**Common Genetic Determinants of Glucose Homeostasis in Healthy Children**

**The European Youth Heart Study**

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**OBJECTIVE**—The goal of this study was to investigate whether the effects of common genetic variants associated with fasting glucose in adults are detectable in healthy children.

**RESEARCH DESIGN AND METHODS**—Single nucleotide polymorphisms in MTNR1B (rs10830963), G6PC2 (rs560887), and GCK (rs4607517) were genotyped in 2,025 healthy European children aged 9–11 and 14–16 years. Associations with fasting glucose, insulin, homeostasis model assessment (HOMA)-insulin resistance (IR) and HOMA-B were investigated along with those observed for type 2 diabetes variants available in this study (CDKNA2A/B, IGF2BP2, CDKAL1, SLC30A8, HHEX-IDE, and Chr 11p12).

**RESULTS**—Strongest associations were observed for G6PC2 and MTNR1B, with mean fasting glucose levels (95% CI) being 0.084 (0.06–0.11) mmol/l, P = 7.9 × 10^{-11} and 0.069 (0.04–0.09) mmol/l, P = 1.9 × 10^{-7} higher per risk allele copy, respectively. A similar but weaker trend was observed for GCK (0.028 [−0.006 to 0.06]) mmol/l, P = 0.11). All three variants were associated with lower β-cell function (HOMA-B P = 9.38 × 10^{-5}, 0.004, and 0.04, respectively). SLC30A8 (rs13266634) was the only type 2 diabetes variant associated with higher fasting glucose (0.033 mmol/l [0.01–0.06]) mmol/l, P = 0.01). Calculating a genetic predisposition score adding the number of risk alleles of G6PC2, MTNR1B, GCK, and SLC30A8 showed that glucose levels were successively higher in children carrying a greater number of risk alleles (P = 7.1 × 10^{-15}), with mean levels of 5.34 versus 4.91 mmol/l comparing children with seven alleles (0.6% of all children) to those with none (0.5%). No associations were found for fasting insulin or HOMA-IR with any of the variants.

**CONCLUSIONS**—The effects of common polymorphisms influencing fasting glucose are apparent in healthy children, whereas the presence of multiple risk alleles amounts to a difference of >1 SD of fasting glucose. *Diabetes* **58**:2939–2945, 2009

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**D**iabetes is characterized by chronic hyperglycemia resulting from a defect in insulin secretion by the pancreatic β-cells and/or insulin action in peripheral tissues. Although the exact mechanisms underlying the development of type 2 diabetes remain unclear, it is known to be triggered by environmental and lifestyle factors in genetically susceptible individuals (1). Since 2006, an unprecedented number of novel genetic loci that are reproducibly associated with type 2 diabetes have been identified in genome-wide association (GWA) studies of adults (1,2). However, the contribution of known type 2 diabetes genes to differences in fasting glucose in healthy individuals is only small (3), and in contrast to the success in the discovery of these genes, much less is known about common genetic determinants of fasting glucose.

Common genetic variants in G6PC2 (glucose-6-phosphatase catalytic 2) (4), GCK (glucokinase) (5), GCKR (glucokinase regulator) (6), and MTNR1B (melatonin receptor 1B) (7,8,9) have only recently been identified as the first loci regulating fasting glucose in GWA studies of healthy diabetes-free adults. G6PC2, GCK, and GCKR all encode proteins that are key regulators of the provision of fasting glucose. Rare mutations in GCK play a role for the development of maturity-onset diabetes of the young (MODY), a disorder characterized by mild stable hyperglycemia (10). G6PC2, GCK, and GCKR thus represent likely candidates for altering an individual’s physiologic glucostat set point in the absence of disease. In contrast, MTNR1B was the only fasting glucose locus shown to alter the risk of type 2 diabetes in addition to fasting glucose levels in healthy individuals (7,8,9). The reported associations are most likely due to increased expression of MTNR1B in pancreatic β-cells and melatonin-mediated impaired insulin secretion in risk allele carriers (8) and demonstrate that the identification of fasting glucose genes through GWA studies of healthy individuals can lead to the discovery of type 2 diabetes loci and provide important insight into the pathogenesis of type 2 diabetes.

The majority of diabetes diagnosed before adulthood has until recently been attributed to type 1 diabetes, and with the majority of research focusing on adults only, limited data exist for children and adolescents with type 2 diabetes (11,12,13). Concomitant with the obesity epidemic, the prevalence and incidence of type 2 diabetes in youth have risen worldwide (11,12,14), and it is estimated that 45% of pediatric patients now diagnosed with diabetes in the U.S. have type 2 diabetes (12). Exposure to common genetic polymorphisms recently shown to contribute to...
elevated glucose levels in adulthood start at conception, yet it is unknown whether their effects can be detected in childhood. To understand whether common glucose-raising alleles exert an influence on glycemic control early in life and in the relative absence of insulin resistance, secondary to chronic obesity commonly present in older individuals (13), we studied associations of 6GPC2, GCK, and MTNRIIB as well as levels of fasting glucose, insulin, homeostasis model assessment (HOMA)-insulin resistance (HOMA-IR), and HOMA-B in a population-based study of healthy European children (n = 2,025) aged 9–11 and 14–16 years.

RESEARCH DESIGN AND METHODS

We studied children who participated in the European Youth Heart Study (EYHS), a mixed longitudinal population-based study of which the design and data collection have been described previously (15,16). DNA from children from Estonia (city and county of Tartu) and Denmark (city of Odense) was available for the study. Baseline measurements took place between 1997 and 1999 in Denmark and Estonia, and another survey of children aged 9 years was conducted in 2003 in Denmark only. Similar protocols for data collection were used in both countries. The study complied with international guidelines on biomedicine and ethical procedures of each participating country. Written informed consent was obtained from the child’s parent or legal guardian after they were given a full written explanation of the goals of the study and its possible hazards, discomfort, and inconvenience. In addition, children had all procedures verbally explained to them, together with any possible discomfort they might encounter, and were given the option to withdraw at any time.

At each study location a defined population of children was identified, and from this population a two-stage cluster sample of boys and girls aged 9–11 and 14–16 years was randomly selected. The primary sampling units were schools, and secondary units were school registers. Age-groups 9–11 and 14–16 years were chosen to broadly represent children either side of puberty; in addition, detailed assessment of pubertal stage was performed as outlined below. In total, 2,194 children agreed to participate, with a similar proportion participating in each country (76% in Estonia and 75% in Denmark).

Each child had a blood sample taken and underwent a physical examination including anthropometric and blood pressure measurements using the same equipment in both countries. Blood samples were collected after an overnight fast and analyzed by a Clinical Pathology Accreditation (CPA) accredited laboratory in Bristol and Cambridge, England. Glucose concentrations were measured by standard methods using Olympus AU600 random-access analysers. Plasma-specific insulin was determined by two-site immunometric assays with either 125I or alkaline phosphatase labels. Between-laboratories correlations were 0.94–0.98 for 30 randomly selected samples analyzed in both Bristol and Cambridge. HOMA was used to estimate insulin resistance (HOMA-IR = [fasting glucose (mmol/l) × insulin (mU/ml)]/22.5) and HOMA-B = 1 – [0.056 × fasting glucose (mmol/l) – 3.5]) (17), both of which have been validated as surrogate markers in healthy adults. Variants rs560887 in G6PC2 showed the largest effect size, with fasting glucose being a mean 0.084 mmol/l (95% CI 0.06–0.11; P = 7.9 × 10^{-11}) higher for each copy of the common C-allele (frequency 0.70 in HapMap CEU). For rs10830663 in MTNRIIB, glucose levels were 0.069 mmol/l (0.04–0.09; P = 1.9 × 10^{-5}) higher for each copy of the minor G-allele (frequency 0.30 in HapMap CEU). A similar but weaker trend was observed for rs4607517 in GCK (0.028 mmol/l [−0.006 to 0.06; P = 0.11]). Each of the three variants was also associated with significantly lower β-cell function (P = 9.38 × 10^{-5}, 0.004, and 0.04, respectively).

Of the type 2 diabetes–susceptibility genes that were investigated, rs13266634 in SLC30A8 was the only variant significantly associated with fasting glucose, with an effect size of 0.053 mmol/l (95% CI 0.01–0.06; P = 0.01) per copy of the common C-allele (frequency 0.75 in HapMap CEU); no significant association was observed with HOMA-B. The three SNPs in CDKAL1 were associated with HOMA-B (P ≤ 0.03) but not fasting glucose (Table 3). None of the observed associations were attenuated by adjustment for measures of adiposity estimated by either BMI or sum of the skin-fold thicknesses. No significant associations were present between any of the variants and fasting insulin or HOMA-IR (see supplemental Tables 1 and 2 in the online appendix, available at http://diabetes.diabetesjournals.org/cgi/content/full/db09-0374/DC1).

Using the genetic risk score, we examined the additive effect of an increasing number of risk alleles of glucose-associated variants on children’s glucose levels (Fig. 1). Mean fasting glucose was 0.06 mmol/l (95% CI 0.04–0.07; F_{trend} = 7.1 × 10^{-5}) greater for each additional risk allele.
of \( G6PC2,\) \( GCK,\) \( MTNR1B,\) and \( SLC30A8.\) \( GCK\) was included in this score despite not reaching conventional levels of statistical significance in this study because previous evidence demonstrated its association with fasting glucose in healthy children (5). In addition, the fasting glucose effect sizes of \( GCK\) and \( SLC30A8\) were found to be of similar magnitude. The total difference in fasting glucose between individuals carrying zero (0.5% of all children) compared with seven (0.6%) glucose-rising risk alleles was 0.43 mmol/l.

Alternative scores using risk alleles of \( G6PC2,\) \( MTNR1B,\) and \( GCK\) or \( G6PC2,\) \( MTNR1B,\) and \( SLC30A8\) showed a similar trend. Similar results were obtained when investigating the additive effect of fasting glucose risk alleles on HOMA-B levels, with children having a greater number of risk alleles showing successively lower \( \beta\)-cell function (\( P_{\text{trend}} = 3.0 \times 10^{-3}\); supplemental Fig. 2 in the online appendix).

We observed no difference in associations by age-group, sex, or country (all interaction \( P \) values > 0.05), except for rs10830963 in \( MTNR1B\) for which a significantly stronger effect on fasting glucose was observed in the older age-group (interaction \( P \) value = 0.004). Among the 9–11 year olds, fasting glucose levels were 0.037 mmol/l (95% CI 0.005–0.07) higher for each minor G-allele, whereas this effect was 0.11 mmol/l (0.07–0.15) for children aged 14–16 years. More detailed investigation showed similar effect modification of rs10830963 on fasting glucose by pubertal status based on Tanner stage, with greater effect sizes at later stages of maturity (interaction \( P \) value = 0.02), independent of age, sex, or country. In prepubertal children (Tanner stage 1) the per-allele difference in fasting glucose was 0.046 mmol/l (0.01–0.08) but 0.071 mmol/l (−0.04 to 0.18) at Tanner stages 2–3 and 0.11 mmol/l (0.07–0.16) at Tanner stages 4–5. Although the effect of rs10830963 on HOMA-B did not differ significantly by age-group (\( P = 0.41\)), its effect was found to be marginally stronger at later Tanner stages (interaction \( P \) value = 0.079), mirroring the interaction observed for fasting glucose.

**DISCUSSION**

This is the first study to show that common genetic variants in \( G6PC2,\) \( MTNR1B,\) and \( GCK\) all of which are associated with fasting glucose in diabetes-free adults, significantly influence levels of fasting glucose and/or \( \beta\)-cell function in healthy children.

Importantly, the joint effects of these common variants were additive and substantial. Higher levels of glucose were observed in children carrying more risk alleles, with a difference of >1 SD of fasting glucose comparing the small proportion of children in the extreme groups with the lowest, opposed to the highest, genetic susceptibility.

Effect sizes of \( MTNR1B\) and \( G6PC2\) variants in children of this study were close to those recently reported in adults, with differences in fasting glucose of 0.08 and 0.06 mmol/l per risk allele, respectively (7,4). Weedon et al. (5) previously showed that rs1799884 in \( GCK\) is associated with fasting glucose in adults and also children of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. Compared with this study and a more recent meta-analysis of adults reporting an effect size of 0.06 mmol/l (7), we observed a somewhat weaker and nonsignificant effect for rs4607517, a SNP in perfect linkage disequilibrium with rs1799884 in European-descent HapMap participants (\( r^2 = 1\)), suggesting that low power is likely to underlie the lack of statistical significance in our study.

In the absence of any direct measure of \( \beta\)-cell function, we use HOMA-B. We report significant associations for \( MTNR1B, GCK,\) and \( G6PC2\) with HOMA-B in healthy children, adding to the evidence from initial GWA studies (7) and showing for the first time that early effects on \( \beta\)-cell function can be demonstrated for these loci. \( GCK\) and \( G6PC2\) are expressed in the pancreas and code for

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**TABLE 1**

Mean values of selected characteristics of the study population by country, sex, and age-group

| Characteristic          | Denmark         | Estonia        |
|-------------------------|-----------------|----------------|
|                         | 9–11 years      | 14–16 years    | 9–11 years     | 14–16 years    |
| n                       | 409             | 177            | 234            | 257            |
| Age (years)             | 9.6             | 15.5           | 9.5            | 15.4           |
| Prepubertal children/Tanner 1 (%) | 96.7          | 0.0            | 91.5           | 0.0            |
| Pubertal children/Tanner 2–3 (%) | 3.3            | 6.0            | 8.6            | 8.6            |
| Pubertal children/Tanner 4–5 (%) | 0.0            | 94.0           | 0.0            | 91.4           |
| Fasting glucose (mmol/l) | 5.0             | 5.1            | 4.9            | 5.0            |
| Fasting insulin (pmol/l)* | 45.9           | 73.2           | 36.6           | 70.7           |
| HOMA-IR*                | 1.7             | 2.8            | 1.3            | 2.6            |
| HOMA-B*                 | 101.7           | 144.7          | 90.0           | 164.0          |
| Triglycerides (mmol/l)  | 0.83            | 1.04           | 0.77           | 0.85           |
| HDL cholesterol (mmol/l)| 1.49            | 1.40           | 1.44           | 1.45           |
| LDL cholesterol (mmol/l)| 2.68            | 2.45           | 2.71           | 2.56           |
| Systolic blood pressure (mmHg) | 101.5         | 108.8          | 100.0          | 107.3          |
| Diastolic blood pressure (mmHg) | 60.8           | 64.1           | 59.1           | 64.1           |
| Height (cm)             | 139.5           | 165.9          | 137.3          | 164.9          |
| Weight (kg)             | 34.0            | 57.5           | 31.4           | 55.4           |
| BMI (kg/m²)             | 17.4            | 20.9           | 16.6           | 20.3           |
| Sum of skin-fold measurements (cm) | 40.1          | 53.2           | 31.5           | 44.3           |

*Data are median values.
| Gene         | SNP       | Non-risk allele (1) | Risk allele (2)† | Risk allele frequency (HapMap) | Risk allele frequency (EYHS) | Mean Glucose | β-coefficient (95% CI) | P‡ | P§ |
|-------------|-----------|---------------------|------------------|--------------------------------|-----------------------------|--------------|-----------------------|-----|-----|
| G6PC2       | rs560887  | T                   | C                | 0.70                           | 0.70                        | 4.95         | 5.04                  | 5.12 | 0.084 (0.06-0.11)    | 7.98 x 10^{-11} | 6.73 x 10^{-11} |
| MTNR1B      | rs10830963| C                   | G                | 0.30                           | 0.29                        | 5.03         | 5.10                  | 5.13 | 0.000 (0.04-0.09)    | 1.90 x 10^{-7}  | 1.93 x 10^{-7}  |
| GCK         | rs4607517 | G                   | A                | 0.20                           | 0.14                        | 5.06         | 5.10                  | 5.10 | 0.028 (-0.006 to 0.06) | 0.11               | 0.11             |
| SLC30A8     | rs13266364| T                   | C                | 0.75                           | 0.67                        | 5.05         | 5.04                  | 5.10 | 0.033 (0.01-0.06)    | 0.01               | 0.01             |
| CDKAL1      | rs77569922| A                   | G                | 0.25                           | 0.30                        | 5.05         | 5.09                  | 5.07 | 0.024 (-0.002 to 0.05) | 0.07               | 0.07             |
|             | rs10946403| A                   | G                | 0.15                           | 0.18                        | 5.05         | 5.11                  | 5.03 | 0.029 (-0.002 to 0.06) | 0.07               | 0.06             |
|             | rs10946338| A                   | C                | 0.31                           | 0.34                        | 5.06         | 5.08                  | 5.09 | 0.019 (-0.01 to 0.04) | 0.14               | 0.14             |
| CDKN2A/B    | rs1063192 | G                   | A                | 0.60                           | 0.54                        | 5.05         | 5.08                  | 5.06 | 0.003 (-0.02 to 0.03) | 0.81               | 0.82             |
|             | rs10811661| C                   | T                | 0.79                           | 0.84                        | 5.06         | 5.07                  | 5.07 | 0.002 (-0.03 to 0.03) | 0.92               | 0.93             |
|             | rs11705729| T                   | A                | 0.71                           | 0.55                        | 5.09         | 5.05                  | 5.09 | 8.11 x 10^{-5} (-0.02 to 0.02) | 1.00               | 0.99             |
| Chr 11p12   | rs1828390 | T                   | C                | 0.12                           | 0.10                        | 5.07         | 5.05                  | 5.03 | -0.033 (-0.07 to 0.01) | 0.09               | 0.09             |
| HHEX-IDE    | rs5015480 | T                   | C                | 0.57                           | 0.61                        | 5.10         | 5.06                  | 5.06 | -0.014 (-0.04 to 0.01) | 0.26               | 0.26             |

*Alleles are annotated according to the positive strand (NCBI35). †Allele associated with higher glucose and/or risk of diabetes in previously published GWA studies. ‡Adjusted for country, age, sex, and biochemistry laboratory. §Additionally adjusted for BMI.

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| Gene         | SNP       | Non-risk allele (1) | Risk allele (2)† | Risk allele frequency (HapMap) | Risk allele frequency (EYHS) | Median HOMA-B¶ | β-coefficient (95% CI) | P‡ | P§ |
|-------------|-----------|---------------------|------------------|--------------------------------|-----------------------------|--------------|-----------------------|-----|-----|
| G6PC2       | rs560887  | T                   | C                | 0.70                           | 0.70                        | 109.19       | 107.35                | 98.25 | -0.09 (-0.13 to 0.04) | 9.38 x 10^{-5}  | 3.53 x 10^{-4}  |
| MTNR1B      | rs10830963| C                   | G                | 0.30                           | 0.29                        | 108.10       | 98.80                | 103.33 | -0.07 (-0.12 to -0.02) | 0.004              | 0.003           |
| GCK         | rs4607517 | G                   | A                | 0.20                           | 0.14                        | 104.92       | 101.47              | 80.49  | -0.03 (-0.10 to 0.04)  | 0.04                | 0.01            |
| SLC30A8     | rs13266364| T                   | C                | 0.75                           | 0.67                        | 103.97       | 105.11              | 101.67 | -0.04 (-0.08 to 0.01)  | 0.39                | 0.39            |
| CDKAL1      | rs77569922| A                   | G                | 0.25                           | 0.30                        | 105.92       | 103.33              | 96.87 | -0.07 (-0.12 to -0.02) | 0.002               | 0.002           |
|             | rs10946403| A                   | G                | 0.15                           | 0.18                        | 104.45       | 100.54              | 110.22 | -0.03 (-0.09 to 0.02)  | 0.03                | 0.03            |
|             | rs10946398| A                   | C                | 0.31                           | 0.34                        | 105.16       | 102.19              | 103.33 | -0.07 (-0.11 to -0.02) | 0.02                | 0.02            |
| CDKN2A/B    | rs1063192 | G                   | A                | 0.60                           | 0.54                        | 105.31       | 101.54              | 106.43 | -0.004 (-0.05 to 0.04) | 0.28                | 0.16            |
|             | rs10811661| C                   | T                | 0.79                           | 0.84                        | 89.31        | 104.52              | 104.16 | 0.02 (-0.04 to 0.08)   | 0.80                | 0.96            |
|             | rs11705729| T                   | A                | 0.71                           | 0.55                        | 105.51       | 101.74              | 105.08 | 0.005 (-0.04 to 0.05)  | 0.43                | 0.51            |
| Chr 11p12   | rs1828390 | T                   | C                | 0.12                           | 0.10                        | 103.33       | 101.78              | 82.09  | 0.06 (-0.02 to 0.13)   | 0.68                | 0.70            |
| HHEX-IDE    | rs5015480 | T                   | C                | 0.57                           | 0.61                        | 106.78       | 100.56              | 106.12 | 0.02 (-0.02 to 0.07)   | 0.24                | 0.22            |

*Alleles are annotated according to the positive strand (NCBI35). †Allele associated with higher glucose and/or risk of diabetes in previously published GWA studies. ‡Adjusted for country, age, sex, and biochemistry laboratory. §Additionally adjusted for BMI. ¶Median untransformed HOMA-B levels; adjusted regression analyses are based on log-normalized HOMA-B (β, P values).
proteins that play an important role for the regulation of glucose levels. MTNR1B is a less obvious candidate, and expression of MTNR1B in pancreatic β-cells and the role of MTNR1B risk alleles for impaired insulin secretion has only recently been identified (8).

Importantly, adjustment for BMI or skin-fold thickness did not alter the observed associations, and our findings thus demonstrate that the effects of genetic variants contributing to elevated levels of fasting glucose are present from an early age and can help to identify children at different levels of β-cell function, independent of their level of adiposity. We provide epidemiological evidence for common genetic variants contributing to variation in the human homeostatic set point for blood glucose levels from an early age, which may or may not translate into clinically significant differences and longer term complications related to chronic hyperglycemia.

In contrast, SLC30A8 was the only type 2 diabetes locus investigated that was found to be associated with variations in fasting glucose in children, with an effect that did not follow a clear linear trend/additive model and did not influence levels of HOMA-B. SLC30A8 encodes a zinc transporter involved in insulin secretion by the β-cell (2) and has previously been shown to be associated with fasting glucose levels in healthy adults (3) but not children. Studies of adults have likewise shown an effect of SLC30A8 (3,23) and also HHEX (23,24) and CDKAL1 (24) on β-cell function assessed by HOMA-B (3) as well as oral glucose tolerance test or hyperinsulinemic-euglycemic clamp (23,24) measures. In children, CDKAL1 was the only locus significantly associated with HOMA-B, and future studies including a larger number of children may be able to detect significant effects for loci of smaller effect sizes.

We did not observe any associations with fasting insulin or HOMA-IR, consistent with previous studies in adults that showed little or no association between glucose or type 2 diabetes–susceptibility genes with insulin levels or insulin resistance (3,7,23,24), pointing toward β-cell function rather than insulin action underlying the higher glucose levels and risk of type 2 diabetes caused by variants identified in recent GWA studies (8,25). It is important to consider the clinical and public health implications of such interindividual differences in fasting glucose among normoglycemic individuals. Elevated adult glucose concentration per se is a strong predictor of future type 2 diabetes (26), and Morrison et al. (27) have shown that the presence of impaired fasting glucose in girls of Caucasian and African descent aged 9–10 years is associated with an increased risk of type 2 diabetes 1 decade later. Higher levels of fasting glucose have been linked to an increased risk of coronary heart disease in healthy individuals and those with type 2 diabetes (28,29), but the strength of this association in the non-diabetic glucose range is a matter of debate (30). Whether early differences in fasting glucose levels due to genetic susceptibility translate into an increased risk of type 2 diabetes and related metabolic and cardiovascular disorders and whether or how these are modified by environmental risk factors remain to be investigated.

Children included in this study were randomly selected by age to broadly represent groups before and after entering puberty. Although we found no evidence for differences in the observed associations by age, sex, or country, one exception is noteworthy. The MTNR1B variant, recently associated with fasting glucose in adults (7) and located in a gene coding for one of the two known human melatonin receptors (31), displayed a significantly stronger effect on fasting glucose—and to a somewhat lesser degree on HOMA-B—in older or pubertal children compared with younger or prepubertal children. The MTNR1B gene is expressed in β-cells in both human and rodent islets, and the translated receptor is thought to mediate the inhibitory effect of melatonin on insulin secretion (8,32). During puberty, children go through a transient state of relative insulin resistance (12,14,33). Although our cross-sectional epidemiological findings do not allow strong causal or temporal inference, they may point toward the effect of MTNR1B on β-cell function being more pronounced in the context of insulin resistance and increased secretory demand. The recent observation that the increased expression of MTNR1B in G-allele carriers of rs10830963 was greater in older individuals than those <45 years of age (8) lends some support to this hypothesis.

We conclude that effects of genetic variants contributing to differences in fasting glucose and β-cell function are apparent at early ages. Although the strength of each
individual association appears to be of limited clinical significance, joint additive effects are substantial, amounting to a difference in 1 SD in fasting glucose in healthy children. Ongoing efforts in the identification of novel fasting glucose genes will help develop more comprehensive genetic risk scores that can identify a larger proportion of children with elevated fasting glucose levels and decreased β-cell function and provide useful tools for future studies of the longer-term consequences of chronic elevations in fasting glucose, as well as opportunities for targeted prevention of diabetes.

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