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Advances in the Genetics of Youth-Onset Type 2 diabetes

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Abstract

Purpose of review: To provide an update on knowledge the role of genetics in youth-onset type 2 diabetes (T2D).

Recent findings: The prevalence of T2D, once thought to be exclusively a disease of adults, has increased by over 35% since 2001. Youth with T2D tend to have higher rates of complications, more aggressive disease, with more rapid loss of beta-cell function and a less favorable response to treatment than adults. Obesity is the most important risk factor for T2D, and the rise in childhood overweight and obesity appears responsible for the dramatic increase in T2D in youth. However, some obese children do not develop T2D, consistent with genetic differences in susceptibility to the disease in the setting of obesity/insulin resistance, currently far less well characterized in youth than in adults. Recent studies have begun to show associations of several established adult T2D genetic risk variants with youth T2D and related glycemic quantitative traits, including the strongest known cross-population T2D genetic contributor *TCF7L2*. Maturity onset diabetes of the young (MODY), a diabetes subtype distinct from type 1 diabetes (T1D) and T2D, is now known to result from a highly penetrant gene mutation in one of several genes. MODY has been shown to account for or contribute to at least 4.5% of clinically diagnosed T2D, even among those who are overweight or obese, impacting treatment decisions. The recently formed ProDiGY (Progress in Diabetes Genetics in Youth) Consortium is using genome-wide association studies and whole exome sequencing to understand the genetic architecture of T2D in youth, including how it differs from that of adults.

Summary: The limited amount of research conducted to date on the genetics of youth-onset T2D, which tends to be a more aggressive disease than adult T2D, suggests some overlap with genes involved in adult T2D and a sizeable influence of highly penetrant monogenic diabetes

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Conflict of Interest

Jennifer N. Todd, Shylaja Srinivasan, and Toni I. Pollin declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with animal subjects performed by any of the authors. All procedures reported that were performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

variants. The ProDiGY Consortium is expected to provide a more comprehensive understanding of youth T2D genetics.

Keywords

type 2 diabetes; youth; genetics; monogenic diabetes

Introduction: The burden of Type 2 Diabetes (T2D) in youth

Type 2 diabetes (T2D), once thought to be exclusively a disease of adulthood, has increased at a considerable rate in youth, particularly in minority groups, paralleling the rise in obesity. The increase in the prevalence of T2D in youth has been observed in the United States and worldwide [1–5]. The SEARCH for Diabetes in Youth study is a population-based observational study of diabetes in youth in the United States funded by the Centers for Disease Control and Prevention and the National Institutes of Health which reported data demonstrating the increase in prevalence of diabetes between 2001 and 2009. The overall prevalence of T2D in youth was 0.34 per 1000 (95% CI, 0.31–0.37) in 2001 and 0.46 per 1000 (95% CI, 0.43–0.49) in 2009, representing an alarming relative increase of 35% (95% CI, 21.4%-50.0%) [1]. However, despite the large-scale epidemic of obesity in youth, there remains a mismatch between rates of childhood obesity and T2D, which is likely due to the substantial latency between onset of obesity and the related risk for T2D [6].

Type 2 diabetes and its comorbidities are significant long-term risk factors for the development of cardiovascular and microvascular complications. The risk of complications increases with the duration of the disease, placing children with T2D at extremely high risk for the development of these complications. Follow-up studies from the Treatment Options for Type 2 Diabetes in Youth (TODAY) study, a landmark clinical trial of therapeutic strategies for T2D in children and SEARCH indicate that youth with T2D have a substantial prevalence of microvascular complications of diabetes as early as in adolescence and young adulthood [7–10]. While there is lack of formal evidence on the incidence of cardiovascular complications in children with T2D, evidence from adult studies indicate that the combination of long-standing poor glycemic control and additional risk factors such as hyperlipidemia and hypertension increase the risk of these complications. Youth with T2D have higher rates of complications when compared with adults with T2D or children with type 1 diabetes [11,12]. Presently, we have limited therapeutic options for the treatment of T2D in youth, with metformin and insulin being the only two FDA-approved treatment options.

Pathophysiology and evidence for genetic susceptibility to T2D in youth

The pathogenesis of T2D in youth is similar to but apparently more aggressive than the disease process in adults, with the lack of adequate compensatory beta-cell insulin secretion in the presence of increased insulin resistance, the critical factor necessary for the development of the disease. While little is known about the natural history of T2D in children, available literature suggests that the rate of beta-cell decline is more rapid than in adults [13,14] and youth with T2D fail metformin therapy at a higher rate than adults [13,14]. Puberty is a unique factor in the pathogenesis of T2D in youth and a period in which many

adolescents first manifest clinical evidence of the disease. Puberty is associated with a transient physiological increase in insulin resistance even in lean healthy children and is normally associated with a compensatory increase in insulin secretion, a phenomenon that is impaired in children with T2D. The increase in insulin resistance in puberty is believed to be related in part to an increase in growth hormone levels, as growth hormone acts as a counterregulatory hormone to insulin.

Type 2 diabetes is a complex disease, characterized by the interplay between genetic, epigenetic and environmental factors. Obesity is overwhelmingly the most important risk factor for the development of T2D, and predisposes to T2D by increasing peripheral resistance to insulin-mediated glucose uptake. However, not all obese children go on to develop T2D and some children develop T2D at a relatively lower body mass index percentile than others, highlighting the involvement of other factors in the disease pathogenesis.

Type 2 diabetes is a heritable condition. The high concordance rates of T2D in identical twins [14,15], the typical presence of family history of T2D in children with the disease and the disproportionate prevalence of T2D among certain populations such as Native-Americans, Hispanics and African-Americans [13] all provide evidence for the genetic susceptibility to T2D in youth. In the TODAY study, almost 60% of subjects reported at least one parent, full sibling, or half-sibling with diabetes, and almost 90% had an affected grandparent with T2D [13].

Role of common genetic variation in youth onset T2D

Our understanding of the genetics underlying youth-onset T2D has lagged behind our understanding of adult-onset T2D [16]. Several studies have examined the impact of genetic risk in healthy children and children with prediabetes. The Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) analyzed genetic associations with fasting glycemic traits from 1,602 self-reported white European children aged 5.9–17.2 years and found consistent direction of effect with observations in adults; the largest effect sizes were observed for risk alleles in *GCK*, *G6PC2*, and *MTNR1B* [17]. Kelliny and colleagues [18] investigated the association of glycemic traits with common genetic variants in 2,025 healthy European children, finding that variants in *MTNR1B, G6PC2, GCK*, and *SLC30A8* were associated with higher fasting glucose; all except the latter were also associated with lower beta-cell function as estimated by the homeostasis model assessment (HOMA-B) (Table 1). A later study by the same group including additional cohorts for a total of 6,000 children found an additional 5 loci, *GLIS3, PROX1, SLC2A2, ADCY5,* and *CRY2*, were also associated with higher fasting glucose; effect sizes were similar to those seen in adults [19] (Table 1). Giannini and colleagues showed that in a multi-ethnic cohort of obese children, a genetic risk score of five T2D risk variants known to modulate insulin secretion in the genes *TCF7L2, IGF2BP2, CDKAL1, HHEX,* and *HNF1A*, was associated with higher risk of impaired glucose tolerance (IGT), lower insulin secretion, and increased risk of progressing from normal glucose tolerance to IGT or diabetes [20] (Table 1). To date, only one study has examined the relationship between common genetic variation and T2D in youth, finding that a variant in *TCF7L2* was associated with T2D in African American youth, with

an effect size greater than previously seen in African American adults [21] (Table 1). As this study only examined the *TCF7L2* variant, whether other known variants in T2D-associated genes associate with T2D or glycemic traits in youth is still unknown.

Role of Monogenic Diabetes in Clinically Diagnosed T2D in Youth

The lack of insulin requirement in some youth with diabetes was recognized as early as 1921, and the notion of a dominantly inherited young onset, mild form of diabetes that could occur in lean individuals was recognized as early as 1928 [22]. In 1960, Fajans reported that some nonobese children had mild diabetes that responded to sulfonylureas [23,24]. In 1974, Tattersall published a paper entitled “Mild Familial Diabetes with Dominant Inheritance,” [25], and shortly thereafter, Tattersall and Fajans coined the term “maturity-onset diabetes of the young (MODY)” [26] (similar to “maturity-onset type diabetes of childhood of the young” first used by Fajans in 1964 [24]), and subsequently proposed a working definition of “fasting hyperglycemia in a patient under 25 years old which could be controlled without insulin for more than 2 years” [27]. Genes in which single highly penetrant variants were responsible for the majority of these cases were identified in the 1990s as *GCK* (encoding glucokinase) [28], *HNF1A* (encoding hepatic nuclear factor 1-alpha) [29], *HNF4A* (encoding hepatic nuclear factor 4-alpha) [30], and *HNF1B* (encoding hepatic nuclear factor 1 beta) [31]. Today there are 14 genes defined as MODY genes, with the remaining ten accounting for small numbers of cases (reviewed in [32]).

In 2004, a survey of health care providers of 112 UK children under 16 years of age with non-type 1 diabetes revealed that 20 (18%) were diagnosed with MODY (19 with known mutations) [33]. While there have been numerous studies of MODY prevalence worldwide (reviewed in [32], it was not until 2013 that the first systematic study of MODY prevalence in youth in the United States was undertaken, as part of the SEARCH Study[34]. The three genes implicated in the majority of MODY cases (*HNF4A*, *GCK* and *HNF1A* in MODY 1, 2, and 3) were sequenced in 586 participants under the age of 20 years who were antibody negative and had fasting C-peptide ≥ 0.8 ng/mL. Forty-seven (8%) patients were identified to have MODY-causing mutations: 25 with an *HNF1A* (MODY3) mutations, 7 with an *HNF4A* (MODY1) mutations, 14 with a *GCK* (MODY2) mutation, one with two *HNF1A* mutations and one with both an *HNF1A* and an *HNF4A* mutation. Of these 47 individuals, only three (6%) had a clinical diagnosis of MODY, with most of the remainder previously diagnosed as T1D (36%) or T2D (51%). Accordingly, 51% of MODY cases were treated with insulin and 41% with metformin, and only 2/33 (6%) *HNF4A*/*HNF1A* cases were treated with sulfonylureas [34], the preferred therapy for *HNF4A/HNF1A*-MODY at low doses [35]. In the TODAY Study, 488 overweight/obese adolescents aged 10–17 with recently diagnosed T2D enrolled in a clinical trial of metformin ± lifestyle modification or rosiglitazone interventions underwent sequencing of 40 genes known or predicted to cause monogenic diabetes, including the 13 MODY genes known at the time. Twenty-two participants (4.5%) were found to have pathogenic or likely pathogenic variants classified according to American College of Medical Genetics/ Association of Molecular Pathologists (ACMG/AMP) Guidelines [36] in MODY genes, including seven in *HNF4A*, seven in *GCK*, 5 in *HNF1A*, one in *KLF11* (MODY7) and two in *INS* (MODY10), along with 26 variants of uncertain significance. Notably, the *HNF4A* cases were significantly more likely to fail metformin

treatment (HR = 5.03, $p = 0.0002$), and all *GCK* cases maintained HBA1c levels below 8%, both consistent with expectations for the specific molecular etiology. Taken together, these findings indicate that in a non-trivial number of cases, monogenic diabetes or MODY is the cause or major contributor to what is often clinically diagnosed as T2D, even in the presence of overweight or obesity, and therefore sequencing monogenic diabetes genes should be considered in all cases of antibody-negative, C-peptide positive (therefore likely non-type 1), youth onset diabetes. Minimally, emerging additional stratification indices such as low type 1 diabetes risk scores [37] should be used to identify candidates for testing. These findings and methodologies underscore the importance of the specific molecular diagnosis for optimal treatment and provide a glimpse into the potential that further understanding of the genetic etiology of clinically diagnosed T2D will likely have for individualizing and optimizing therapy.

Conclusions and future directions: the ProDiGY Consortium

Given the relatively unexplored genetic landscape of youth-onset T2D, we and our colleagues formed the Progress in Diabetes Genetics in Youth (ProDiGY) Consortium, a collaboration of the TODAY and SEARCH for Diabetes in Youth studies along with the Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) consortium, a large collaborative effort to find genetic variants that influence risk of T2D [16]. This multi-ethnic resource includes over 3000 cases and 6000 diabetes-free adult controls with both genome-wide genotyping and whole exome sequence data, allowing analysis of common and rare genetic variation predisposing to youth-onset T2D. With these data, we plan to explore whether variants known to be associated with T2D in adult populations associate with youth-onset T2D, and if so, whether the effect sizes are significantly different in youth. Given prior success of leveraging younger, leaner T2D cases to uncover T2D-associated loci [38], we postulate that the extreme phenotype of youth-onset T2D will also discover novel genetic T2D loci. Using treatment data from the TODAY study, we will explore whether genetic variation associates with response to diabetes treatment. We will also be able to estimate the frequency of pathogenic variants, both known and novel, in genes associated with monogenic diabetes, lipodystrophy, or obesity, in youth meeting clinical criteria for T2D. These pursuits will move us closer to the goal of understanding the genetic architecture of T2D in youth and individualizing and therefore optimizing treatment for all children currently falling into the heterogeneous category of T2D.

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Table 1:

Genetic variants associated with glycemic traits and/or type 2 diabetes in youth

Marker	Nearest gene	Trait	Reference(s)
rs560887	*G6PC2*	FG, HB	17–19
rs10830963	*MTNR1B*	FG, HB	17–19
rs4607517	*GCK*	FG, HB	17–19
rs13266634	*SLC30A8*	FG	18,19
rs7034200	*GLIS3*	FG	19
rs340874	*PROX1*	FG	19
rs11920090	*SLC2A2*	FG	19
rs11708067	*ADCY5*	FG	19
rs11605924	*CRY2*	FG	19
rs7903146	*TCF7L2*	IS, IGT/T2D*; T2D	20,21
rs4402960	*IGF2BP2*	IS, IGT/T2D*	20
rs7754840	*CDKAL1*	IS, IGT/T2D*	20
rs1111875	*HHEX*	IS, IGT/T2D*	20
rs1169288	*HNF1A*	IS, IGT/T2D*	20

Legend: FG, fasting glucose; HB = HOMA-B; IS, insulin secretion; IGT, impaired glucose tolerance; T2D, type 2 diabetes;

* association assessed as part of genetic risk score