its ability to down-regulate T cell receptor signaling. With an odds ratio of between 1.7 and 2.0 of the "autoimmunity” allele which is relatively common (5-10% allele frequency) there is a large genetic effect that is much greater than CTLA-4 polymorphisms associated with diabetes risk (55). Combining known diabetogenic polymorphisms of LYP, the insulin gene, alleles of DP, DQ, and DR class II immune response genes, as well all of the new loci account for approximately 48% of the familial aggregation of type 1A diabetes, with DR and DQ loci accounting for 41% of this 48% (45). A recent study suggests that for a major subset of individuals with the highest risk HLA genotype (DR3/4-DQ2/DQ8 heterozygotes) who share both HLA haplotypes with a diabetic sibling, risk of activating anti-islet autoimmunity is as high as 80% (33).

**AUTOIMMUNITY**

Insulin autoantibodies are usually the first autoantibody to appear in children followed from birth for the development of type 1 diabetes (84,85). These autoantibodies can appear in the first six months of life. Once insulin autoantibodies appear in such young children there is a high risk of development of additional anti-islet autoantibodies and progression to diabetes. More than 90% of children developing type 1 diabetes prior to age 5 have insulin autoantibodies while less than 50% of children developing diabetes after age 12 have such autoantibodies (86). Therapy with human insulin induces insulin antibodies that cannot at present be distinguished from insulin autoantibodies. Thus, if an individual has been treated with insulin for more than several weeks, positive insulin autoantibodies are not interpretable. For all autoantibodies measured in the first 9 months of life, the antibodies may be transplacental in origin, a particular problem if a mother has type 1 diabetes and is treated with insulin.

There are a number of important caveats in the utilization of anti-islet autoantibody assays. The field developed from the initial observation that patient's sera "stained” islets of cut sections of human pancreas, the cytoplasmic islet cell antibody (ICA) assay (83). This assay, given its utilization of human pancreas from cadaveric donation and subjective reading of slides, has proven the most difficult to standardize (69). The assay predominantly detects antibodies reacting with GAD65, IA-2 and ZnT8, but does not detect anti-insulin autoantibodies. Given the difficulty in standardization, reliability over time, and major overlap with defined autoantibody assays, a number of investigators no longer utilize this assay. For research purposes and potentially in older adults with what has been termed LADA (latent autoimmune diabetes of adults) the ICA assay may have utility in that there is evidence of one or more additional autoantibodies detected with this assay and not with GAD65, IA-2, ZnT8 and insulin autoantibody determination.

A single autoantibody, even when present on multiple occasions, is associated with only a modest risk of progression to diabetes: approximately 10% (87,88). Once two or more anti-islet autoantibodies are present in children, progression to diabetes is very high, approaching almost 100% after 15 years of follow-up (89). In addition, once multiple autoantibodies are present it is very unusual for an individual to lose all expression of autoantibodies prior to the development of overt diabetes. Following the development of diabetes, IA-2 and more slowly GAD65 (over decades) autoantibodies wane. Following islet or pancreatic transplantation expression of GAD65 and IA-2 autoantibodies can be induced in patients with long-standing diabetes (90).

The most specific of the autoantibodies react with the molecule IA-2, but IA-2 autoantibodies are usually detected following the appearance of insulin and/or GAD65 autoantibodies (84). Even with IA-2 autoantibodies, however, there are apparent "false” positives in terms of diabetes risk. We evaluated approximately 10 individuals with either transient IA-2 autoantibodies or normal controls with IA-2 autoantibodies. None of these individuals expressed an additional anti-islet autoantibody. In contrast to patients diagnosed with or developing type 1 diabetes, the ICA512/IA-2 autoantibodies of nine out of ten of these normal individuals did not recognize multiple ICA512 epitopes and did not react with the dominant ICA512 autoantigenic domain (91). This indicates that even with a highly specific radioassay, if one screens tens of thousands of sera, one can find sera that presumably by chance cross-react with some epitope of the IA-2 molecule. It is much less likely to find an individual with antibodies that by chance react with two different islet autoantigens using fluid phase radioassays set with specificity at the 99th percentile of controls.

**LOSS OF INSULIN SECRETION**

At present, beta cell mass is not readily measured over time in humans, so it is not possible to absolutely define progression of beta cell loss. There is however no doubt that measurable anti-islet autoimmunity precedes the development of diabetes in terms of anti-islet autoantibodies in humans, and autoantibodies and T cell invasion in animal models. In the NOD mouse there is evidence of some beta cell destruction and beta cell regeneration prior to the onset of diabetes (92). There is also evidence for a change in the immune system close to the time of onset of diabetes (i.e., Th2 to Th1) (93-96). This change is associated with more rapid disease progression, ability to transfer diabetes by T cells, and a time window during which a specific immunotherapy (monoclonal anti-CD3 antibodies) is effective (97). In humans the best evidence for progressive loss of beta cell function comes from studies of insulin and C-peptide secretion (98). C-peptide, the connecting peptide of proinsulin, is secreted in equimolar amount to insulin, but C-peptide is not present in insulin preparations utilized to treat diabetes. Thus, C-peptide has become an important indicator of remaining beta cell function. Following the onset of diabetes, it has long been appreciated that C-peptide secretion progressively declines, until for most patients with type 1 diabetes C-peptide becomes non-detectable, associated with true insulin dependence. In a similar manner, first phase insulin secretion following a bolus of glucose on intravenous glucose tolerance testing is progressively lost for relatives followed to the development of type 1 diabetes (99). Such metabolic abnormalities may result in part from functional inhibition of beta cell secretion, but pathologic studies indicate that beta cell mass is normal for identical twins of patients that have not activated anti-islet autoimmunity, and for new onset patients that bulk of beta cells are destroyed (100). Within the pancreas of a patient with type 1 diabetes there is heterogeneity of islet lesions, with most islets lacking all beta cells and with no lymphocytic infiltrates (pseudoatrophic islets), few normal islets with no infiltrates, and few islets with remaining beta cells and infiltrates. This is perhaps analogous to the progressive development of vitiligo in patients, with patches of skin with all melanocytes destroyed, whereas other skin is normal.

**OVERT DIABETES**

The development of type 1 diabetes is usually perceived as an abrupt event, and some individuals may rapidly manifest severe hyperglycemia. Now that we can follow individuals to the development of type 1 diabetes, we can see that anti-islet autoantibodies can precede hyperglycemia by years, and there is usually some deterioration in glucose tolerance more than one year prior to diabetes onset (particularly with intravenous glucose tolerance testing) (101). The majority of individuals identified to be diabetic following autoantibody testing are found to have a diabetic 2-hour glucose on oral glucose tolerance testing (>200mg/dl) rather than fasting hyperglycemia. The acute presentation with severe hyperglycemia and ketoacidosis is life threatening, and it is estimated that approximately 1/200 children die at the onset of type 1 diabetes (102,103). Such children typically have a medical history where the first health care providers have failed to make the diagnosis of diabetes; the child then presents again later and dies with cerebral edema. The classic symptoms of polyuria, polydipsia, and weight loss are usually present but the initial diagnosis is still missed. The alternative diagnosis of nausea and vomiting due to viral illness is the most common mistaken diagnosis, and with the ready availability of glucose determination from a finger or heel stick, there should be a low threshold in emergency rooms and physicians’ offices for ruling out diabetes. Though transient hyperglycemia can occur, such children obviously need close follow up. We usually arrange glucose monitoring for children thought to have transient hyperglycemia, and measure anti-islet autoantibodies (104). Of those with anti-islet autoantibodies and transient hyperglycemia, almost all progress to type 1 diabetes within several months.

At the onset of type 1 diabetes, almost all individuals have residual insulin secretion, and there is convincing evidence that residual insulin secretion as measured by C-peptide secretion is of clinical benefit (less hypoglycemia, less microvascular complications, and much easier diabetes management).

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