Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes

Ping An
Washington University School of Medicine in St. Louis

Aldi Kraja
Washington University School of Medicine in St. Louis

Michael A. Province
Washington University School of Medicine in St. Louis

Ingrid B. Borecki
Washington University School of Medicine in St. Louis

et al.

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation
https://digitalcommons.wustl.edu/open_access_pubs/4566

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact engeszer@wustl.edu.
Meta-Analysis of Genome-Wide Association Studies in African Americans Provides Insights into the Genetic Architecture of Type 2 Diabetes


1 Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America, 2 Center for Diabetes Research, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America, 3 Center for Research on Genomics and Global Health, National Human Genome Research Institute, Bethesda, Maryland, United States of America, 4 Program on Genomics and Nutrition, School of Public Health, University of California Los Angeles, Los Angeles, California, United States of America, 5 Center for Metabolic Disease Prevention, School of Public Health, University of California Los Angeles, Los Angeles, California, United States of America, 6 Center for Public Health Genomics, University of Virginia, Charlottesville, Virginia, United States of America, 7 Department of Public Health Sciences, University of Virginia, Charlottesville, Virginia, United States of America, 8 Institute for Translational Genomics and Population Sciences, Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, United States of America, 9 Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, United States of America, 10 Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, United States of America, 11 The GeneSTAR Research Program, Division of General Internal Medicine, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, 12 Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, United States of America, 13 Center for Public Health Genomics, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America, 14 Department of Bistatistics Sciences, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America, 15 Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States of America, 16 Cardiovascular Health Research Unit, University of Washington, Seattle, Washington, United States of America, 17 Department of Medicine, University of Washington, Seattle, Washington, United States of America, 18 San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, California, United States of America, 19 Department of Epidemiology and Biomedical Informatics, Emory University, Atlanta, Georgia, United States of America, 20 Division of Statistical Genomics, Washington University School of Medicine, St. Louis, Missouri, United States of America, 21 Division of Sleep Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, United States of America, 22 The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, 23 The Genetics of Obesity and Related Metabolic Traits Program, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, 24 Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America, 25 Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States of America, 26 Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America, 27 Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America, 28 Department of Biology, Center for Health Disparities, East Carolina University, Greenville, North Carolina, United States of America, 29 Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America, 30 Medical Genetics Research Institute, Cedars-Sinai Medical Center, Los Angeles, California, United States of America, 31 Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, United States of America, 32 Jackson State University, Tougaloo College, Jackson, Mississippi, United States of America, 33 Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America, 34 Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, United States of America, 35 Human Genetics Center, University of Texas Health Science Center at Houston, Houston, Texas, United States of America, 36 Division of Allergy and Clinical Immunology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, 37 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, 38 Laboratory of Personality and Cognition, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, United States of America, 39 Department of Epidemiology and Biostatistics, Case
Abstract

Type 2 diabetes (T2D) is more prevalent in African Americans than in Europeans. However, little is known about the genetic risk in African Americans despite the recent identification of more than 70 T2D loci primarily by genome-wide association studies (GWAS) in individuals of European ancestry. In order to investigate the genetic architecture of T2D in African Americans, the MEta-analysis of type 2 Diabetes in African Americans (MEDIA) Consortium examined 17 GWAS on T2D comprising 8,284 cases and 15,543 controls in African Americans in stage 1 analysis. Single nucleotide polymorphisms (SNPs) association analysis was conducted in each study under the additive model after adjustment for age, sex, study site, and principal components. Meta-analysis of approximately 2.6 million genotyped and imputed SNPs in all studies was conducted using an inverse variance-weighted fixed effect model. Replications were performed to follow up 21 loci in up to 6,061 controls in African Americans, and 8,130 cases and 38,987 controls of European ancestry. We identified three known loci (TCF7L2, HMG2A and KCNQ1) and two novel loci (HLA-B and INS-IGF2) at genome-wide significance (4.15 × 10^{-9} < P < 5 × 10^{-8}, odds ratio (OR) = 1.09 to 1.36). Fine-mapping revealed that 88 of 158 previously identified T2D or glucose homeostasis loci demonstrated nominal to highly significant association (2.2 × 10^{-5} < \text{locus-wide} \ P < 0.05). These novel and previously identified loci yielded a sibling relative risk of 1.19, explaining 17.5\% of the phenotypic variance of T2D on the liability scale in African Americans. Overall, this study identified two novel susceptibility loci for T2D in African Americans. A substantial number of previously reported loci are transferable to African Americans after accounting for linkage disequilibrium, enabling fine mapping of causal variants in trans-ethnic meta-analysis studies.
from the NIH National Cancer Institute (NCI) under contract N01-SC-12400 and the Intramural Research Program of the NIH-NCI Center for Cancer Research. This work also was supported by the National Center for Research Resources for the General Clinical Research Center grants: Case Western Reserve University, M01 RR000035; Wake Forest University, M01-RR-07122; Harbor-University of California, Los Angeles Medical Center, M01-RR-00425; College of Medicine, University of California, Irvine, M01-RR-00827-29; University of New Mexico, HSC, M01-RR-00997; and Frederic C. Bartter, M01-RR-01346. The CHOICE Study was supported in part by HS08365 from the Agency for Healthcare Research and Quality, NIH, and HL02985 from the National Heart, Lung, and Blood Institute, Bethesda, MD. Genetic Study of Atherosclerosis Risk (GENET) was supported by NIH grants HL078650, HL100245 and HL100185 from the National Heart, Lung, and Blood Institute. Healthy Aging in Neighborhoods of Diversity across the Life Span Study (HANDLS) was supported by the Intramural Research Program of the NIH, National Institute on Aging and the National Center on Minority Health and Health Disparities (project # 201-KG000513 and intramural protocol # 2009-1493). HealthAging Study (was supported by NIA contracts N01AG62161, N01AG62163, N01AG62106. The genome-wide association study was funded by NIA grant 1R01AG029308-01A1 to Wake Forest University Health Sciences and genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to the Johns Hopkins University, contract number HHSN26820072006C. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. Howard University Family Study (HUFS) was supported by National Institutes of Health grants S06GM00816-32017010 to CNR and S06GM00816- 32011-0001 SA. Patent enrollment was carried out at the Howard University General Clinical Research Center, supported by National Institutes of Health grant 2M01RR010284. The Charles Bronfman Institute for Personalized Medicine (IPM) BioBank Program is supported by The Andrea and Charles Bronfman Philanthropies, Insulin Resistance Atherosclerosis Study (IRAS) was supported by the National Heart, Lung, and Blood Institute (HL074887, HL074889, HL074890, HL7902). IRAS Family Study was supported by the National Heart, Lung, and Blood Institute (HLO6094, HLO6098, HLO61210). The Jackson Heart Study (JHS) is supported by contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, HHSN268201300050C from the National Heart, Lung, and Blood Institute and the National Center for Minority Health and Health Disparities. Multi-Ethnic Study of Atherosclerosis (MESA), MESA Family, and the MESA SHARE project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts N01-HC-95159 through N01-HC-95169 and UL1-RR-024156. Funding for MESA Family is provided by grants R01-HL-071051, R01-HL-071205, R01-HL-071250, R01-HL-071251, R01-HL-071252, R01-HL-071258, R01-HL-071259, and UL1-RR-025050. Funding for genotyping was provided by NHBLI Contract N02-HL-42278 and N01-HC-65226. NHBLI Air is funded by the EPA - Science to Achieve Results (STAR)Program Grant R8281367. The project described was supported by the National Center for Research Resources, Grant UL1RR033176, and is now at the National Center for Advancing Translational Sciences, Grant UL1TR000124. In Southern Community Cohort Study (SCCS), sample preparation was conducted at the Survey and Biospecimen Shared Resources, which is supported in part by Vanderbllng-滇湖 University, The Center of Excellence in Genetic Epidemiology (CEGE) is supported by U01 HG005029. In Seattle, the Inheritable Disease Network (SIGNET) - Reasons for Geographic And Racial Differences in Stroke (SIGNET-REGARDS), the REGARDS Study is supported by a cooperative agreement U01 NS041588 (PI George Howard) and SIGNET was supported at the Survey and Biospecimen Shared Resources. In the Wake Forest School of Medicine (WFSM), genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to the Johns Hopkins University, contract number HHSN26820072006C. The work at Wake Forest was supported by NIH grants K99 DK081350 (NDP), R01 DK066358 (DWB), R01 DG05591 (DWB), R01 HL56265 (BIF), R01 TO079491 (BIF) and by the General Clinical Research Center of the Wake Forest School of Medicine grant R01 DK066358. John Hopkins' Health Initiative (JHI) Program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01-WH-22110, 24152, 32100-2, 32105-6, 32108-9, 32113-13, 32115-32118, 32122, 42107-26, 42129-32, and 42231. Funding for WHI SHARE genotyping was provided by NHBLI Contract N02-HL-64278. BHC was funded by the Burroughs Wellcome Fund Inter-school Training Program in Genomic and Population Sciences and UCLA Genomic Analysis Training Program (NHGRI T32-HG002536). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: simin_liu@brown.edu (SL); rotmic@mail.nih.gov (CNR); dbowden@wakehealth.edu (DWB)

** These authors contributed equally to this work.

| SL, CNR and DWB are joint senior authors on this work.

$Membership$ of the FIND Consortium, the eMERGE Consortium, the DIAGRAM Consortium, and the MuTHER Consortium is provided in the Acknowledgments.

Introduction
The prevalence of type 2 diabetes (T2D) among adults in the USA is currently 11.3%, with substantially higher prevalence in African Americans (18.7%) than in European Americans (10.2%) [1]. To date, genome-wide association studies (GWAS) have identified >70 susceptibility loci for T2D [2-8]. While it is known that T2D is heritable in African Americans [9], it is unclear how much heritability is explained by the known genetic associations discovered primarily from European ancestry populations and whether there are risk loci specific to African Americans. Given that individuals of African ancestry tend to harbor more genetic diversity than individuals of other ancestries [10], we hypothesized that large-scale association analyses in African Americans could shed light on the genetic architecture of T2D and the risk attributable to cosmopolitan vs population-specific variants.

Results
Study overview
We conducted a meta-analysis of 17 African American GWAS on T2D comprising 28,834 cases and 15,543 controls (Tables S1 and S2). Missing genotypes in individual studies were imputed to one of the HapMap reference panels (Phase II release 21-24 CEU+YRI. Phase II release 22 all populations, Phase II-III release 27 CEU+YRI, Phase II+III release 27 CEU+YRI+ASW or Phase II-III release 27 all populations) using MACH, IMPUTE2 or BEAGLE (Table S3). Genomic control corrections [11] were applied to each study (λ = 1.01–1.08) and after meta-analysis (λ = 1.106) due to modest inflated association results (Table S3) [12]. Association results for ~2.6M SNPs were subsequently examined.

From stage 1 meta-analysis, 49 SNPs moderately associated with T2D (P<10^-3) and two candidate SNPs near the p value threshold (rs231356 at KCNQ1, P = 2.84 x 10^-3 and rs2244020 at HLA-B, P = 1.02 x 10^-3) totaling 51 SNPs in 21 loci were followed up for replication. rs231356 is 14 kb downstream of the reported T2D index SNP, rs231362, in Europeans [3]. Moderate associations have also been observed across the HLA region in Europeans [3]. The stage 2 replication included m silico and de novo replication in up to 11,544 African American T2D cases and controls, as well as in s silico replication in 47,117 individuals of European ancestry from DIAGRAMv2 [3] (Table S4). Meta-analyses were performed to combine results from African Americans (stage 1+2a, n=33,371, Table S4) and both African Americans and Europeans (stage 1+2a+2b, n=82,468, Table S4).

T2D loci reaching genome-wide significance
Five independent loci reached genome-wide significance (P< 5 x 10^-8). Stage 1 meta-analysis identified the established TCF7L2 locus. Stage 1+2a meta-analysis identified the established KCNQ1 and HMGA2 loci. Stage 1+2a+2b meta-analysis identified a second signal at KCNQ1 and a novel HLA-B locus. Secondary analysis including body mass index (BMI) adjustment in stage 1+2a meta-analysis identified the second novel locus at INS-IGF2 (Table 1 and Figure 1). None of the most strongly associated SNPs at these loci demonstrated significant heterogeneity of effect sizes among studies within each stage, between African Americans in Type 2 Diabetes GWAS in African Americans

| PLOS Genetics | www.plosgenetics.org 3 August 2014 | Volume 10 | Issue 8 | e1004517 |
Author Summary

Despite the higher prevalence of type 2 diabetes (T2D) in African Americans than in Europeans, recent genome-wide association studies (GWAS) were examined primarily in individuals of European ancestry. In this study, we performed meta-analysis of 17 GWAS in 8,284 cases and 15,543 controls to explore the genetic architecture of T2D in African Americans. Following replication in additional 6,061 cases and 5,483 controls in African Americans, and 8,130 cases and 38,987 controls of European ancestry, we identified two novel and three previous reported T2D loci reaching genome-wide significance. We also examined 158 loci previously reported to be associated with T2D or regulating glucose homeostasis. While 56% of these loci were shared between African Americans and the other populations, the strongest associations in African Americans are often found in nearby single nucleotide polymorphisms (SNPs) instead of the original SNPs reported in other populations due to differential genetic architecture across populations. Our results highlight the importance of performing genetic studies in non-European populations to fine map the causal genetic variants.

stages 1 and 2a, or between African Americans in stage 1+2a and Europeans in stage 2b after Bonferroni correction of multiple comparisons ($P_{corr}>0.001$) (Figure S1).

At the TCF7L2 locus, the most strongly associated SNP in stage 1+2a African Americans samples was rs7903146 (OR = 1.13, $P = 4.78 \times 10^{-44}$, Table 1 and Figure 2), rs7903146 is also the index SNP (most significantly associated with T2D in prior studies) in Europeans (OR = 1.40, $P = 2.21 \times 10^{-51}$) [3], South Asians (OR = 1.25, $P = 3.41 \times 10^{-15}$) [4] and East Asians (OR = 1.48, $P = 2.44 \times 10^{-15}$) [13].

Two association signals were observed at KCNQ1 (Table 1 and Figure 2). The first association signal was represented by rs2283228 located at the 3' end of KCNQ1 (stage 1+2a OR = 1.20, $P = 9.90 \times 10^{-11}$; stage 1+2a+2b OR = 1.19, $P = 4.87 \times 10^{-13}$). Using data from individuals of African ancestry in Southwest USA (ASW) from the 1000 Genomes Project (IKGP) [14], rs2283228 mapped to the same linkage disequilibrium (LD)-based interval as index SNPs from other populations (rs2283228 [15] and rs2237892 [16-17] in Japanese, rs2237892 in Hispanics [18], rs163182 [19] and rs2237895 [20] in Han Chinese). The second association signal was represented by rs231356 ($r^2 = 0$ with rs2283228 in both ASW and CEU) (stage 1+2a OR = 1.11, $P = 1.94 \times 10^{-5}$; stage 1+2a+2b OR = 1.09, $P = 3.93 \times 10^{-7}$), located 144 kb upstream of the first signal, rs231356 is located at the same LD interval as the index SNPs rs231362 in Europeans [3] and rs231359 in Chinese [20].

At the HMGAI4 locus, the most strongly associated SNP was rs343092 (stage 1+2a OR = 1.16, $P = 8.79 \times 10^{-5}$; stage 1+2a+2b OR = 1.14, $P = 2.75 \times 10^{-12}$, Table 1 and Figure 2), rs343092 is located 76 kb downstream and at the same LD interval as of the index SNP rs1531343 reported in Europeans [3].

Two novel T2D loci were identified. The effect sizes of rs2244020 located near HLA-B were similar in African Americans and Europeans (OR = 1.11 vs. 1.07, $P_{corr} = 0.26$; stage 1+2a+2b $P = 6.57 \times 10^{-4}$ (Table 1 and Figure 2). HLA-B encodes the class I major histocompatibility complex involved in antigen presentation in immune responses.

The most strongly associated SNP near INS-IGF2 was rs3842770 in African Americans (OR = 1.14, $P = 2.73 \times 10^{-5}$, stage 1+2a BMI adjusted, Table 1 and Figure 2) but the risk A allele was absent in the CEU population. Insulin plays a key role in glucose homeostasis. Mutations at INS lead to neonatal diabetes, type 1 diabetes, and hyperinsulinemia [21]. Insulin-like growth factor 2 (IGF2) is involved in growth and development. IGF2 overexpression in transgenic mice leads to islet hyperplasia [22] and IGF2 deficiency in the Goto-Kakizaki rat leads to beta cell mass anomaly [23].

Associations at previously reported T2D and glucose homeostasis loci

We investigated index SNPs from 158 independent loci associated with T2D and/or glucose homeostasis from prior genome-wide and candidate gene studies in individuals of European, East Asian, South Asian, or African American ancestry (Table S5). Among the 104 T2D-associated index SNPs, 19 were associated with T2D in stage 1 African American samples ($P < 0.05$). Most of the 17 T2D-associated SNPs that showed consistent direction of effects had similar effect sizes between this study and prior reports, despite that rs10448033 at CDKAL1 had substantially stronger effect size in Europeans (OR = 1.25) than in African Americans (OR = 1.06, $P_{corr} = 3.86 \times 10^{-6}$). Additionally, 3 out of 54 trait-increasing alleles from glucose homeostasis-associated index SNPs were associated with increased T2D risk in African Americans ($P < 0.05$).

We also performed a locus-wide analysis to test for associations of all SNPs within the LD region at $r^2 \geq 0.03$ with the previously reported index SNPs and results were corrected for the effective number of SNPs [24]. Since the causal variant(s) at each locus may be different or reside on different haplotypes across populations with different LD structures, this approach allows the identification of the most strongly associated SNPs in African Americans that may or may not be in LD with the index SNPs reported in other populations. A total of 55 T2D- and 29 glucose-associated loci were associated with T2D in African Americans ($P_{corr} < 0.05$, corrected for LD in ASW for SNPs within a locus; Table S6). We compared the genetic architecture between the previously reported index SNPs and our fine-mapped SNPs for these 84 loci. The respective average risk allele frequencies were 0.51 and 0.46, and the distributions or pairwise differences of risk allele frequencies were not significantly different ($P = 0.255$, Wilcoxon rank sum test; and $P = 0.295$, Wilcoxon signed-rank test, respectively, Figure S2). In contrast, the average odds ratios for the risk alleles were higher for the fine-mapped SNPs as compared to the index SNPs (1.14 vs. 1.05). The distributions and pairwise differences of risk allele odds ratios were significantly different ($P = 1.18 \times 10^{-14}$ and $5.55 \times 10^{-14}$, respectively, Figure S2). Thus, the locus-wide analysis identified variants with larger effect sizes and similar allele frequencies.

We leveraged differences in LD between African Americans and Europeans to fine-map and re-annotate several established loci. The association signal spanning ~100 kb at INTS8 in African Americans overlapped the ~200 kb TP53INP1 T2D locus in Europeans [3]. The most strongly associated SNP in MEDIA tended to have larger effect size in African Americans than in Europeans (rs17359493, OR = 1.13 vs. 1.06, $P = 1.39 \times 10^{-7}$ vs. $3.20 \times 10^{-5}$, respectively, $P_{corr} = 0.06$ (Table S4). However, rs17359493 at intron 10 of INTS8 was only in weak LD with the reported index SNP rs896854 in Europeans ($r^2 = 0.21$ in CEU, 0.10 in ASW). Neither the reported index SNP rs896854 nor its proxies from the CEU data demonstrated significant association to T2D in African Americans (Table S6 and Figure S3a,b), suggesting that rs17359493 may be an independent novel signal. INTS8 encodes a subunit of the integrator complex which is involved in the cleavage of small nuclear RNAs. At KCNQ1, the most strongly associated SNP rs231356 was in weak LD with the
Table 1. Novel and previously identified loci associated with T2D at $P<5 \times 10^{-8}$.

<table>
<thead>
<tr>
<th>Loci</th>
<th>Chr</th>
<th>Position (Build 36)</th>
<th>SNP</th>
<th>Alleles*</th>
<th>RAFb</th>
<th>OR (95% CI)</th>
<th>$P$</th>
<th>$P_{\text{het}}$</th>
<th>OR (95% CI)</th>
<th>$P$</th>
<th>$P_{\text{het}}$</th>
<th>OR (95% CI)</th>
<th>$P$</th>
<th>$P_{\text{het}}$</th>
<th>OR (95% CI)</th>
<th>$P$</th>
<th>$P_{\text{het}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previously identified T2D loci</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCF7L2</td>
<td>10</td>
<td>114748339</td>
<td>rs7903146</td>
<td>T/C</td>
<td>0.30</td>
<td>1.32 (1.25–1.4)</td>
<td>6.62E-24</td>
<td>1.81E-01</td>
<td>1.34 (1.26–1.43)</td>
<td>8.38E-20</td>
<td>6.01E-03</td>
<td>1.33 (1.28–1.39)</td>
<td>4.78E-44</td>
<td>7.34E-01</td>
<td>1.4 (1.34–1.46)</td>
<td>2.21E-51</td>
<td>1.36</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>11</td>
<td>2661919</td>
<td>rs231356</td>
<td>T/A</td>
<td>0.27</td>
<td>1.14 (1.07–1.21)</td>
<td>2.84E-05</td>
<td>9.11E-01</td>
<td>1.05 (0.98–1.14)</td>
<td>1.68E-01</td>
<td>3.26E-01</td>
<td>1.11 (1.06–1.16)</td>
<td>1.94E-05</td>
<td>1.08E-01</td>
<td>1.08 (1.04–1.13)</td>
<td>4.37E-04</td>
<td>1.09</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>11</td>
<td>2806106</td>
<td>rs2283228</td>
<td>A/C</td>
<td>0.89</td>
<td>1.22 (1.14–1.31)</td>
<td>6.10E-08</td>
<td>9.48E-02</td>
<td>1.17 (1.06–1.28)</td>
<td>1.04E-03</td>
<td>7.10E-01</td>
<td>1.2 (1.14–1.27)</td>
<td>9.90E-11</td>
<td>4.34E-01</td>
<td>9.75E-04 (1.06–1.26)</td>
<td>1.19 (1.13–1.24)</td>
<td>4.87E-13</td>
</tr>
<tr>
<td>HMGAl2</td>
<td>12</td>
<td>64537207</td>
<td>rs343092</td>
<td>T/G</td>
<td>0.81</td>
<td>1.16 (1.09–1.24)</td>
<td>1.91E-06</td>
<td>9.48E-01</td>
<td>1.15 (1.04–1.26)</td>
<td>3.99E-03</td>
<td>3.37E-01</td>
<td>1.16 (1.12–1.22)</td>
<td>8.79E-09</td>
<td>7.93E-01</td>
<td>1.12 (1.06–1.19)</td>
<td>5.43E-05</td>
<td>1.14</td>
</tr>
<tr>
<td><strong>Newly identified T2D loci</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B</td>
<td>6</td>
<td>31455430</td>
<td>rs2244020</td>
<td>G/A</td>
<td>0.69</td>
<td>1.12 (1.06–1.17)</td>
<td>1.02E-05</td>
<td>2.11E-02</td>
<td>1.1 (0.98–1.22)</td>
<td>1.01E-01</td>
<td>1</td>
<td>1 (1.07–1.16)</td>
<td>1.14E-06</td>
<td>7.57E-01</td>
<td>1.07 (1.03–1.12)</td>
<td>7.67E-04</td>
<td>1.09</td>
</tr>
<tr>
<td>INS-IGF2</td>
<td>11</td>
<td>2135246</td>
<td>rs3842770</td>
<td>A/G</td>
<td>0.23</td>
<td>1.18 (1.11–1.25)</td>
<td>8.18E-08</td>
<td>7.16E-01</td>
<td>1.07 (0.99–1.16)</td>
<td>8.09E-02</td>
<td>7.16E-01</td>
<td>1.14 (1.09–1.19)</td>
<td>2.78E-08</td>
<td>7.37E-02</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Chr, chromosome; SNP, single nucleotide polymorphism; RAF, risk allele frequency; OR, odds ratio for risk allele; CI, confidence interval; $P_{\text{het}}$, heterogeneity $P$ value.

*Alleles are ordered as risk allele/other allele aligned to the forward strand of NCBI Build 36.

*Risk allele frequency in Stage 1 samples.

*Associations were performed with adjustment for age, sex, study sites, and study-specific principal components.

*Associations were performed with adjustment for age, sex, study sites, study-specific principal components and body mass index.

$P<5 \times 10^{-8}$ are in bold.

doi:10.1371/journal.pgen.1004517.t001
SNP rs1531343 (r² = 0.60 in CEU and 0.32 in ASW). Despite associated SNP rs343092 was in moderate LD with the index blue. (T2D in African American (P = 0.04) and was in weak LD (r² = 0.21 to 0.46 in CEU) with other associated SNPs in this region (Table S6 and Figure S3c,d), the results suggest a refinement of the localization of causal variant(s) to variants in strong LD with rs231356. At HMGA2, the most strongly associated SNP rs343092 was in moderate LD with the index SNP rs1531343 (r² = 0.60 in CEU and 0.32 in ASW). Despite rs1531343 and its proxies in high LD were not associated with T2D in African Americans (P >0.05), several SNPs in moderate LD, including rs343092, showed nominal to strong associations (Table S6 and Figure S3e,f). Trans-ethnic fine mapping will be LD, including rs343092, showed nominal to strong associations.

**Effect of obesity on T2D susceptibility loci**

We investigated the influence of obesity by comparing the stage 1 meta-analysis results with or without adjustment for BMI at the 51 most significantly associated SNPs from the GWAS for follow up (Tables S4 and S7) and 158 established T2D or glucose homeostasis index SNPs (Table S5). Association results were highly similar with and without BMI adjustment (correlation coefficients were 0.99 for both effect sizes and −logP values). Of particular note, FTO is suggested to influence T2D primarily through modulation of adiposity in Europeans [3,25], but evidence is contradictory across multiple ethnic groups [26–28]. The index SNP rs11642841 was not significantly associated with T2D in African Americans without and with BMI adjustment (P = 0.06 and 0.23, respectively) (Table S5). The frequency of the risk A allele was 0.13 in this study. It had 100% power to detect association at the reported OR of 1.13 at type 1 error rate of 0.05, suggesting that FTO is unlikely a key T2D susceptibility gene in African Americans.

**Gene expression and bioinformatics analyses**

Among the six genome-wide significant loci (Table 1), we found no coding variants in the most significantly associated SNPs or their proxies. These SNPs demonstrated only weak associations with expression quantitative trait loci (eQTLs) (P >0.001, Table S8). Examination of the ENCODE data [29] revealed that several SNPs at TCF7L2, KCNQ1, and HMGA2 were located at protein binding sites or were predicted to alter motif affinity for transcription factors implicated in energy homeostasis (Table S9). The most strongly associated SNP rs7903146 in TCF7L2 is predicted to alter the binding affinity for a POU3F2 regulatory motif [30], POU3F2 is a neural transcription factor that enhances the activation of genes regulated by corticotropin-releasing hormone which stimulates adrenocorticotropic hormone (ACTH). ACTH is synthesized from pre-pro-opiomelanocortin (pre-POMC) which regulates energy homeostasis. For the 3′ signal at KCNQ1, several tag SNPs are predicted to alter the binding affinity for regulatory motifs, including SREBP, CTCF and HNF4A. SREBP is a transcription factor involved in sterol biosynthesis. CTCF regulates the expression of IGF2 [31], HNF4A is a master regulator of hepatocyte and islet transcription. The tag SNP rs2257883 at HMGA2 is predicted to alter the binding affinity of MEF2, which regulates GLUT4 transcription in insulin responsive tissues [32].

**Discussion**

We have performed the largest genetic association analysis to date for T2D in African Americans. Our data support the hypothesis that risk for T2D is partly attributable to a large number of common variants with small effects [7]. We identified HLA-B and INS-IGF2 as novel T2D loci, the latter specific to African Americans. We found evidence supporting association for 88 previously identified T2D and glucose homeostasis loci. Taken together, these 90 loci yielded a sibling relative risk of 1.19. The phenotypic variance measured on the liability scale is substantially larger in African Americans than in European Americans (17.5% vs. 5.7%) [7] due to larger effect sizes upon fine-mapping as well as higher disease prevalence in African Americans.

The two novel T2D loci, HLA-B and INS-IGF2, have been implicated in type 1 diabetes (T1D) risk in Europeans [33–35]. One limitation of our study is the lack of autoantibody measurement. However, our results are unlikely to be confounded by the presence of misclassified patients. Among diabetic youth
aged <20 years, T2D characterized by insulin resistance without autoimmunity is more prevalent in African Americans (40.1%) than in European Americans (6.2%), while African Americans less often present with autoimmunity and insulin deficiency resembling T1D compared to European Americans (32.5% vs. 62.9%, respectively) [36]. Autoimmunity is also uncommon in African American diabetic adults [37]. Furthermore, associations for T1D are stronger at HLA class II (HLA-DRB1, -DQA1, and -DQB1) than HLA class I regions in Europeans [33–34,38–41] (http://www.t1dbase.org). In African Americans, T1D individuals showed both shared and unique risk and protective HLA class II haplotypes as compared to European T1D individuals [42–43].
More importantly, these individuals also showed substantially stronger associations at HLA class II (P<1×10^{-25}) than class I regions (P<1×10^{-18}) [42], which is in contradiction with our finding of stronger associations at HLA class I than class II regions in T2D individuals (HLA-B, Figure S4). The observed HLA-B association may be due to LD with nearby causal gene(s) since there is long range LD in this region. Recently, rs3130501 near POU5F1 and TCF7L9 was reported for association with T2D in a trans-ancestry meta-analysis [8]. rs3130501 was located 211 kb upstream of rs2244020 and mapped to the same LD interval. However, the two SNPs were not correlated in both CEU and ASW (D’ = 0.57, r^2 = 0.05) and ASW (D’ = 0.68, r^2 = 0.16) from 1KGP, nor strongly associated with T2D in the stage 1 meta-analysis (P = 0.04). Other potential non-HLA candidate genes may include TNFA, which regulates immune and inflammatory response. It has been hypothesized that activated innate and adaptive immune cells stimulate release of cytokines such as TNFα and IL-1β, which promote both systemic insulin resistance and β-cell damage [44]. On the other hand, evidence has implicated T1D loci HLA-DQ/DR, GLIS3 and INS in the susceptibility of latent autoimmune diabetes in adults (LADA) and/or T2D (7,34,45–46), while T2D loci such as PPARG and TCF7L2 was associated with T1D [47] and LADA [46,48], respectively. More comprehensive studies are needed to understand the shared and distinct genetic risks in different forms of diabetes which will facilitate diagnosis and personalized treatment.

Our results have several implications regarding the genetic architecture of T2D. First, fine-mapping suggests that currently known loci explain more of the risk than previously estimated. Second, the loci conferring the largest risk for T2D appear to act through regulatory rather than protein-coding changes. Third, many, but not all, of the previously identified T2D loci are shared across ancestries. The differential LD structure of African-ancestry populations at shared loci provides an opportunity for fine mapping in trans-ethnic meta-analysis. Fourth, the ∼2.6M MEDIA SNPs achieved only 43.3% coverage of the 1KGP ASW common SNPs, suggesting that risk loci that are specific to African-ancestry individuals are difficult to discover with the genotyping arrays being used. Large-scale sequencing studies, such as those focusing on whole genomes, exomes, and targeted resequencing for associated non-coding regions, will be necessary to further delineate the causal variants for T2D risk in African Americans.

Materials and Methods
Samples and clinical characterization
Stage 1 discovery and clinical characterization included 17 T2D GWAS studies (ARIC, CARDIA, CFS, CHS, FamHS, GenESTAR, GENOA, HANDLS, Health ABC, HUFS, JHS, MESA, MESA Family, SIGNET-REGARDS, WFSM, FIND, and WHI) with up to 23,827 African American subjects (8,284 cases and 15,543 controls). Stage 2 replication samples included up to 11,544 African American subjects (6,061 cases and 5,483 controls), using in silico replication of GWAS data from eMERGE and IPM Biobank and de novo genotyping in IRAS, IRASFS, SCGS, and WFSM. In general, T2D cases were defined as having at least one of the following: fasting plasma glucose ≥126 mg/dl, 2 hour glucose during oral glucose tolerance test (OGTT) ≥200 mg/dl, random glucose ≥200 mg/dl, oral hypoglycemic agent or insulin treatment, or physician-diagnosed diabetes. All cases were diagnosed at ≥25 years (or age at study ≥25 years if age at diagnosis was not available). For cohort studies, individuals who met the criteria at any of the visits were defined as cases. Controls with normal glucose tolerance (NGT) were defined by satisfying all the following criteria: fasting plasma glucose <100 mg/dl, 2 hour OGTT<140 mg/dl (if available), no treatment of diabetes, and age ≥25 years. For cohort studies, individuals who met the criteria at all visits were defined as controls. All study participants provided written informed consent, except for eMERGE that use an opt out program, and approval was obtained from the institutional review board (IRB) from the respective local institutions. Detailed descriptions of the participating studies are provided in Text S1.

Statistical analysis
Single SNP association was performed for each study by regressing T2D case/control status on genotypes. To account for uncertainty of genotype calls during imputation, genotype probabilities or dosage were used for association tests in imputed SNPs. The association tests assumed an additive genetic model and adjusted for age, sex, study centers, and principal components. Principal components were included to control for confounding effects of admixture proportion and population structure. Secondary analysis with additional adjustment for BMI was performed for SNPs with P<1×10^{-5} in stage 1 meta-analysis and index SNPs previously reported to be associated with T2D or glucose homeostasis traits. BMI adjustment allows increasing power to detect T2D loci independent of BMI effect and diminish associations at T2D loci with effects modulated through BMI. Logistic regression was used for samples of unrelated individuals. Generalized estimating equations [52] or SOLAR [53] were used for samples of related individuals. Association results with extreme values (absolute beta coefficient or standard error >10), primarily due to low cell counts resulting from small sample sizes and/or low minor allele frequencies, were excluded (Table S3).

Type 2 Diabetes GWAS in African Americans
Among the 51 SNPs carried forward for replication, heterogeneity of effect sizes across studies within each stage was assessed using Cochran’s Q statistic implemented in METAL. Meta-analysis results from stages 1 and 2a, stage 1+2a and 2b were used to assess heterogeneity of effect sizes between discovery and replication stages in African Americans, and between African Americans and Europeans, respectively. For SNPs with significant heterogeneous effect size after multiple comparison corrections ($P_{het} < 0.001$), meta-analysis results including studies of all stages assessed by the random effect model implemented in GWAMA [55] were reported. Heterogeneous associations may partly due to differences in ascertained scheme across studies. For index SNPs reported in prior studies, assessment of heterogeneity using Cochran’s Q statistic between prior studies and this study were also reported.

Transferability analysis
Index SNPs associated with T2D or glucose homeostasis traits from prior GWAS and candidate gene studies were examined for association with T2D in African Americans (Table S5). For the index SNP association tests, a per-SNP $P$ value < 0.05 was defined as significant. In the locus-wide analysis, the boundaries of a locus were defined by the most distant markers (within $\pm 500$ kb) using the 1KGP CEU data with $r^2 \geq 0.3$ with the index SNP. All MEDIA SNPs within these bounds were examined for association analysis. All pairwise LD values within each locus were estimated using the 1KGP CEU and ASW data. To estimate the effective number of SNPs at a locus, we retrieved genotypes from the 1KGP ASW data for markers present in MEDIA, estimated the sample covariance matrix from those genotypes, and spectrally decomposed the covariance matrix [24]. The effective number of SNPs was estimated using the relationship $N_{eff} = \left( \sum_{k=1}^{K} \lambda_k^2 \right)^2 / \left( \sum_{k=1}^{K} \lambda_k \right)^2$, in which $\lambda_k$ is the $k$th eigenvalue of the $K \times K$ covariance matrix for the $K$ SNPs in the locus [24]. The per-locus significance level was defined as 0.05/effective number of SNPs (Table S6). By accounting for all SNPs within the bounds of LD, the per-locus significance level is corrected to account for markers in LD with the index SNP as well as markers not in LD with the index SNP, thereby potentially allowing for discovery of new associations at markers not tagged by the index SNP.

Liability-scale variance explained
For each independent locus, we estimated the sibling relative risk using the most strongly associated SNP within that locus. Let $p_i$ and $\psi_i$ be the risk allele frequency and the corresponding odds ratio at the $i$th SNP, respectively. Assuming the additive genetic model and independence between SNPs, the contribution to the sibling relative risk $\lambda_i$ for a set of $N$ SNPs is given by $\lambda_i = N \sum_{i=1}^{N} \left[ 1 + \frac{p_i(1-p_i)(\psi_i-1)^2}{2(1-p_i)+p_i\psi_i} \right]^2$ [36]. Let $K$ be the disease prevalence. The liability-scale variance $h^2_l$ explained by the set of $N$ SNPs is given by $h^2_l = \frac{2(T-T_1)^2}{\omega + K(T-T_1)}$, in which $T = \phi^{-1}(1-K)$, $T_1 = \phi^{-1}(1-\lambda_i K)$, and $\omega = \frac{z}{K}$ with $\phi^{-1}$ representing the standard normal quantile function and $z$ representing the standard normal density at $T$ [57].

Coverage
The coverage of MEDIA SNPs to the human genome was estimated using HaploView [38] via pairwise tagging at the $r^2 \geq 0.8$ threshold. We used all SNPs with minor allele frequencies $\geq 1\%$ in both MEDIA and the 1KGP ASW sequence data. Coverage was estimated using non-overlapping bins of 1,000 SNPs.

Power analysis
Study power was calculated using the genetic power calculator [59]. For SNPs with MAF $\geq 0.3$, our study had $>80\%$ power to detect odds ratios for T2D at OR $\geq 1.06$ and $\geq 1.13$ at $P < 0.05$ and $P < 5 \times 10^{-5}$, respectively, in stage 1 samples under an additive model. The observed odds ratios among our stage 1 most significantly associated SNPs with $P < 1 \times 10^{-5}$ ranged from 1.11 to 1.56 (Table S4). Given our African American sample size in stage 1+2a, our study had $>80\%$ power to detect OR $\geq 1.1$ at $P < 5 \times 10^{-5}$ at MAF $\geq 0.3$, thus provided good power to detect genome-wide significance among the most significantly associated SNPs using all African American samples. For T2D SNPs reported from the literature, power was also calculated from the reported effect size using the risk allele frequency from this study for stage 1 samples at $P < 0.05$ and $P < 5 \times 10^{-5}$, respectively (Table S5).

Gene expression analysis
The MuTHER resource (www.muther.ac.uk) includes lymphoblastoid cell lines (LCLs), skin, and adipose tissue derived simultaneously from a subset of well-phenotyped healthy female twins from the TwinsUK adult registry [60]. Whole-genome expression profiling of the samples, each with either two or three technical replicates, was performed using the Illumina Human HT-12 V3 BeadChips (Illumina Inc.) according to the protocol supplied by the manufacturer. Log2-transformed expression signals were normalized separately per tissue as follows: quantile normalization was performed across technical replicates of each individual followed by quantile normalization across all individuals. Genotyping was performed with a combination of Illumina arrays (HumanHap300, HumanHap610Q, 1M-Duo, and 1.2MDuo 1M). Untyped HapMap2 SNPs were imputed using the IMPUTE2 software package. In total, 776 adipose and 777 LCL samples had both expression profiles and imputed genotypes. Association between all SNPs (MAF $>5\%$, IMPUTE info $>0.8$) within a gene or within 1 Mb of the gene transcription start or end site and normalized expression values were performed with the GenABEL/ProbABEL packages [61–62] using the polygenic linear model incorporating a kinship matrix in GenABEL followed by the ProbABEL mmscore score test with imputed genotypes. Age and experimental batch were included as cofactors.

Genotype and gene expression in LCL in HapMap samples were also available [63]. Association of genotypes and gene expression of transcripts within 1 Mb of tested SNPs were analyzed separately for CEU and YRI populations. The variance components model implemented in SOLAR was used for association analysis which accounts for correlation among related individuals [53].

In this study, we examined the association of the most significantly associated SNPs from the six genome-wide significant loci and their proxies ($r^2 \geq 0.8$ in ASW) within 1 Mb of the associated SNPs with cis-expression quantitative trait loci (eQTLs) in peripheral blood leukocytes (LCL) and adipose tissue (Table S8).

ENCODe data analysis
We examined putative functional role of non-coding genome-wide significant SNPs and their proxies within 1 Mb ($r^2 \geq 0.8$ in 1KGP ASW) using HaploReg [30] and RegulomeDB [64]. These databases interrogated multiple chromatin features from the
Supporting Information

Figure S1  Forest plots of the most strongly associated SNPs at five previously and newly identified T2D loci in African Americans. Odds ratio and 95% CIs are presented for individual studies (black circle and line) and meta-analysis results (red diamond and line). At KCNQ1, two independent associated SNPs are shown.

Figure S2  (A) Distributions of risk allele frequencies for the previously reported index SNPs (in black) vs. the MEDIA most strongly associated SNPs (in red) in African Americans from stage 1 meta-analysis. (B) Distributions of odds ratios for risk alleles of the index SNPs (in black) vs. the most strongly associated MEDIA SNPs (in red) in African Americans from stage 1 meta-analysis.

Figure S3  Regional plots of stage 1 meta-analysis association results in African Americans for the most strongly associated SNPs from this study and the MEDIA SNPs from previous studies. (A-B) INTS8-TP53INP1 region; (C-D) KCNQ1 region; (E-F) HMGAI2 region. (A, C, E) The most strongly associated SNP in MEDIA is denoted by a purple circle and a red arrow with LD colored based on the HapMap 2 YRI data. (B, D, F) The index SNP is denoted by a purple circle and a blue arrow with LD colored based on the HapMap 2 CEU data.

Figure S4  Regional plots of HLA-B and HLA-DQ/DR regions for (A, C) stage 1 meta-analysis association results in African Americans and HapMap 2 YRI LD data, and (B, D) stage 3 DIAGRAMv2 results in Europeans using HapMap 2 CEU LD data. (A, B) The most strongly associated SNP rs2244020 at HLA-B region from this study is denoted by a purple circle and a red arrow. (C, D) The index SNP rs9272346 from Burton PR et al (2007) [65] is denoted by a purple circle and a blue arrow.

Table S1  Design of studies in stage 1 GWAS and stage 2a replication in African Americans.

Table S2  Clinical characteristics of study samples in stage 1 GWAS and stage 2a replication studies in African Americans.

Table S3  Genotyping methods, quality controls, imputation and statistical analysis in stage 1 GWAS and stage 2a replication studies in African Americans.

Table S4  SNPs with $P$ value $\leq 1 \times 10^{-5}$ from stage 1 GWAS meta-analysis (BMI unadjusted) selected for stage 2 in silico and de novo replication in African Americans and in silico replication in individuals of European ancestry from DIAGRAMv2.

Table S5  Stage 1 GWAS meta-analysis results for index SNPs at established T2D or glucose homeostasis loci in African Americans.

Table S6  Locus-wide association at established T2D or glucose homeostasis loci in stage 1 GWAS meta-analysis in African Americans.

Table S7  BMI-adjusted association for SNPs from stage 1 GWAS meta-analysis selected for replication.

Table S8  Expression Quantitative Trait Loci (eQTL) analysis for the genome-wide significant SNPs for T2D. Results are shown for suggestive evidence of cis-association ($P<0.05$) between the genome-wide significant SNPs and their proxies within 1 Mb of the associated SNPs.

Table S9  Putative regulatory SNPs predicted from the ENCODE project for the genome-wide significant SNPs and their proxies at TCF7L2, INS-IGF2, KCNQ1 and HMGAI2.
Members of the MuTHER Consortium are:

Kourosh R. Ahmadi,1 Chrysanthi Amali,2 Amy Barrett,2 Veronique Bataille1, Jordana T. Bell1,4, Alfonso Buil2,3, Panos Deloukas3, Emmanouil Kerrin S. Small1,6, Nicole Soranzo1,6, Tim D. Spector1, Gabriela Leopold Parts6, Simon Potter6, Magdalena Sekowska6, So-Youn Shin6, Paola di Meglio12, Josine L. Min4, Stephen B. Montgomery5, Frank O. Christopher E. Lowe9,10, Mark I. McCarthy3,4,11, Eshwar Meduri1,6, Daniel G. Rees1,2,13, Paul de Boer13, Christopher E. Lowe9,10, Mark I. McCarthy5, Frank O. Christopher E. Lowe9,10, Elin Grundberg9,10, Elisa Marini13, Michael G. Zullo13, Nicola Soranzo1,6, Tim D. Spector5, Gabriel Burdiles1, Mary E. Travers1, Louka Tzaprouni3, Sophia Tsoka1, Alison Wilk1, Tsun-Pyo Yang2, Krista T. Zondervan1

1 Nordic-Bronelag Health Study (HUNT) Research Center, Department of Community Medicine and General Practice, Norwegian University of Science and Technology, Trondheim, Norway.
2 Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, University of Exeter, Exeter, UK.
3 Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, University of Exeter, Exeter, UK.
4 Institute of Bioinformatics and Epidemiology, German Diabetes Center, Leipzig.
5 Institute of Diabetes Research, Heinrich Heine University, Düsseldorf, Düsseldorf, Germany.
6 Department of Human Genetics, McGill University, Montreal, Canada.
7 McGill University and Genome Quebec Innovation Centre, Montreal, Canada.
8 Department of Metabolic Diseases, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
9 Department of Endocrinology and Diabetes, Norfolk and Norwich University Hospital National Health Service Trust, Norwich, UK.
10 General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, USA.
11 Institut inter régional pour la Santé (IRSA), La Riche, France.
12 Department of Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland.
13 Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands.
14 Molecular Genetics, Medical Biology Section, Department of Pathology and Medical Biology, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands.
15 Department of Genetics, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands.
16 Department of Physiology and Biophysics, University of Southern California School of Medicine, Los Angeles, California, USA.
17 National Institute of Health, Bethesda, Maryland, USA.
18 Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden.
19 University of Southern Denmark, Odense, Denmark.
20 Centre for Diabetes, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
21 Department of Medicine, The Hospital of Levanger, Levanger, Norway.
22 Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA.
23 Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Bolzano, Italy.
24 Croatian Centre for Global Health, Faculty of Medicine, University of Split, Split, Croatia.
25 Institute for Clinical Medical Research, University Hospital ‘Sestre Milosrdnice’, Zagreb, Croatia.
26 Department of Public Health, University of Helsinki, Helsinki, Finland.
27 South Ostrobothnia Central Hospital, Seinäjoki, Finland.
28 Red RECVA Groep RD06/0014/0015, Hospital Universitario La Paz, Madrid, Spain.
29 Diabetes Research Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK.
30 Department of Preventive Medicine, Keck Medical School, University of Southern California, Los Angeles, California, USA.
31 Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, USA.
32 Department of Biomedical Science, Panum, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark.
33 Faculty of Health Science, University of Aarhus, Aarhus, Denmark.
34 Klinikum Grosshadern, Munich, Germany.
35 Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA.
36 Faculty of Medicine, University of Iceland, Reykjavik, Iceland.
37 Genomic Medicine, Imperial College London, Hammersmith Hospital, London, UK.
38 Oxford National Institute for Health Research Biomedical Research Centre, Churchill Hospital, Oxford, UK.
39 A full list of members is provided in the supplementary Note of the original publication.
40 These authors contributed equally.
References


