The Genetics of Type 2 Diabetes in Youth: Where We Are and the Road Ahead

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The incidence of type 2 diabetes (T2D) is on the rise in youth in the US[1,2] and worldwide.[3] T2D is characterized by hyperglycemia from a combination of insulin resistance and relative deficiency of insulin secretion. The contribution of insulin resistance to diabetes pathogenesis explains the clinical association of diabetes with obesity and, subsequently, the coincidence of increasing T2D prevalence with increasing prevalence and severity of obesity in children.[4] Differences have been described in the natural history of youth-onset T2D and adult-onset T2D. Compared with adults, T2D in youth appears to progress more rapidly, with higher rates of metformin treatment failure and more rapid rates of beta cell decline.[5-7]

The presence of diabetes encumbers those affected with a long-term burden of chronic disease and an increased risk of cardiovascular and microvascular complications. This risk increases with the duration of the disease, putting children with T2D at extremely high risk for complications. Follow-up data from both the SEARCH for Diabetes in Youth study and the Treatment Options for Diabetes in Youth (TODAY) trial have found a substantial presence of diabetes complications as early as adolescence and young adulthood.[8-11] Moreover, the prevalence of complications and overall mortality are higher in youth with T2D compared with adults with T2D or even youth with type 1 diabetes.[12,13] This burden of disease underscores the need to improve our understanding of diabetes risk, prevention, and optimal treatment in youth.

T2D is a complex, multifactorial disease influenced by both environmental factors and genetic variation as well as their interactions.[14,15] The heritability of T2D is demonstrated by both the high concordance rates in identical twins[16,17] and the typical presence of a family history of T2D in those with the disease.[18,19] Investigations of the genetics of diabetes risk have examined both overall T2D risk as well as individual glycemic traits that may predispose to diabetes, such as fasting glucose levels, insulin secretion, insulin resistance, and β-cell function. Understanding the genetic underpinnings of diabetes risk offers an opportunity to improve both our knowledge of the mechanisms contributing to diabetes pathogenesis and our understanding of how best to individualize diabetes treatment and prevent complications. Here we review the current state of T2D genetics, specifically as it pertains to children and adolescents.

Monogenic Diabetes

Diabetes as a result of a single gene abnormality, or monogenic diabetes, shares clinical overlap with T2D, particularly T2D in youth. There are 3 major subgroups of monogenic diabetes: neonatal diabetes, syndromic diabetes, and maturity-onset diabetes of the young (MODY). Neonatal diabetes presents in infancy, although only a subset of infants develops diabetes in the neonatal period (the first 30 days of life); the majority of patients become symptomatic within the first 6 months of life.[20] Syndromic diabetes presents with additional extrapancreatic features, typically also in infancy.[20] MODY is characterized by non–insulin-dependent diabetes diagnosed at a young age (<25 years) demonstrating an autosomal dominant inheritance pattern.[21] Subtypes of MODY are based on specific genetic defects, with involvement of different genes associated with differences in clinical and physiologic phenotypes.[22]

Monogenic diabetes can be caused by pathogenic mutations in genes that disrupt glucose sensing, insulin transcription, the potassium–adenosine triphosphate channel that transduces the signal for insulin release, the insulin gene, or pancreatic development. Understanding the genes associated with monogenic forms of diabetes has provided insight into the disease mechanisms of diabetes. Eleven different genes have been identified as causal for MODY in the Online Mendelian Inheritance in Man catalog: *HNF4A* (MODY 1), *GCK* (MODY 2), *HNF1A* (MODY 3), *PDX1* (MODY 4), *HNF1B* (MODY 5), *NEUROD1* (MODY 6), *CEL* (MODY 8), *INS* (MODY 10), *ABCC8* (MODY 12), *KCNJ11* (MODY 13), and *APPL1* (MODY 14). Note that the genes previously reported as causal for MODY 7, MODY 9, and MODY 11 are absent from this list, owing to the recent proposal to eliminate them from the list of causal MODY genes based on updated genetic evidence.[23] Mutations in the *HNF4A* and *HNF1A* genes lead to abnormal insulin secretion, and MODY caused by variants in these genes can be effectively managed with oral sulfonylurea therapy.[24,25] MODY caused

GRS	Genetic risk score
GWAS	Genome-wide association study
MODY	Maturity-onset diabetes of the young
ProDiGY	Progress in Diabetes Genetics in Youth
T2D	Type 2 diabetes
TODAY	Treatment Options for Diabetes in Youth

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by pathogenic variants in *GCK*, the gene encoding glucokinase, which phosphorylates glucose to glucose-6-phosphate in pancreatic cells and acts as a glucose sensor, is characterized by a mild, stable hyperglycemia with a low risk of complications that commonly does not require any treatment.[26]

Given the clinical overlap between T2D and rarer forms of diabetes, a long-held hypothesis is that the genetic underpinnings of both common and rare forms of diabetes might not be entirely distinct. Multiple studies have shown that MODY affects a small but not insignificant subset of youth with diabetes, including those clinically diagnosed with T2D. The SEARCH for Diabetes in Youth Study published the first systematic study of MODY prevalence in US youth, which reported a 1.2% overall prevalence of MODY.[27] A genetic sequencing study of participants in the TODAY study found that 4.5% carried a pathogenic variant in a MODY gene.[28] A larger genetic study conducted by the Progress in Diabetes Genetics in Youth (ProDiGY) consortium that included the TODAY cohort, a second cohort recruited by the TODAY researchers for genetic studies, and a subset of the SEARCH for Diabetes in Youth study participants identified a 2.8% incidence of MODY.[28,29] These studies focused on rare, highly penetrant variants in known MODY genes. In adult studies of T2D genetics, there is increasing overlap of common variant associations and genes associated with monogenic diabetes.[30] Although such associations have not yet been shown in youth with T2D, it is possible that further examination of rarer variants will find associations along a spectrum of disease risk in genes or pathways relevant to diabetes.

Candidate Gene Studies

Many efforts to understand the genetic underpinnings of T2D in children have focused on genetic variants with known associations with glycemic traits or T2D risk in adults, examining whether similar associations exist in youth. Individual variants have been shown to have similar associations in children for both fasting glucose[31,32] and the homeostasis model assessment of β cell function.[31] Several T2D risk genes have been associated with youth-onset T2D, including *TCF7L2*,[33,34] *SLC16A11*, and *ABCA1*.[34]

Genetic risk scores (GRSs), which allow for the assessment of the aggregate genetic risk of a given trait, have demonstrated association of GRSs constructed from variants associated in adults with glycemic traits and/or T2D risk with fasting glucose and measures of β-cell function,[35-37] as well as measures of insulin resistance[35,36,38] in youth. Two studies have examined the ability of GRSs to identify children at risk of progressing to T2D; even though the scores were shown to be associated with T2D risk,[36,39] in one of the studies clinical factors such as body mass index (BMI) and family history of T2D had higher predictive utility.[34]

Genome-Wide Association Studies

Since the first genome-wide association study (GWAS) for T2D in adults was published in 2007,[40] there has been an explosion of genetic discoveries related to adult T2D with extremely well-powered studies and advanced analytic techniques. At the time of this publication, >400 variants have been associated with T2D in adults.[41] In comparison, large scale studies of pediatric T2D have not been conducted, largely due to limited sample sizes. To address this gap, we and colleagues formed the ProDiGY Consortium, which is a collaboration of 3 research groups: the TODAY study,[42] SEARCH for Diabetes in Youth,[43] and the Type 2 Diabetes Genetic Exploration by Next-Generation Sequencing in Multi-Ethnic Samples (T2D-GENES) Consortium.[44] The ProDiGY study is a collaborative effort to increase understanding of the genetics of T2D in youth by combining the sample sizes and rich phenotypic data of 2 pediatric T2D studies with the genetic prowess and resources of a large-scale adult diabetes genetics consortium.

In ProDiGY, we conducted the first GWAS for T2D in youth to identify genetic variants specifically predisposing to youth-onset T2D.[45] We performed our genetic analysis in 3006 multiethnic youth with T2D who were autoantibody-negative for selected pancreatic autoantibodies and 6061 adult controls aged >50 years and diabetes-free. We identified 7 genome-wide significant loci, including the novel locus rs10992863 in *PHF2* with an OR of 1.23 for T2D, implying that each copy of the G risk allele conferred a 23% greater odds of having T2D compared with the wild-type A allele. The remaining 6 loci were previously identified in adults and included *TCF7L2*, *MC4R*, *CDC123*, *KCNQ1*, *IGFBP2*, and *SLC16A11*.[45]

At the outset of our ProDiGY collaboration, our hypothesis was that genetic effects were greater in youth with T2D compared with adults, given the "extreme" T2D phenotype with respect to early age of presentation. To explore this premise, we constructed GRSs in ProDiGY from known T2D variants identified in adults.[46] Our comparison of the association of the polygenic risk score between youth and adult cases and controls showed a significantly higher OR for T2D in the youth analysis compared with the adult analysis, in accordance with our hypothesis.[45] Overall, the efforts of the ProDiGY consortium have provided initial insight into the genetic architecture of T2D in youth and have shown that the genetic architecture of T2D in youth largely overlaps with that in adults but with a greater aggregate genetic risk burden. Functional studies of candidate genes are needed to understand how the identified genetic variants affect disease risk. Studies evaluating the interplay between lifestyle and genetic factors are also needed to comprehensively evaluate T2D risk in youth.

Applications of Genetics in Youth-Onset T2D

There has been substantive growth in our understanding of the genetics of T2D in youth secondary to large-scale improvements in genotyping technology, next-generation sequencing techniques, and collaborative approaches such as ProDiGY to increase sample sizes. Here we appraise the various applications of genetics as it pertains to pediatric T2D.

Characterizing Disease Subtypes

Pediatric T2D is a heterogenous disease likely because of differing contributions from both environmental and genetic factors, as well as varying degrees of insulin resistance and β-cell dysfunction among individuals. The benefit of sulfonylureas in MODY 3 is a concrete example of how genetics can be used to characterize disease and dictate treatment. Although not always as targeted, genetics also can be used to characterize subtypes for the more common form of T2D. A soft clustering approach has been used to deconstruct the heterogeneity of T2D with groups of loci representing various mechanisms of disease based on β cell function, insulin resistance, and fat distribution[47,48] (**Figure**). These efforts to categorize subtypes help to better characterize pathophysiology, with the hope of informing clinical management and the risk of complications in the future. The benefit of using genetic data to characterize disease is that it remains unchanged over an individual's lifetime and can be measured even before symptoms develop, a particularly valuable characteristic for high-risk children who often have very short latent periods before full-blown T2D develops.

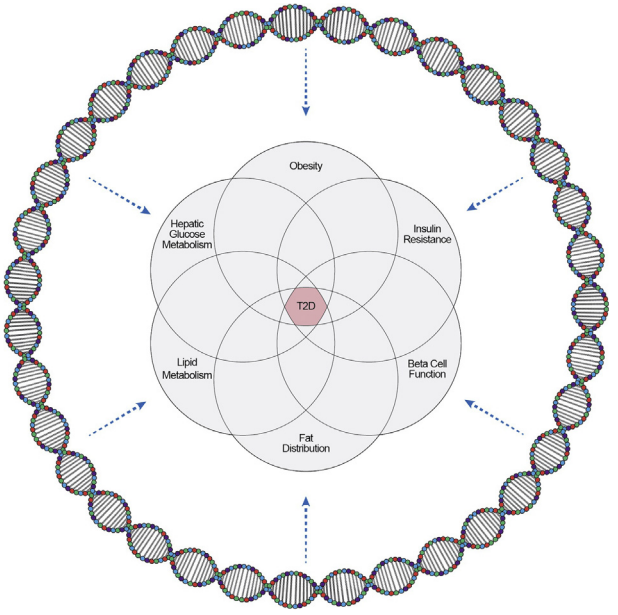

Figure. Schematic depicting how various pathophysiologic mechanisms that contribute to diabetes risk have underlying genetic contributions that can be distinct or overlapping with other processes. (Adapted from American Diabetes Association.[49])

Risk Prediction

Current guidelines from the American Diabetes Association recommend screening youth with obesity for T2D based on the presence of certain additional risk factors, including a family history of T2D, high-risk race/ethnicity, maternal history of gestational diabetes, and physical features associated with insulin resistance, such as acanthosis nigricans.[49] Although these criteria allow clinicians to readily identify youth requiring diabetes screening, it is not clear which of these youth will go on to develop T2D. In addition, there is no simple or direct correlation between clinical features as body mass index, fasting insulin level, or C-peptide level and the progression to T2D.

In the early days of T2D GWAS efforts, studies showed that a polygenic risk score for T2D in adults does not outperform clinical models of prediction, but when added to routine clinical risk factors, genetic information may enhance predictive utility, particularly for populations of younger adults in whom risk factors, such as glucose intolerance, might not have fully manifested.[50] Recently, a trans-ancestry polygenic risk score (PRS) of 1 259 754 HapMap3 variants and weights showed that the top 2% of the PRS distribution can identify adults with a roughly 2.5- to 4.5-fold increase in T2D risk. Using the top 2% of the PRS as the classifier, the reported prevalence-adjusted positive predictive value was 0.26 and the negative predictive value was 0.90.[51] Although the current clinical utility of PRSs remains limited, in the future more sophisticated scores derived from diverse populations likely will continue to improve the predictive performance of these scores.

Insight into Biologic Mechanisms

Genetic discovery can help uncover underlying biology related to T2D with the interrogation of pathways related to the genetic loci. For example, the intronic SNP rs7903146 in *TCF7L2*, which has one of the strongest known effect sizes for common variants in both youth and adults with T2D,[33,40,45] has been localized to islet-selective open chromatin in β cells using a method called formaldehyde-assisted isolation of regulatory elements sequencing. The high-risk T allele has been associated with increased transcription in islets and increased expression on cellular luciferase assays compared with the C allele, highlighting a mechanism by which this polymorphism may contribute to T2D risk.[52] Complementary approaches of studying diabetes and glycemic traits as well as regulatory and functional data can help improve our understanding of the underlying mechanisms contributing to T2D risk and progression. This is particularly important in youth, who have slightly different underlying pathogenic mechanisms compared with adults with T2D, such as β cell hyperresponsiveness in the early disease phase and a higher rate of β cell decline.[53-55]

Predicting Response to Interventions

Often in clinical medicine, patients do not respond or have adverse effects to medications that take time to uncover, leading to delays in optimal management, patient dissatisfaction, and wasted resources. Genetics may help identify those patients who may benefit the most from a certain intervention, allowing us to stratify patients, which in turn could lead to better targeting of clinical or public health interventions. For example, the Diabetes Prevention Program showed that an intensive lifestyle intervention was effective even in the participants with the greatest genetic risk burden for

established insulin resistance variants.[56] In adults, there has been extensive work evaluating the genetic determinants of metformin response, given the significant interindividual variability in metformin response[5] and evidence of significant heritability,[57] with GWASs so far identifying 5 variants associated with metformin response.[58-60] Similarly, sulfonylureas are metabolized predominantly by cytochrome p450 2C9 (CYP2C9), and loss-of-function alleles in *CYP2CP* have been associated with a greater response to sulfonylureas.[61] There have been no pharmacogenetic studies of T2D in youth reported to date, and this is an area where additional research is needed. For example, 50% of youth on metformin therapy do not have sustained glycemic control,[5] a greater proportion than seen in adults.[62] The mechanisms behind this difference is unclear, and identifying genetic variants associated with metformin response in youth potentially could help elucidate the reasons for treatment failure.

Conclusions

Given the exponential rise in the incidence of T2D in youth, the aggressive nature of the disease compared with adults, and the significant heritability of the disease, it is critical that we strive to better understand the genetic basis of T2D in youth. Although studies of pediatric T2D genetics have lagged behind adult studies largely because of the difficulty conducting studies with large sample sizes, technological advances and collaborative efforts have helped moved the field forward. However, much remains to be discovered, and further large-scale efforts with computational and functional follow-up of findings are needed to continue to advance our understanding of the genetic underpinnings of T2D in youth. The knowledge of genetics can be used to better understand the pathophysiology of the disease in youth, characterize subtypes, assist with disease prediction, and aid the targeting of pharmacologic interventions with the ultimate goal of developing a personalized medicine approach to tackle youth-onset T2D. ■

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