Association of Genetic Loci With Glucose Levels in Childhood and Adolescence

A Meta-Analysis of Over 6,000 Children

Adam Barker, 1 Stephen J. Sharp, 1 Nicholas J. Timpson, 2,3 Nabila Bouatia-Naji, 4,5 Nicole M. Warrington, 6 Stavroula Kanoni, 7,8 Lawrence J. Bellin, 9 Soren Brage, 1 Panos Deloukas, 8 David M. Evans, 2,3 Anders Grøntved, 10 Neelam Hassanali, 11 Deborah A. Lawlor, 2,3 Cecile Lecoeur, 4,5 Ruth J.F. Loos, 1 Stephen J. Lye, 12 Mark I. McCarthy, 1,13 Trevor A. Mori, 9 Ndeye Coumba Ndaiye, 14 John P. Newnham, 6 Ioanna Natella, 7 Craig E. Pennell, 6 Beate St Pourcain, 3,15 Inga Prokopenko, 11,13 Susan M. Ring, 3,15 Naveed Sattar, 16 Sophie Visvikis-Siest, 14 George V. Dedoussis, 7 Lyle J. Palmer, 17 Philippe Froguel, 4,5,18 George Davey Smith, 2,3 Ulf Ekelund, 18 Nicholas J. Wareham, 1 and Claudia Langenberg 1

OBJECTIVE—To investigate whether associations of common genetic variants recently identified for fasting glucose or insulin levels in nondiabetic adults are detectable in healthy children and adolescents.

RESEARCH DESIGN AND METHODS—A total of 16 single nucleotide polymorphisms (SNPs) associated with fasting glucose were genotyped in six studies of children and adolescents of European origin, including over 6,000 boys and girls aged 9–16 years. We performed meta-analyses to test associations of individual SNPs and a weighted risk score of the 16 loci with fasting glucose.

RESULTS—Nine loci were associated with glucose levels in healthy children and adolescents, with four of these associations reported in previous studies and five reported here for the first time (GLIS3, PROX1, SLC2A2, ADCY5, and CRY2). Effect sizes were similar to those in adults, suggesting age-independent effects of these fasting glucose loci. Children and adolescents carrying glucose-raising alleles of G6PC2, MTNR1B, GCK, and GLIS3 also showed reduced β-cell function, as indicated by homeostasis model assessment of β-cell function. Analysis using a weighted risk score showed an increase [β (95% CI)] in fasting glucose level of 0.026 mmol/L (0.021–0.031) for each unit increase in the score.

CONCLUSIONS—Novel fasting glucose loci identified in genome-wide association studies of adults are associated with altered fasting glucose levels in healthy children and adolescents with effect sizes comparable to adults. In nondiabetic adults, fasting glucose changes little over time, and our results suggest that age-independent effects of fasting glucose loci contribute to long-term interindividual differences in glucose levels from childhood onwards.

Fast ing glucose levels in humans are tightly regulated within a narrow homeostatic range; elevated glucose levels are a sign of reduced insulin secretion or action and are used to test for and diagnose type 2 diabetes. Elevated fasting glucose levels within the normal nondiabetic range predict future risk of diabetes (1,2) and are associated with incident cardiovascular disease in nondiabetic individuals (3).

Previous studies suggested that fasting glucose levels are heritable (4–7), with estimates from twin studies ranging from 38 to 51%. Since 2006, a total of 16 genetic loci have been identified to be associated with fasting glucose levels in healthy adults (8–12). Longitudinal cohort studies with multiple repeated measures of fasting glucose have shown that trajectories of fasting glucose show only modest increases over time in nondiabetic individuals (13), suggesting that variation in fasting glucose is largely unaffected by age-related changes in risk factors in healthy populations and that genetic factors may be key determinants of long-term interindividual differences in fasting glucose levels. This raises the question whether the genetic contribution to population differences in fasting glucose is established early in life and evident in childhood.

We have previously shown associations between genetic variants in MTNR1B, G6PC2, and SLC30A8 and fasting glucose in children and adolescents from the European Youth Heart Study (EYHS), with additional evidence from Weedon et al. reporting that common variation in GCK is
**RESEARCH DESIGN AND METHODS**

We designed this study to meta-analyze results from over 6,000 children and adolescents from European (ALSPAC, EYHS, GENDAI, Raine, and Australian (Raine) studies. Children and adolescents of European descent without a personal history of diabetes and with fasting glucose levels via effects on the glucose-sensing ability of pancreatic beta-cells contributed by each study are included in Supplementary Data (Table 1). The earliest identified genetic loci and glucose levels in children are associated with fasting glucose in children from the recent genome-wide association studies (GWASs) performed by different criteria to exclude low-quality samples and SNPs before imputation; full details of the methods and materials are provided in Supplementary Table 1. EYHS and Raine studies provided de novo genotyping results; French case and control sub-studies, and those of similar age, were included in silico data. Studies used slightly different study-specific exclusions, and the number of children and/or adolescents contributed by each study are included in Supplementary Data (Table 1).

**Statistical analysis.** In each study, effect alleles were defined as the allele that is associated with lower glucose or insulin concentration. Differences in genotype frequencies at SNPs were tested with the chi-square test (Supplementary Table 1). The strength of association between genotype and phenotype was estimated by effect size using natural log-transformed fasting insulin, HOMA-B, and HOMA-IR were used to estimate insulin resistance concentration was measured using immunoassays (Supplementary Table 1). Analysis of variance (ANOVA) or analysis of covariance (ANCOVA) was used to compare group means and adjusted for potential confounding factors, as detailed in Supplementary Table 1.

**TABLE 1**

| Study | ALSPAC | EYHS | French obese case subjects | French control subjects | GENDAI | Raine |
|-------|--------|------|---------------------------|-------------------------|--------|-------|
|       | Males  | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males | Females |
| n     | 894    | 860    | 927   | 1077    | 263   | 320    | 310   | 324    | 491   | 556    | 549   | 502    |
| Age (years) | 15.4 (0.3) | 15.4 (0.3) | 11.9 (2.9) | 12.0 (2.9) | 11.2 (2.9) | 10.8 (3.4) | 11.9 (2.4) | 11.9 (2.2) | 11.2 (0.7) | 11.2 (0.7) | 14.1 (0.2) | 14.1 (0.2) |
| Fasting glucose (mmol/L) | 5.3 (0.4) | 5.1 (0.4) | 5.1 (0.4) | 5.0 (0.4) | 4.9 (0.5) | 4.9 (0.5) | 4.9 (0.4) | 4.9 (0.4) | 4.8 (0.5) | 4.7 (0.5) | 4.9 (0.4) | 4.7 (0.4) |
| Triglycerides (mmol/L) | 0.8 (0.4) | 0.9 (0.3) | 0.78 (0.3) | 0.9 (0.4) | 1.1 (0.6) | 1.1 (0.6) | 0.7 (0.4) | 0.8 (0.4) | 0.7 (0.3) | 0.7 (0.2) | 1.0 (0.7) | 1.0 (0.5) |
| HDL (mmol/L) | 1.2 (0.3) | 1.3 (0.3) | 1.5 (0.4) | 1.5 (0.3) | 1.2 (0.3) | 1.2 (0.3) | 1.4 (0.4) | 1.4 (0.3) | 1.4 (0.3) | 1.3 (0.3) | 1.4 (0.3) | 1.4 (0.3) |
| LDL (mmol/L) | 2.0 (0.5) | 2.2 (0.6) | 2.5 (0.6) | 2.6 (0.7) | 2.7 (0.7) | 2.8 (0.7) | 2.9 (0.8) | 3.1 (0.7) | 3.2 (0.6) | 3.1 (0.6) | 2.3 (0.6) | 2.4 (0.7) |
| Systolic blood pressure (mmHg) | 125.8 (10.4) | 121.1 (10.7) | 107.8 (11.8) | 103.8 (9.5) | 115.5 (15.5) | 112.2 (13.9) | 111.2 (10.5) | 108.8 (8.8) | 120.2 (13.5) | 120.2 (14.1) | 116.0 (11.1) | 111.0 (10.0) |
| Diastolic blood pressure (mmHg) | 68.1 (9.2) | 66.8 (8.2) | 61.3 (7.1) | 61.7 (6.7) | 69.2 (11.7) | 67.9 (11.6) | 55.2 (10.0) | 55.0 (10.3) | 75.1 (11.2) | 74.9 (10.9) | 59.2 (7.2) | 59.4 (7.8) |
| Height (cm) | 174.0 (7.5) | 165.0 (6.0) | 152.3 (18.5) | 149.4 (14.6) | 155.1 (16.8) | 149.1 (16.5) | 150.1 (15.0) | 149.3 (12.5) | 148.7 (7.9) | 148.7 (7.5) | 166.7 (8.8) | 162.6 (6.1) |
| Weight (kg) | 63.7 (11.8) | 59.3 (11.0) | 44.3 (16.2) | 42.4 (13.6) | 74.4 (28.1) | 68.1 (26.3) | 40.4 (12.3) | 40.2 (10.6) | 44.6 (9.7) | 44.3 (9.8) | 59.4 (14.5) | 57.9 (12.1) |
| BMI (kg/m²) | 20.9 (3.3) | 21.7 (3.7) | 18.4 (2.8) | 18.5 (3.1) | 29.9 (6.4) | 29.4 (6.6) | 17.5 (2.2) | 17.7 (2.5) | 20.3 (3.4) | 19.8 (3.4) | 21.2 (4.2) | 21.9 (4.2) |

*Medians (IQR) are provided.
which is defined as the percentage of the total variation across studies due to heterogeneity between studies. Effect alleles of proxy SNPs were coded according to the effect allele frequency of the lead SNP. Highest probability to heterogeneity between studies. Effect alleles of proxy SNPs were coded (rs11708067), (rs790094), (rs4607517), (rs780094) in GCKR with both of these traits. We observed no associations between any of the variants investigated in this study and fasting insulin or HOMA-IR in children or adolescents (all P values > 0.12). In addition, the associations for the two insulin/HOMA-IR loci were shown to be of much smaller size for GCKR in comparison with the adult study and have inconsistent directions across studies for IGF1.

The weighted risk score including all variants investigated for association with fasting glucose in the current study followed a normal distribution, with a mean score (range) of 17.4 (7.2–27.5). Fasting glucose levels increased by 0.026 mmol/L (0.021–0.031) (P = 5.6 × 10^−25) for each unit increase in the score (Fig. 2). Comparison of children and adolescents at low (score ≤12) versus high (score ≥23) genetic susceptibility showed a difference of 0.25 mmol/L between these groups.

Effect sizes for fasting glucose associations in children, adolescents, and adults appeared to be similar for all loci with the exception of DGKB, GCKR, and TCF7L2, which showed smaller point estimates in children. Effect sizes for ADRARA2 and SLC2A2 also suggested heterogeneity between adults, adolescents, and children, but these differences were not statistically significant (Fig. 1 and Supplementary Table 3).

Comparison of results for the weighted genetic risk score in children and adolescents with the same risk score in adults on the basis of the Framingham Heart Study showed a difference (mean [95% CI]) of 0.34 mmol/L (0.25–0.43) in fasting glucose between adults with a score of ≤12 and those with a score ≥23 (8) compared with children and adolescents who showed a difference of 0.25 mmol/L (0.15–0.35) for the same groups; this mean difference was not significantly different between adults and children (P = 0.19). There was also no significant difference between the genetic scores if the weights used in the children and adolescent analysis were calculated using replication effect sizes from the MAGIC GWAS in adults.

The MAGIC study of adults used data from replication cohorts to investigate the proportion of variance in fasting glucose explained by the 14 fasting glucose–associated loci with replication data (all fasting glucose loci except for those on TCF7L2 and SLC30A8) and found an R^2 value ranging from 3.2 to 4.4% in the six replication studies used in their analysis. In the current study, the 14 fasting glucose–associated loci investigated in the MAGIC study of adults had an R^2 value of 4.3% (5.1% including TCF7L2 and SLC30A8) in the EYHS study sample, consistent with the estimates from adult study samples.

We observed little heterogeneity for fasting glucose associations between studies (Supplementary Table 2), with the exception of rs10830963 in MTNR1B and rs4607517 in GCK, which displayed an appreciable level of heterogeneity visible in forest plots and indicated by I^2 values of 72.4 and 30.3%, respectively. Meta-regression analyses showed that differences in mean age between studies explained the majority of the heterogeneity in the analysis for MTNR1B. In studies where the mean age of children was <12 years, the association between MTNR1B and fasting glucose was 0.040 (0.018–0.062) (β per allele).
[95% CI]), whereas in children and adolescents ≥12 years of age, the association was 0.106 (0.067–0.146).

None of the factors considered in the meta-regression (age, fasting glucose levels, BMI, proportion of boys in the study sample) explained an appreciable amount of heterogeneity observed for GCK, with only 5.5% of the between-study variance explained.
DISCUSSION

Novel loci recently identified to be associated with fasting glucose in adults have an important contribution to differences in fasting glucose levels from an early age. Using data from over 6,000 children and adolescents, we show that variants identified by their association with fasting glucose in adults are associated with fasting glucose levels in children and adolescents with substantial additive effects. As in studies of adults, associations of variants with fasting glucose in children and adolescents appear to be mediated via reduced β-cell function rather than insulin sensitivity, with associations being independent of obesity levels.

Effect sizes in adults, adolescents, and children did not differ in magnitude for the majority of glucose variants, suggesting that genetically determined population differences in fasting glucose are not only present at an early age, but are maintained and constant over time.

The reason for effect estimates of ADRA2A, DGKB, GCKR, and TCF7L2 being somewhat smaller in children and adolescents is unclear. It is possible that associations of these variants with glucose increase with age. However, longitudinal analyses of repeated measures of fasting glucose in nondiabetic adults do not provide evidence to support this, as reported in a recent article that found no differences in the effect sizes of these variants over time (24).

**Determinants of fasting glucose trajectories in non-diabetic individuals.** The results of our meta-analysis of fasting glucose levels in children and adolescents and our comparison with effect sizes in adults indirectly support previous studies investigating fasting glucose trajectories over time in nondiabetic individuals. Trajectories of fasting glucose in nondiabetic individuals show only modest increases over time (13), suggesting that age-related changes in risk factors have little influence on fasting glucose levels in these individuals, and similar effect sizes in children, adolescents, and adults for the majority of established fasting glucose loci also point toward the associations of fasting glucose loci being age independent, a property that has not been previously reported. This study supports a model in which genetic variants have an important contribution to fasting glucose levels from an early age with differences in the normal fasting glucose range between individuals being partly determined by the constellation of variants inherited, with each person having a specific fasting glucose "set point" that results from the combined effects of multiple fasting glucose loci behaving in an additive manner. Although age-related risk factors (e.g., BMI) contribute to variance in fasting glucose at a cross-sectional level, because of the time-independency displayed by fasting glucose loci and the lack of effect of age-related risk factor changes on fasting glucose levels, genetic population differences in fasting glucose are maintained long term over the course of a lifetime.

**Investigation of heterogeneity.** Our meta-regression analyses suggested that the between-study heterogeneity observed for the MTNRIIB SNP is largely explained by differences in the age distribution between these studies of children and adolescents. This result is consistent with our previous result that the influence of MTNRIIB on glucose levels shows interaction with pubertal stage (14), possibly resulting from the transient period of insulin resistance that occurs during puberty (25) and indicating the effects of the MTNRIIB variant may be greater in the context of greater insulin secretory demand. Importantly, the range of effect sizes observed at various stages of puberty is consistent with the effect size observed in adults.

It has not yet been investigated whether effects of MTNRIIB are also more pronounced in risk allele–carrying adults exposed to chronically increased secretory demand and at higher risk for type 2 diabetes; for example, in the
context of obesity and insulin resistance. However, the current data suggest that at least in children and adolescents, the effect of MTNR1B does not differ by BMI, with both meta-regression analysis and visual inspection of effect sizes suggesting no difference in effect size in studies of children and adolescents with different mean BMI.

**Strengths and limitations.** This is the first study to demonstrate that the majority of novel fasting glucose loci identified in GWASs of adults are detectable in childhood and with effect sizes comparable to those reported in replication studies of adults. We used a diverse selection of study samples including “hypernormal” control children in addition to obese case subjects increasing the generalizability of results and underlining the fact that associations of the established fasting glucose loci are independent of obesity levels. Previous studies of children and adolescents investigating fasting glucose loci were based on relatively small sample sizes. Single studies are mostly underpowered to detect associations for all but earliest reported GWAS variants displaying the largest effect sizes, also demonstrated by individual study results included in our meta-analysis. In the current study, we have overcome the problem of false-negative replication results by meta-analyzing a total of six studies including >6,000 children and adolescents, constituting the largest study of fasting glucose–associated loci in children and adolescents to date.

The original MAGIC GWASs showed associations with β-cell function, as measured by HOMA-B, for at least 10 of the 16 fasting glucose variants (8), and subsequent more detailed physiological characterization confirmed defects in insulin processing and/or insulin secretion for fasting glucose, raising alleles in or near TCFTL2, SCL30A8, C2CD4B, MTNR1B, GCK, FADS1, DGBP, and PROX1 (26). The fasting glucose-raising allele of MADD was associated with abnormal insulin processing, with no association with insulin secretion, whereas the fasting glucose-raising allele of rs5068887 in G6PC2 was associated with greater insulin secretion (26). In the current study, we show inverse associations of fasting glucose-raising alleles of G6PC2, MTNR1B, GCK, and GLIS3 with HOMA-B (and potentially weaker associations for ADCY5 and PROX1), consistent with HOMA-B results in adults. Being restricted to investigation of a surrogate measure based on fasting glucose and insulin is a limitation of our study. More detailed characterization of β-cell function would be required to distinguish effects on insulin secretion from HOMA-B associations that simply exist by virtue of each variant’s fasting glucose link, as potentially the case for ADCY5 and GLIS3, which showed no associations with insulin processing, secretion, or sensitivity in adults (26). However, epidemiological measures of β-cell function or insulin secretion are invasive and require regular blood draws during an oral glucose tolerance test, not commonly performed in studies of children and adolescents.

An additional limitation is that the use of proxies or imputed SNPs for some of the variants may have lead to diluted effects, and, as such, the lack of association observed for some of the variants in this study may be due to potential measurement error or nondifferential misclassification of imputed SNPs.

**Public health implications.** The finding that the majority of fasting glucose loci have comparable effect sizes in adolescents, children, and adults demonstrates that genetically susceptible individuals are exposed to higher levels of glucose and their detrimental effects on the vasculature from an early age and raises the question about the clinical relevance of long-term small elevations in fasting glucose levels in normoglycemic individuals. Stable fasting hyperglycemia is observed in individuals with GCK maturity-onset diabetes of the young (MODY), a mono- genic form of diabetes caused by mutations in the GCK gene, and is maintained over the course of a lifetime (27), with many of these individuals showing no symptoms, suggesting that stable mild fasting hyperglycemia may not in itself be detrimental. However, differences in fasting glucose levels between extremes of the fasting glucose genetic susceptibility show a substantial effect size given the narrow physiological range of fasting glucose, which is similar to that seen in adults if one considers the different fasting glucose SDs in children, adolescents, and adults (0.35–0.53 mmol/L in the included studies of children and adolescents and 0.43–1.4 mmol/L in nondiabetic adults included in fasting glucose GWASs) (8). Fasting glucose levels within the normal range are associated with an increase in the risk of future type 2 diabetes (1,2), with a >50% increased risk estimated for the fasting glucose difference seen between extremes of the fasting glucose score in adults (8). For cardiovascular complications, a recent large meta-analysis suggested that elevations of fasting glucose <7 mmol/L in nondiabetic individuals carry a modestly elevated risk for coronary heart disease, with hazard ratios (95% CI) of 1.17 (1.08–1.26) and 1.11 (1.04–1.18) when comparing adults at levels of 6.1–7.0 and 5.6–6.1 mmol/L, respectively, to the reference group with low levels of 3.9–5.6 mmol/L (3). The degree to which early genetic differences in fasting glucose that remain stable throughout life translate into type 2 diabetes or its cardiovascular complications remains to be quantified. However, the availability of multiple SNPs associated with fasting glucose will allow assessment of the causal nature of associations between this trait with type 2 diabetes and cardiovascular disease using the Mendelian randomization approach.

In conclusion, novel fasting glucose loci identified in studies of adults are associated with fasting glucose levels in healthy children and adolescents with effect sizes comparable to adults for individual and combined SNP associations. In nondiabetic individuals, fasting glucose changes little over time, and our results suggest that age-independent associations of fasting glucose loci contribute to long-term interindividual differences in glucose levels from childhood onward. The mechanisms through which individuals that are genetically susceptible to higher fasting glucose throughout life are at increased risk for type 2 diabetes and the potentially associated risk of cardiovascular complications remain to be investigated.

**ACKNOWLEDGMENTS**

**ALSPAC.** The U.K. Medical Research Council (grant 74882), The Wellcome Trust (grant 076467), and the University of Bristol provided core support for ALSPAC. Funding for fasting glucose and insulin, and for D.A.L.’s contribution to this manuscript, was provided by the U.S. National Institutes of Health (NIH): National Institute of Diabetes and Digestive and Kidney Diseases (grant R01DK-077658). This publication is the work of the authors, and A.B. et al. will serve as guarantors for the contents of this article.

The authors are extremely grateful to all families who took part in the ALSPAC study. The authors thank the midwives for help with recruiting the families and the
The authors gratefully acknowledge the NH&MRC and their parents for their participation in the study. The investigators for samples and data collection and all children assisting of the Telethon Institute for Child Health Research (U.K.) and the Centre National de Genotypage (France) for generating the ALSpac GWA data.

**EYHS.** The EYHS was funded by grants from The Danish Heart Foundation; The Danish Medical Research Council Health Foundation; The Danish Council for Sports Research; The Foundation in Memory of Asta Florida Bolding Renée Andersen; The Faculty of Health Sciences, University of Southern Denmark; The Estonian Science Foundation (grants 3277 and 5209); and The Medical Research Council, U.K.

The authors are very grateful to all children participating in the EYHS and their families. The authors are also grateful for the contribution of all members of the EYHS Group and the MRC Epidemiology laboratory team. The authors acknowledge B. Heude for providing DNA samples of the lean children from the Fleurbaix-Laventie study. The authors are deeply grateful for the cooperation of the families participating in the STANISLAS cohort, and the authors thank the staff of the “Centre de Médecine Préventive” of Vandoeuvre-lès-Nancy (France) for their involvement in the recruitment of the STANISLAS cohort.

**GENDAI.** The work of I.P. was in part funded through the ENGAGE Consortium grant from the European Community’s Seventh Framework Programme (HEALTH-F4-2007-201413). Genotyping was supported in part by Diabete U.K. grant RD08/0003704.

The GENDAI investigators would like to thank all the field investigators for samples and data collection and all children and their parents for their participation in the study.

**Raine.** The authors gratefully acknowledge the NH&MRC for their long-term contribution to funding the study over the last 20 years and also the following institutions for providing funding for Core Management of the Raine study: The University of Western Australia (UWA); Raine Medical Research Foundation; UWA Faculty of Medicine, Dentistry and Health Sciences; The Telethon Institute for Child Health Research and Women and Infants Research Foundation. The authors gratefully acknowledge the assistance of the Western Australian DNA Bank (a national Health and Medical Research Council of Australia National Enabled Facility). The authors also acknowledge the support of the National Health and Medical Research Council of Australia (grant MOP-82893). The authors thank the assistance of the Telethon Institute for Child Health Research and the Raine Medical Research Foundation of the University of Western Australia.

The authors are grateful to the Raine study participants and their families and to the Raine study research staff for cohort coordination and data collection. No potential conflicts of interest relevant to this article were reported. A.B. wrote the initial draft of the manuscript, researched data, contributed to discussion, and reviewed and edited the manuscript. S.J.S., N.J.T., N.B.-N., N.M.W., and S.K. wrote sections of the manuscript, researched data, contributed to discussion, and reviewed and edited the manuscript. L.J.B., S.B., P.D., D.M.E., A.G., N.H., D.A.L., C.L., R.J.F.L., S.J.L., M.I.M., T.A.M., N.C.N., J.P.N., I.N., C.E.P., B.S.P., I.P., S.M.R., N.S., S.V.-S., G.V.D., L.J.P., P.F., G.D.S., and U.E. contributed to discussion and reviewed and edited the manuscript. N.J.W. and C.L. designed the study, wrote and edited the manuscript, contributed to discussion, and reviewed and edited the manuscript.

**REFERENCES**

1. Tiross A, Shai I, Teles-Manova D, et al. Normal fasting plasma glucose levels and type 2 diabetes in young men. N Engl J Med 2005;353:1454–1462.
2. Nichols GA, Hillier TA, Brown JB. Normal fasting plasma glucose and risk of type 2 diabetes diagnosis. Am J Med 2008;121:519–524.
3. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2237–2222.
4. Katoh S, Lehtovirta M, Kaprio J, et al. Genetic and environmental effects on fasting and postchallenge plasma glucose and serum insulin values in Finnish twins. J Clin Endocrinol Metab 2009;90:2642–2647.
5. Snieder H, Boomsma DI, van Doozen NL, Neale MC. Bivariate genetic analysis of fasting insulin and glucose levels. Genet Epidemiol 1999;16:426–446.
6. Schousboe K, Viesscher PM, Henriksson JE, Hopper JL, Sorensen TI, Kylvik KO. Twin study of genetic and environmental influences on glucose tolerance and indices of insulin sensitivity and secretion. Diabetologia 2003;46:1276–1283.
7. Leslie RD, Boyan H, Sawtell P, Boehm BO, Spector TD, Snieder H. Level of an advanced glycated end product is genetically determined: a study of normal twins. Diabetes 2003;52:2441–2444.
8. Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 2010;42:105–116.
9. Prokopenko I, Langenberg C, Florez JC, et al. Variants in MTNR1B influence fasting glucose levels. Nat Genet 2009;41:77–81.
10. Bouatia-Naji N, Bonnefond A, Cavalcanti-Proenca C, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet 2009;41:89–94.
11. Chambers JC, Zhang W, Zabaneh D, et al. Common genetic variation near the melatonin receptor MTNR1B contributes to raised plasma glucose and increased risk of type 2 diabetes among Indian Asians and European Caucasians. Diabetes 2009;58:2703–2708.
12. Bouatia-Naji N, Rocheleau G, Van Lomme L, et al. A polymorphism within the G6PC2 gene is associated with fasting plasma glucose levels. Science 2008;320:1085–1088.
13. Andres R, Tobin JD. Aging and the disposition of glucose. Adv Exp Med Biol 1975;61:239–249.
14. Kelliny C, Ekemul U, Anderson LB, et al. Common genetic determinants of glucose homeostasis in healthy children: the European Youth Heart Study. Diabetes 2008;57:2909–2915.
15. Weeden MN, Clark VJ, Qian Y, et al. A common haplotype of the glucokinase gene alters fasting glucose and birth weight: association in six studies and population-genetics analyses. Am J Hum Genet 2006;79:991–1001.
16. Sparso T, Andersen G, Nielsen T, et al. The GCKR rs780094 polymorphism is associated with elevated fasting serum triacylglycerol, reduced fasting and OGTT-related insulinemia, and reduced risk of type 2 diabetes. Diabetologia 2008;51:70–75.
17. Orho-Melander M, Melander O, Guiducci C, et al. Common variant in the glucokinase regulatory protein gene is associated with increased plasma triglyceride and C-reactive protein but lower fasting glucose concentrations. Diabetes 2008;57:3112–3121.
18. Chen WM, Erdos MR, Jackson AU, et al. Variations in the G6PC2/ABCB11 genomic region are associated with fasting glucose levels. J Clin Invest 2008;118:2620–2628.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
20. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. J Pediatr 2004;144:47–55
21. Li Y, Mach Abecasis GR. 1.0: Rapid haplotype reconstruction and missing genotype inference. Am J Hum Genet 2006;S79:2290
22. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. Nat Genet 2007;39:906–913
23. Stata Corp. Stata Statistical Software: Release 10. College Station, TX, StataCorp LP, 2007
24. Jensen AC. Genetic impact on glucose levels in a longitudinal study. In European Diabetes Epidemiology Group. Port Hel, Greece, EDEG, 2010
25. Lee JM. Insulin resistance in children and adolescents. Rev Endocr Metab Disord 2006;7:141–147
26. Ingelsson E, Langenberg C, Ilivert MF, et al. Detailed physiologic characterization reveals diverse mechanisms for novel genetic Loci regulating glucose and insulin metabolism in humans. Diabetes 2010;59:1266–1275
27. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus. Part 1: Diagnosis and Classification of Diabetes Mellitus. 1999