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Consistent Directions of Effect for Established Type 2 Diabetes Risk Variants Across Populations

The Population Architecture using Genomics and Epidemiology (PAGE) Consortium

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Diabetes Risk Variants Across Populations
Common genetic risk variants for type 2 diabetes (T2D) have primarily been identified in populations of European and Asian ancestry. We tested whether the direction of association with T2D risk variants generalizes across six major racial/ethnic groups in the U.S. as part of the Population Architecture using Genomics and Epidemiology Consortium (16,235 diabetes case and 46,122 control subjects of European American, African American, Hispanic, East Asian, American Indian, and Native Hawaiian ancestry). The percentage of positive (odds ratio [OR] > 1) for putative risk allele) associations ranged from 68% in American Indians to 100% in European Americans. Of the nine variants where we observed significant heterogeneity of effect by racial/ethnic group (P heterogeneity < 0.05), eight were positively associated with risk (OR > 1) in at least five groups. The marked directional consistency of association observed for most genetic variants across populations implies a shared functional common variant in each region. Fine-mapping of all loci will be required to reveal markers of risk that are important within and across populations. Diabetes 2012:1642–1647, 2012

Over the past decade, genome-wide association studies (GWAS) and candidate gene association studies have been successful in identifying common risk variants for type 2 diabetes (T2D) (1–15). The loci revealed have provided insight into the genetic basis of this common disease, as well as biological pathways important in its pathogenesis. Most of these previously reported risk variants were identified in very large studies or meta-analyses conducted among populations of European and Asian ancestry and have been associated with modest increases in T2D risk (per-allele odds ratios [ORs] between 1.1 and 1.4) (12). Subsequent testing of these well-established variants in other racial and ethnic groups has been limited (12,16–24), and most of the studies have been undersized and underpowered to provide reliable risk estimates and clarity regarding generalizability of the associations in non-European populations. Aggregating results from multiple studies conducted among racially and ethnically diverse populations is one approach to amass an adequate sample size for replicating these modest genetic associations and extend our understanding of T2D genetics to non-European populations. As part of the Population Architecture using Genomics and Epidemiology (PAGE) Consortium, we have tested 20 validated risk variants for association with T2D. These 20 variants represent 18 risk regions and were examined in as many as 16,235 diabetes case and 46,122 control subjects from six major U.S. population groups (European Americans, African Americans, Hispanics, East Asians, Native Hawaiians, and American Indians) from six large population-based studies.

RESEARCH DESIGN AND METHODS
The PAGE Consortium consists of large ongoing population-based studies or consortia (25). The following studies are included in the current study: from the CALCo (Causal Variants Across the Life Course) consortium, ARIC (the...
Atherosclerosis Risk in Communities Study) (26), CHS (Cardiovascular Health Study) (27), and SHS (Strong Heart Study) (28,29); EAGLE (Epidemiologic Architecture of Genes Linked to Environment, based on three National Health and Nutrition Examination Surveys [NHANES]) (30–33); MEC (The Multiethnic Cohort: Cohort of Multiple Minority Groups in the U.S.) (34). In parallel with these GWAS, we genotyped a number of additional variants, which are detailed in the Supplementary Data about each study can be found in Supplementary Data.

**Diabetes case and control definitions.** To facilitate harmonization of diabetes case definitions across studies, data-collection methods were reviewed and compared between studies. All studies collected self-reported information on previous diagnosis by a physician or medical professional and use of medication for diabetes. However, not all studies measured fasting blood glucose levels, which more specifically define uncontrolled or undiagnosed T2D. In order to incorporate the T2D information across studies, two case definitions were allowed: self-report and exam based. To be classified as a case subject according to the self-report definition, participants had to report both a previous diagnosis of diabetes and use of medication to treat diabetes. To be classified as a control subject (self-report), participants had to report neither previous diagnosis nor use of diabetes medications. To be classified as a case subject according to the exam-based definition, participants had to either meet the self-report case definition or have a fasting (≥8 h) blood glucose ≥126 mg/dL. To be classified as a control subject (exam based), participants had to be classified as a control subject per the self-report definition and have a fasting blood glucose <126 mg/dL. Both prevalent and incident cases were included. For both definitions, self-reported diabetes diagnosis before age 30 years was excluded. Sensitivity analyses in the ARIC study suggested that the magnitude of association between candidate variants and T2D did not differ systematically according to the case definitions we applied (Supplementary Data). Additional study-specific details on the data-collection methods and case definitions can be found in the Supplementary Data.

A total of 16,235 diabetes case and 46,123 control subjects were included in this study (case and control subjects, respectively, by study: ARIC: 1,348/10,078; CHS: 8,504/4,488; SHS: 1,575/1,249; MEC: 6,298/9,980; EAGLE/NHANES: 1,029/6,690; and WHI, 5,120/14,925). None of these studies was involved in the initial discovery efforts of these T2D risk loci. The data from the MEC have previously been reported (37).

**Genotyping.** The 20 variants evaluated in the current study were selected from 18 genomic regions found to be significantly associated with risk of T2D in studies as of September 2009 (Supplementary Table 1). In the CDKN2A/CDKN2B, WFS1, and KCNQ1 regions, more than one variant was investigated, as many of the index signals identified in the initial GWAS populations are not perfectly correlated. An additional variant, rs8050136, at the CHS, 859/4,488; SHS, 1,575/1,249; MEC, 6,298/9,980; EAGLE/NHANES, 1,029/6,690; and WHI, 5,120/14,925. Of these none of these studies was involved in the initial discovery efforts of these T2D risk loci. The data from the MEC have previously been reported (37).

Genotyping was conducted in study-specific laboratories using a number of different platforms. Cross-laboratory and cross-platform reproducibility was assessed by genotyping 360 HapMap samples from populations most relevant to PAGE samples in each laboratory. A description of the platforms and quality-control metrics from each study/laboratory is provided in Supplementary Data. The genotype concordance for single nucleotide polymorphisms (SNPs) evaluated in the HapMap samples in more than one laboratory was >85.5% per SNP, with an average concordance of 99.8%.

We excluded results for SNP rs13266634 (SLC30A8) in all populations except European Americans and Hispanics, as there is an adjacent SNP 1 bp away (rs18880462) that has a frequency of 10% in African Americans, 4% in Asians, and 2% in Native Hawaiians (<1% in Hispanics and Europeans) and interferes with genotyping assays, thus resulting in genotype misclassification.

Genetic markers that distinguish the major ancestral populations (African, European, and Asian) were available in three studies. For ARIC, principal components of ancestry were derived from 200,000 SNPs genotyped on a custom array. For WHI (all populations) and MEC (African Americans and Native Hawaiians), ~100 ancestry-informative markers were used in a principal-components analysis to assess major axes of variation (38,39). For a subset of the MEC: Latinos, principal components were derived from markers on the Illumina 2.5M array for 12,600 CHS and MEC participants included in this analysis (Supplementary Table 1). In the CDKN2A/CDKN2B and KCNQ1 regions, more than one variant was investigated, as many of the index signals identified in the initial GWAS populations are not perfectly correlated. An additional variant, rs8050136, at the CDK2 locus, was also examined but not associated with risk in any population after adjustment for BMI (data not shown).

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We examined 20 validated risk variants for T2D, representing 18 risk regions, in as many as 16,235 diabetes case and 46,122 control subjects from six major population groups. The vast majority of the variants were positively associated with risk in the five non-European populations. These findings are highly consistent with a previous multiethnic study in the MEC, which contributed a large fraction of the case subjects to this meta-analysis (American Indians 0%, European Americans 11%, African Americans 31%, Hispanics 66%, East Asians 84%, and Native Hawaiians 100%) (37), and suggest that the majority of these variants are likely to be generalized markers of T2D risk across populations.

We did not find evidence of substantial confounding by population stratification in European Americans or African Americans. However, adjustment for population structure using principal components did affect the association with several variants for Native Hawaiians and Hispanics. Native Hawaiians are highly admixed with the three main groups being Polynesian, Asian, and European. The first few principal components capture European admixture, with European ancestry lower in Hawaiian case subjects than in control subjects (41). Therefore, adjustment for European admixture reduced the strength of association for some of the variants that were more common in Polynesians and increased the strength of some of the variants more common in Europeans. Similar differences were noted for some SNPs after principal-components adjustment in Hispanics. Unfortunately, ancestry-informative markers were not available to address the issue of population stratification in the admixed American Indian populations.

The marked directional consistency of association for most genetic variants across populations implies a shared functional common variant in each region. This general pattern of consistency provides little support for the “synthetic association” model (42), which suggests that GWAS signals with common alleles are due to rare alleles, many of which are likely to be ethnically distinct. The inability to replicate associations with variants in populations where statistical power is sufficient may highlight loci for which fine-mapping may be helpful. For example, in African Americans, power was high (≥94%) to detect significant

estimated effects (total number of tests: SNP × population), 91 had ORs >1 (84%). Removing European Americans, the population in which most of the original signals were reported, only reduced this percentage to 80%. We observed significant heterogeneity of effect by racial/ethnic group for nine SNPs ($P_{heterogeneity} < 0.05$). However, aside from rs7901681 at TSPAN8, eight of these variants (at THADA, IGF2BP2, WFS1, CDKAL1, CDKN2A/CDKN2B [rs2383208], TCF7L2, KCNQ1 [rs2237895], and KCNJ11) were positively associated with risk (OR >1) in at least five populations (Fig. 1). Thus, even for variants that displayed evidence of significant heterogeneity across population, the direction of effect was generally consistent in the majority of the populations.

**DISCUSSION**

We examined 20 validated risk variants for T2D, representing 18 risk regions, in as many as 16,235 diabetes case and 46,122 control subjects from six major population groups. The vast majority of the variants were positively associated with risk in the five non-European populations. These findings are highly consistent with a previous multiethnic study in the MEC, which contributed a large fraction of the case subjects to this meta-analysis (American Indians 0%, European Americans 11%, African Americans 31%, Hispanics 66%, East Asians 84%, and Native Hawaiians 100%) (37), and suggest that the majority of these variants are likely to be generalized markers of T2D risk across populations.

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**TABLE 1**

Descriptive characteristics of diabetes case and control subjects in PAGE studies

<table>
<thead>
<tr>
<th>Racial/ethnic group study</th>
<th>N</th>
<th>% Male</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Americans</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC</td>
<td>892/8,688</td>
<td>57.0/45.3</td>
<td>54.7 (5.6)/54.1 (5.7)</td>
<td>30.0 (5.0)/26.3 (4.4)</td>
</tr>
<tr>
<td>CHS</td>
<td>660/3,876</td>
<td>53.0/42.0</td>
<td>73.0 (5.5)/72.8 (5.6)</td>
<td>28.1 (4.8)/26.1 (4.4)</td>
</tr>
<tr>
<td>MEC</td>
<td>537/1,827</td>
<td>54.2/47.5</td>
<td>67.7 (8.1)/66.9 (8.6)</td>
<td>30.4 (5.6)/25.5 (4.4)</td>
</tr>
<tr>
<td>EAGLE</td>
<td>438/2,340</td>
<td>54.3/45.2</td>
<td>67.1 (12.8)/57.0 (16.8)</td>
<td>30.9 (6.3)/27.2 (5.4)</td>
</tr>
<tr>
<td>WHI</td>
<td>2,464/10,573</td>
<td>0/0</td>
<td>65.0 (6.9)/67.6 (6.7)</td>
<td>32.1 (6.6)/27.9 (6.0)</td>
</tr>
<tr>
<td>Total</td>
<td>4,991/27,304</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African Americans</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC</td>
<td>456/2,290</td>
<td>37.9/37.0</td>
<td>52.9 (5.5)/53.0 (5.8)</td>
<td>31.9 (6.5)/28.5 (5.6)</td>
</tr>
<tr>
<td>CHS</td>
<td>199/612</td>
<td>40.2/36.6</td>
<td>72.4 (5.3)/73.0 (5.7)</td>
<td>30.4 (5.5)/27.9 (5.4)</td>
</tr>
<tr>
<td>MEC</td>
<td>1,084/1,630</td>
<td>37.6/45.6</td>
<td>69.1 (7.8)/68.0 (8.3)</td>
<td>31.3 (5.8)/27.4 (4.9)</td>
</tr>
<tr>
<td>EAGLE</td>
<td>255/1,037</td>
<td>43.9/45.1</td>
<td>60.0 (12.8)/47.1 (14.0)</td>
<td>31.9 (6.7)/28.8 (6.7)</td>
</tr>
<tr>
<td>WHI</td>
<td>1,456/2,580</td>
<td>0/0</td>
<td>60.9 (6.7)/61.7 (7.3)</td>
<td>33.4 (6.9)/32.7 (7.8)</td>
</tr>
<tr>
<td>Total</td>
<td>3,450/8,149</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEC</td>
<td>2,233/2,607</td>
<td>48.1/49.1</td>
<td>68.4 (7.1)/67.8 (7.9)</td>
<td>29.8 (5.2)/28.6 (4.1)</td>
</tr>
<tr>
<td>EAGLE</td>
<td>336/1,125</td>
<td>50.0/52.1</td>
<td>61.3 (11.8)/49.5 (14.6)</td>
<td>30.1 (6.3)/28.7 (5.2)</td>
</tr>
<tr>
<td>WHI</td>
<td>789/1,154</td>
<td>0/0</td>
<td>60.0 (6.5)/60.4 (6.8)</td>
<td>31.3 (5.8)/29.9 (7.0)</td>
</tr>
<tr>
<td>Total</td>
<td>3,356/4,886</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asians</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEC</td>
<td>1,821/1,736</td>
<td>56.4/53.5</td>
<td>68.8 (8.4)/68.4 (8.4)</td>
<td>27.3 (4.3)/24.2 (3.4)</td>
</tr>
<tr>
<td>WHI</td>
<td>355/1,037</td>
<td>0/0</td>
<td>62.7 (7.1)/65.6 (7.6)</td>
<td>27.0 (4.5)/24.3 (4.2)</td>
</tr>
<tr>
<td>Total</td>
<td>2,176/3,753</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native Hawaiians</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEC</td>
<td>625/1,180</td>
<td>45.0/45.3</td>
<td>65.4 (7.5)/64.6 (8.0)</td>
<td>31.9 (6.0)/27.7 (5.3)</td>
</tr>
<tr>
<td>WHI</td>
<td>1,575/1,249</td>
<td>32.9/44.2</td>
<td>56.7 (7.9)/55.4 (8.0)</td>
<td>32.2 (6.2)/29.4 (5.8)</td>
</tr>
<tr>
<td>Total</td>
<td>1,637/1,498</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are means (SD) unless otherwise indicated. *The exam-based definition for T2D case and control subjects was applied for ARIC, CHS, SHS, and EAGLE, and the self-report–based definition was applied for MEC and WHI.*
associations, with the index variants at five loci (WFS1, HHEX, CDNK2A/B, THADA, and KCNQ1) that were found to be significantly associated with risk in at least one of the other non-European populations. The lack of a statistically significant association in African Americans at these loci could be because the risk allele is relatively invariant in populations of African ancestry or low linkage disequilibrium between the index signal and the functional allele. Fine-mapping of these loci, and others such as TCF7L2 in American Indians, where we observed no evidence of association (OR 1.08 [95% CI 0.90–1.29]) despite >99% power and despite the suggestion that rs7903146 is the biologically functional variant in African Americans (43) and in genomic studies of open chromatin (44), should be of high priority to extract information about any genetic risk conferred at that locus that may be important for these populations.

This study has a number of limitations. In the design, we allowed for both incident and prevalent diabetes cases as well as different case/control criteria depending on study; however, our sensitivity analysis of the different case groups (Supplementary Data) did not suggest systematic differences in effect sizes based on study design, case definition, or analytic approach. We also had no information about type 1 diabetes in some studies, although case subjects known to be diagnosed before age 30 years were excluded and most participants in these studies were middle-aged or older adults.

This is the largest effort to date to investigate the generalizability of T2D susceptibility variants in the major racial/ethnic groups of the U.S. The consistent patterns of association for these variants provide additional support for the importance of these loci in contributing to T2D risk in multiple populations. Identification of the underlying
biological functional allele(s) in each region, through fine-mapping, will be required to determine the extent to which these regions contribute to racial and ethnic disparities in T2D risk.

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No potential conflicts of interest relevant to this article were reported.

C.A.H. performed experiments, analyzed data, and wrote the manuscript. M.D.F., K.L.S., P.B., V.S.V., P.W., J.H., and N.F. performed experiments, analyzed data, and contributed to writing the manuscript. K.R.M., B.V.H., R.D.J., J.C.F., L.N.K., S.B., R.J.G., S.L., J.E.M., J.B.M., K.W., J.K.M., S.A.P., P.S., L.R.W., L.A.H., J.L.A., K.E.N., U.P., D.C.C., and L.L.M. contributed materials and to the study design, analysis tools, and interpretation of results and contributed to writing the manuscript. J.S.P. performed the experiments, analyzed data, and wrote the manuscript. C.A.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study-specific acknowledgments are listed in the Supplemental Data.

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