

Genetic Testing for Type 2 Diabetes in High-Risk Children: the Case for Primordial Prevention

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Reviewable v1

Received: 29 Aug 2017 | Published: 04 Sep 2017

Citation: Wessel J, Marrero D (2017) Genetic Testing for Type 2 Diabetes in High-Risk Children: the Case for Primordial Prevention. Research Ideas and Outcomes 3: e20695. <https://doi.org/10.3897/rio.3.e20695>

Abstract

Extensive research now demonstrates that lifestyle modification can significantly lower risk of developing type 2 diabetes (T2D) in high-risk adults. In children, the evidence for lifestyle modification is not as robust, but the rapidly rising rate of obesity in children coupled with the substantial difficulty in changing behaviors later in life illuminates the need to implement prevention efforts early in the life course of children. Genetic data can now be used early in the life course to identify children at high-risk of developing T2D *before* traditional clinical measures can detect the presence of prediabetes; a metabolic condition associated with obesity that significantly increases risk for developing T2D. Such early detection of risk may enable the promotion of “primordial prevention” in which parents implement behavior change for their at risk children. Young children with genetic risk are a novel target population. Here we review the literature on genetic testing for prevention as it relates to chronic diseases and specifically use T2D as a model. We discuss the history of primordial prevention, the need for primordial prevention of T2D and the role genetic testing has in primordial prevention of high-risk families.

Keywords

type 2 diabetes; genetic testing; primordial prevention; children; whole genome sequencing

The Public Health Challenge: Rising Rates of Obesity and Type 2 Diabetes in Adults and Children

T2D has become one of the most significant public health crises of our times. Currently 10% of the U.S. general population has T2D and another 37% are estimated to have prediabetes (a metabolic abnormality that greatly increases risk for developing T2D) (Benjamin et al. 2017). The single most important predictor of T2D is body mass index (BMI) (Hu et al. 2001), a disturbing fact in that currently 68% of U.S. adults are overweight or obese (Ogden et al. 2014a). In children, the prevalence of obesity and T2D is rising dramatically (May et al. 2012). Currently 32% of U.S. children are overweight or obese (Ogden et al. 2014b). High rates of overweight/obesity begin at birth and continue to grow throughout early childhood Ogden et al. 2010. A study representing 7,738 U.S. children followed from kindergarten through 8th grade showed that part of the course of obesity is already established by age 5 and for those children who were overweight in kindergarten, 45% became obese in the early elementary years (Cunningham et al. 2014). This observation is supported by a study that reported ages 2-6 years is the most critical growth period for prediction of adult obesity (De Kroon et al. 2010). Of importance to this discussion, the effect of genetic variation on obesity begins in childhood and manifests in rapid growth leading to adult obesity (Belsky et al. 2012).

T2D is a slow progressing disease that occurs in genetically predisposed individuals preceded by behaviors (diet and physical activity) established early in life; where ~40% of the variation in T2D can be explained by genetic factors (Kaprio et al. 1992). The clustering of obesity and T2D has been demonstrated in families who share genetic factors and environments that are known to promote obesity (Li et al. 2006). Through the recent successes of genome-wide association studies (GWAS) >250 single nucleotide polymorphisms (SNPs) have been robustly associated with T2D (Fuchsberger et al. 2016), T2D traits (Wessel et al. 2015), and BMI (Locke et al. 2015); more SNPs will be identified in the coming years. The combined effects of multiple SNPs results in large effects for obesity in children (OR=2.4) (Belsky et al. 2012) and adults (2.73 kg/m²) (Speliotes et al. 2010), and T2D in adults (OR=2.6) (Meigs et al. 2008). Not surprising is the genetic architecture of obesity is very similar in children and adults (Bradfield et al. 2012). Given that the effect of genetic variation on obesity begins in childhood and manifests in rapid growth leading to adult obesity (Belsky et al. 2012); the potential utility of genetic testing, particularly as it applies to children, is its ability to identify risk for diabetes before other clinical markers appear such as excessive weight gain.

The Case for Genetic Testing as a Vehicle to Stimulate Primordial Prevention

In 1978 Toma Strasser, a cardiovascular epidemiologist at the World Health Organization, first proposed the term “primordial prevention” in an opinion piece about the future of cardiology (Strasser 1978). At the time, an epidemic of risk factors for coronary heart

disease had occurred in developed countries. Foreseeing the epidemic continuing into other countries, he promoted the idea of preventing precipitating risk factors to decrease the burden on populations and their healthcare systems around the world. Strasser's vision of implementing primordial prevention was to move beyond cardiology and its treatments of heart disease, into screening for the risk factors to promote preventive behaviors at a community and global scale. We suggest that the concept of primordial prevention can be applied to identify children at risk for T2D and promote preventive treatment early in the life course. This concept argues that making parents aware of their child's risk may stimulate them to implement behavior changes that can contribute to risk reduction. Indeed, almost all parents do the best they can to nurture and care for their children.

Lifestyle Modification

Several studies have successfully demonstrated behavioral interventions that focused on modest weight loss and increased physical activity can significantly reduce risk for developing diabetes in adults with prediabetes (Tuomilehto et al. 2001, Knowler et al. 2002). This holds true for adults with high genetic risk where lifestyle modification has been shown to be effective at lowering their diabetes risk (Delahanty et al. 2012).

Of note, lifestyle modification interventions in children have mixed results on weight loss and no substantial outcomes on diabetes prevention have been evidenced (Bradfield et al. 2012, Oosterhoff et al. 2016). This may reflect the way in which most of these interventions have been implemented; at schools. It has become evident that the potential benefits of school-based interventions on the child can be mitigated by parental influence at home where the child has little or no control over many lifestyle choices. Parents have a persuasive role in their child's dietary and physical activity choices (Lindsay et al. 2006, Savage et al. 2007), particularly in the early years. Indeed, children learn their health behaviors from their family (Novilla et al. 2006) and strong correlations between child and parents behaviors are reported (Sonnevile et al. 2012, O'Connor et al. 2010). These studies strongly suggest that in order to be effective, diabetes prevention interventions targeting youth need to activate parents, and not *solely* the child, as the agents of changing behaviors to reduce children's and ultimately the family's risk. In this context, intervention trials in children younger than five years (Golan et al. 1998, Epstein et al. 2007) compared to school aged children (Campbell et al. 2014) have reported promising results. The evidence that obesity begins early in life suggests interventions need to be performed in families with young children to be successful.

Identifying Individuals at Risk for Type 2 Diabetes

The ability to distinguish individuals into those who develop T2D and those who do not is based on an individual's risk factors, such as age, gender, BMI, glucose, lipids, and blood pressure (Mann et al. 2010). With the recent successes of GWAS, adding genetic risk factors (i.e. SNPs) to predict T2D has added incremental improvements over traditional risk

factors (Meigs et al. 2008). However, genetic factors *alone* can significantly predict incident T2D over the life course (Bollinger et al. 2012, Vassy et al. 2012b, Vassy et al. 2012a, de Miguel-Yanes et al. 2011), *before* the traditional risk factors develop. This argues for using genetic test results early in the life course so as to initiate adoption of life-long healthy behaviors to delay or prevent obesity and other subclinical metabolic abnormalities that lead to overt T2D. With the increasing prevalence of T2D in children, this is a pressing need.

Call for Research Into the Clinical Utility of Genetic Testing to Engage Families Early in Promoting Healthy Behaviors

Major advances in genetic technology have decreased costs of genotyping and whole genome sequencing (WGS) exponentially (MacArthur and Lek 2012) making it increasingly cost-effective (Brunham and Hayden 2012, Greeley et al. 2011). In the next few years the cost of sequencing an individual's entire genome will cost less than \$1000 (Kedes and Campany 2011). In light of the cost of WGS becoming clinically feasible, one could imagine patients entire sequence data available at the point of care for clinicians to make screening and treatment decisions. Providers are increasingly using genomic services (Grant et al. 2009, McCarthy et al. 2013). Pediatricians see genetic testing as the first opportunity to predict and preemptively intervene in the progression of obesity and T2D (Bradfield et al. 2012, Cheng et al. 2008), where gene-environment interactions very early in life have overwhelming effects on development of T2D (Eriksson 2007). Patients and consumers report their motivation for utilizing genetic testing is to increase their certainty of disease risk (Esplen et al. 2007) or to motivate behavior change (Bradfield et al. 2012, Grant et al. 2012, Waxler et al. 2012, Committee On 2013) including individuals at high-risk for T2D (Boerschmann et al. 2010, Grant et al. 2009, McCarthy et al. 2013, Cheng et al. 2008, Eriksson 2007, Flegal et al. 2010, Esplen et al. 2007, Markowitz et al. 2011). Parent's intention for genetic testing is to make health-related decisions for both themselves and for their children (Bradfield et al. 2012, Haga et al. 2012, Harris et al. 2012, Bollinger et al. 2012, O'Daniel and Haga 2011, Tercyak et al. 2011, Hay et al. 2012), even when they understand the limitations and risks, including the benefit of knowing genetic risk to make positive lifestyle changes in their children.

Few studies have been conducted on the clinical utility of genetic risk disclosure to improve patient outcomes. Those conducted report mixed results and are limited to a few diseases and only adults (Marteau et al. 2010). Recently, the first study to focus on T2D risk enrolled 108 high-risk adults who were classified as having high or low genetic risk, or control (Grant et al. 2012). The high risk genetic group received the genetic counseling session positively and reported improvement in their perception of control (Waxler et al. 2012). They also reported significant improvements in motivation to make lifestyle changes and participate in the Diabetes Prevention Program (DPP) lifestyle intervention compared to controls (p 's=0.01) (Grant et al. 2012), suggesting genetic risk information can serve as a motivator of behavior change. However high risk participants showed no significant

difference in actual attendance of the 16 DPP sessions when compared to controls ($p > 0.05$).

The American College of Medical Genetics and the American Academy of Pediatrics revised their policy statement on genetic testing and screening in children (Committee On 2013, Ross et al. 2013). For predictive genetic testing, such as T2D, their recommendations were that the decision to offer genetic testing should be driven by the best interest of the child and for an adult onset disease like T2D should only be offered if intervention initiated in childhood may reduce morbidity or mortality. Therefore as T2D is increasingly being diagnosed in childhood coupled with the rising rates of obesity in childhood predictive genetic testing in high-risk families could offer risk information early enough to intervene.

One population that would be particularly suited for investigating the impact of genetic testing is families with a maternal history of gestational diabetes mellitus (GDM). In many respects the children of women with GDM may inherit a substantial genetic risk for T2D. The prevalence of GDM has been rising, alongside the increases in adult BMI, and currently affects ~14% of pregnancies (Jovanovic and Pettitt 2001). GDM is perhaps the most potent risk factor for developing T2D in mothers. Up to 70% of women affected by GDM will develop T2D within 5-10 years (Kim et al. 2002, Vohr and Boney 2008, Hunger-Dathe et al. 2006, Lee et al. 2007). Equally alarming is children exposed to in-utero diabetes are more likely to be larger for gestational age at birth (Wendland et al. 2012, Metzger et al. 2008) and obese in childhood (Crume et al. 2011a, Crume et al. 2011b, Boerschmann et al. 2010). Current estimates suggest up to 40% of youth exposed to GDM will develop T2D, even after adjusting for BMI, making it the single strongest risk factor for developing T2D in children (Dabelea et al. 1998, Dabelea et al. 2008). The in-utero effects of GDM on developing T2D is not well understood but has been postulated that the hormonal events of pregnancy may represent an initiating event that uncovers individuals genetically susceptible to T2D (Ryan et al. 1995). The increasing rates of obesity and T2D in children and carrying this into adulthood, coupled with GDM exposure, make the children of families with a maternal history of GDM prime candidates for primordial prevention.

Genetic testing can illustrate for parents the relative contribution of their child's behaviors, particularly those associated with excessive weight gain. It is known that approximately 40% of the risk for developing T2D is attributable to genetics which allows focus on the 60% that can be attributed to the environment and the role environment plays in developing the condition. This offers the opportunity to promote the prevention of obesity through healthy diet and increased physical activity in young children. Parents learning of their child's elevated genetic risk can serve as an activator to begin making healthy choices about their children's diet, physical activity and weight. For example, parents with a personal history of type 1 diabetes (T1D) have been reported to change their young child's environment (e.g. diet, physical activity) to reduce their child's risk of developing T1D even when the risk factors are not established (Smith et al. 2014). Changing the child's environment ultimately benefits parents as they share similar environments and healthy lifestyle choices.

Conclusions

To date no study has examined using children's genetic risk to motivate parents to make changes before the child's lifestyle risk factors have developed. Research is required to reveal how genetic risk information can be used to benefit families by engaging them in actual changes in their diets, physical activity and weight and to maintain a healthy lifestyle.

Acknowledgements

This work was supported in part by the American Heart Association (15SDG22210003).

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Author contributions

Jennifer Wessel: Dr. Wessel conceptualized the idea, drafted the initial manuscript, and approved the final manuscript as submitted.

David Marrero: Dr. Marrero refined the idea initially conceived by Dr. Wessel, reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

Conflicts of interest

The author reports no conflicts of interest in this work.

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