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Fasting Glucose GWAS Candidate Region Analysis across Ethnic Groups in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Genetic variants associated with fasting glucose in European ancestry populations are increasingly well understood. However, the nature of the associations between these SNPs and fasting glucose in other racial and ethnic groups is unclear. We sought to examine regions previously identified to be associated with fasting glucose in Caucasian GWAS across multiple ethnicities in the Multi-Ethnic Study of Atherosclerosis (MESA). Non-diabetic MESA participants with fasting glucose measured at the baseline exam and with GWAS genotyping were included; 2349 Caucasians, 664 individuals of Chinese descent, 1366 African Americans, and 1171 Hispanics. Genotype data was generated from the Affymetrix 6.0 array and imputation in IMPUTE. Fasting glucose was regressed on SNP dosage data in each ethnic group adjusting for age, gender, MESA study center, and ethnic-specific principal components. SNPs from the three gene regions with the strongest associations to fasting glucose in previous Caucasian GWAS (*MTNR1B* / *GCK* / *G6PC2*) were examined in depth. There was limited power to replicate associations in other ethnic groups due to smaller allele frequencies and limited sample size; SNP associations may also have differed across ethnic groups due to differing LD patterns with causal variants. rs10830963 in *MTNR1B* and rs4607517 in *GCK* demonstrated consistent magnitude and direction of association with fasting glucose across ethnic groups, although the associations were often not nominally significant. In

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conclusion, certain SNPs in *MTNR1B* and *GCK* demonstrate consistent effects across four racial and ethnic groups, narrowing the putative region for these causal variants.

Keywords

GWAS; fasting glucose; SNP

Fasting glucose is an important diabetes-related quantitative trait; investigations into its genetic etiology in non-diabetic individuals will lead to a better understanding of the pathophysiology of diabetes. There has been recent success in identifying genetic variants associated with fasting glucose using GWAS (Genome-Wide Association Studies). Several studies in Caucasians [Bouatia-Naji, et al. 2009; Bouatia-Naji, et al. 2008; Chambers, et al. 2009; Chen, et al. 2008; Prokopenko, et al. 2009] have produced consistent results, showing some variants in regions near *MTNR1B*, *GCK*, and *G6PC2* to be significantly associated ($p < 5 \times 10^{-8}$) with fasting glucose, and a recent large (~100,000 subjects) meta-analysis of fasting glucose replicated the above associations, plus that in *GCKR*, and found variants in 12 novel gene regions to be significantly associated with fasting glucose [Dupuis, et al. 2010].

According to the NHGRI GWAS catalog, to date, all the published GWAS of fasting glucose (with the exception of one study which included Asian Indians [Chambers, et al. 2009]) have taken place in populations of European ancestry. Some studies examining the association of fasting glucose with SNPs identified from previous GWAS have been undertaken in non-Caucasian populations [Abate, et al. 2003; Demirci, et al. 2010; Hu, et al. 2009; Hu, et al. 2010; Kan, et al. 2010; Ramos, et al. 2010; Ronn, et al. 2009; Song, et al. 2011; Takeuchi, et al. 2010; Tam, et al. 2009; Yang, et al. 2010], but most of these studies have examined only 1 or 2 SNPs per gene region in a single ethnic group. There is a need to perform more comprehensive genetic analyses in multiple non-Caucasian populations to see if regions associated with fasting glucose in Caucasians are associated with fasting glucose in other ethnic groups. If some previously detected regions are replicated in other ethnic groups, the differing linkage disequilibrium (LD) patterns across populations may provide the opportunity to narrow the search for causative variants in the regions.

We investigated the three gene regions (*MTNR1B*, *GCK*, and *G6PC2*) shown most consistently to be associated with fasting glucose in Caucasians, across the four ethnic groups in the Multi-Ethnic Study of Atherosclerosis (MESA). MESA represents a unique opportunity to conduct such an analysis as extensive genotype data is available and glucose measurements and other data collection procedures were identical across all sites and ethnic groups, thereby permitting direct comparisons of the direction and magnitude of association.

Materials and Methods

Study Population

From 2000–2002, 6814 participants aged 45–84 with no known clinical cardiovascular disease were enrolled at six field centers located in the United States. Informed consent was obtained from all participants. The study population, which has been described in detail elsewhere [Bild, et al. 2002] included individuals identifying themselves as European American (CAU--38%), African American (AFA--28%), Hispanic (HIS-22%), or Chinese (CHN--12%). We included all MESA participants who underwent GWAS genotying using the Affymetrix 6.0 SNP array as part of the MESA SNP Health Association Resource (SHARe) (study accession phs000209, http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000209.v4.p1). Participants were excluded if they had prevalent

diabetes (defined as fasting glucose ≥7.0mmol/L [126 mg/dl] and/or use of glucose lowering medications) or reported fasting less than 8 hours. After exclusions, there were 2349 CAU, 664 CHN, 1366 AFA, and 1171 HIS.

Measurements

All measurements used in this paper were obtained at the first MESA study visit. BMI was calculated as weight over height squared (kg/m^2). Serum insulin and serum glucose were measured at a central laboratory as reported previously [Lutsey, et al. 2007].

Genotyping

MESA European Americans, Hispanics, and Chinese were typed on the Affymetrix 6.0 SNP array at Affymetrix Research Services Lab. An additional 1738 African American samples were genotyped at Broad as part of the CARe project. Affymetrix performed plate-based genotype calling using Birdseed v2. Sample QC was based on call rates and contrast QC (cQC) statistics. Broad performed similar QC for CARe samples. Additional sample and SNP QC was carried out at University of Virginia, including sample call rate, sample cQC, and sample heterozygosity by ethnicity at the sample level as well as outlier plate checking by call rate, median cQC or heterozygosity at plate level. Four samples were removed due to low call rate (<95%). Plate-based heterozygosity check found no evidence of contamination, so all plates that passed other QC metrics were retained. Cryptic sample duplicates based on IBD/IBS were dropped. We excluded monomorphic SNPs across all samples; SNPs with missing rate > 5% or observed heterozygosity > 53% were also excluded.

Additional genotypes were imputed separately in each ethnic group using the program IMPUTE2 [Howie, et al. 2009]. Prior to imputation, SNPs that were recommended for exclusion were dropped, and therefore imputed if they were in the HM1+2 reference panel. Additionally, IMPUTE dropped monomorphic SNPs within each ethnic group. HapMap CEU was used as the reference population for CAU sample, while the HapMap I + II CEU +YRI+CHB+JPT (rel#22, BCBI Build 36, dbSNP b126) was used as the reference population for the non-Caucasian groups.

Calculation of ethnic-specific PCs

Principal components (PCs) of ancestry were computed for each ethnic group using the program SMARTPCA, which is distributed with EIGENSTRAT [Patterson, et al. 2006; Price, et al. 2006]. The PC analysis was performed using SNPs selected for minimal linkage disequilibrium (LD) within each of the four ethnic groups. Outliers identified by 5 iterations using 10 sigma thresholds (113 CAU, 65 CHN, 21 AA, and 75 HIS) were removed.

Statistical Analyses

For SNP analyses, fasting glucose was regressed on SNP dosage data separately in each self-identified ethnic group using SNPTEST. All regression analyses were adjusted for age, gender, MESA study center, and the first two ethnic-specific principal components from eigenstrat analysis. Power calculations were performed in QUANTO [Gauderman 2002; Gauderman and Morrison 2010] using SNP-specific allelic effect estimates taken from the Dupuis et al. GWAS meta-analysis of fasting glucose in European ancestry individuals [Dupuis, et al. 2010]. Meta-analysis across ethnic groups was performed in METAL using the approach of combining test statistics and standard errors across studies [Willer, et al. 2010].

Selection of candidate SNPs and analysis regions

To generate data for analysis, we performed GWAS analysis of fasting glucose and fasting insulin separately in each ethnic group. No SNPs achieved genome-wide significance ($p < 5 \times 10^{-8}$) for association with fasting glucose in any of the four ethnic groups. This result was not unexpected, given the relatively small sample sizes (for GWAS analysis) in each ethnic group. We then chose to examine regions surrounding index SNPs with the top three largest effect sizes identified in the Dupuis et al. GWAS meta-analysis of fasting glucose (rs10830963 for *MTNR1B*, rs4607517 for *G6PC2*, rs560887 for *GCK*) [Dupuis, et al. 2010]. We selected these regions because we determined we had at least 80% power to detect an association between the index SNP and fasting glucose (given an alpha of .05) in the Caucasian sample in MESA. We felt that, in order to examine the consistency of association across ethnic groups in depth, we needed to be powered to detect a nominal $p < .05$ association in Caucasians, the group in which the index SNPs were originally identified. The Dupuis et al. meta-analysis which detected signals for fasting glucose and fasting insulin included over 100,000 people [Dupuis, et al. 2010] while the MESA Caucasian cohort included only about 2300 individuals. Therefore, for a p-value threshold of $p <.05$ (and given the effect sizes reported in the Dupuis paper), we had less than 50% power to detect to detect an association with fasting glucose or fasting insulin for any of the other reported index SNPs in the MESA Caucasian sample. However, given the interest in the consistency of all the SNP associations reported by Dupuis et al., we have listed SNP association results for fasting glucose (or insulin) across all four ethnic groups for all index SNPs reported in the Dupuis et al. paper in Supplementary Table 1. Meta-analysis results across the three non-Caucasian ethnic groups, and across all four ethnic groups are also presented in this table. Given our limited power and the previous identification of these index SNPs in a rigorous meta-analysis, we considered $p < .05$ to be a threshold for replication when examining the association of index SNPs across ethnic groups.

To identify broader candidate regions for analysis surrounding our three index SNPs of interest, the index SNP and nearest gene start and end locations were obtained from the Hap-Map website, build 36 [2003]. Regions were extended by adding 10 Kb to the end of both sides of the gene range. Because the index SNP for GCK (rs4607517) fell outside the gene range, the analysis region was extended 10 kb beyond the location of this SNP. All available SNPs from each candidate analysis region were analyzed. Supplemental Table 2 details the creation of the candidate analysis regions. From each candidate analysis region in each ethnic group we identified the SNP with the smallest p-value. In recognition of our limited power to detect significant associations in some ethnic groups, we also explored identifying the SNP with the largest β coefficient from regression across ethnic groups. We considered SNPs found to have either the largest beta or smallest p-value across multiple ethnic groups to potentially be interesting SNPs to further the study for causal variants in the region. The approach of examining SNPs with not only the lowest p-value, but also the highest likelihood ratio, effect size, or percentage variance explained has been suggested as a way to further explore several highly correlated SNPs in a single locus [Ioannidis, et al. 2009].

Results

Table 1 lists the characteristics of the study population, by ethnicity, after exclusions. AFA had the largest mean BMI while CHN had the smallest mean BMI. Differences in percentages of each ethnic group recruited at each study center reflect targeted enrollment that occurred at certain study centers.

Table 2 details the association of index SNPs for the three selected regions across the four ethnic groups represented in MESA. The SNPs were most significantly associated with fasting glucose in the CAU subgroup, although none of the three SNPs met the accepted

genome-wide threshold of $p < 5 * 10^{-8}$ [Frayling 2007]. SNP rs10830963 in *MTNR1B* demonstrated a relatively similar magnitude of association (consistent with the magnitude and direction observed in the Dupuis et al. GWAS meta-analysis [Dupuis, et al. 2010]) across all ethnic groups; the range of β coefficient from regression (i.e. the effect of 1 additional copy of the minor allele) was from 1.22–1.66 mg/dl and the association was nominally significant ($p<0.05$) in non-Caucasian ethnic groups. Power analyses in non-Caucasian groups demonstrated lower power to detect reported effect sizes, attributable largely to lower MAF and lower sample size in these three groups. In a meta-analysis across all four ethnic groups, the p-value for association was 1.29 E −12 and the p-value for heterogeneity was.97, indicating the effect size was similar across groups. SNP rs4607517 in *GCK* demonstrated a similar magnitude of association with fasting glucose across ethnic groups (range of β coefficient from regression −1.19– −1.06) but achieved nominal significance only in HIS. In a meta-analysis across all four ethnic groups, the p-value for association was 1.0 E −7 and the p-value for heterogeneity was.99, indicating the effect size was similar across groups. In contrast to the other two SNPs, magnitude and direction of association for rs560887 in *G6PC2* was not consistent across all four ethnic groups, although beta coefficients were similar in CAU and HIS and the association was nominally significant in HIS. In a meta-analysis across all four ethnic groups, the p-value for association was 2.1 E −6 and the p-value for heterogeneity was .15. Additional details about the SNPs in Table 2, including chromosome, position, and meta-analyses across the four ethnic groups and across the three non-white ethnic groups, are available in Supplementary Table 1 (as well as results for all other index SNPs from the Dupuis et al. meta-analysis).

Table 3 shows results from our exploratory analysis-- SNPs with either the most significant association, or largest β coefficient from regression for fasting glucose, by ethnicity in our three selected candidate analysis regions. SNP rs3781637 in the *MTNR1B* region was the SNP with the largest β coefficient from regression for both CHN and HIS, SNP rs2268569 in the *GCK* region was the SNP with the largest β coefficient from regression for both AFA and HIS, while SNP rs3821117 in the *G6PC2* region was the SNP with the largest β coefficient from regression for both CHN and AFA. Finally, SNP rs1799884 in the *GCK* region was the most significant SNP for HIS and the SNP with the largest β coefficient from regression for CAU. Additional details about SNPs rs3781637, rs1799884, rs2268569, and rs3821117, including chromosome, position, association results with fasting glucose in all four ethnic groups, and meta-analyses across the four ethnic groups and across the three non-white ethnic groups, are available in Supplementary Table 1. Supplementary Figure 1 (A–I) shows regional plots of SNP associations in candidate analysis regions with information about LD, by ethnic group.

Discussion

In this analysis we determined SNP rs10830963 in the *MTNR1B* gene and SNP rs4607517 in the *GCK* gene demonstrate a similar magnitude of association with fasting glucose across the four U.S. ethnic groups (Caucasian, African American, Hispanic, and individuals of Chinese descent) represented in MESA. The consistency of the association is reassuring and suggests that a causative variant lies in an area of moderate LD with this SNP for *all four* of these ethnic groups, thereby narrowing the putative region for this causative variant. In contrast, the magnitude of association for SNP rs560887 in *G6PC2* with fasting glucose was not similar across the four ethnic groups. This may suggest this SNP is not in LD with the causal variant for all four groups, but may also be due to chance, (especially as the SNP is rare in CHN and AFA populations resulting in a β coefficient for regression with large standard error in these ethnic groups).

These analyses demonstrate the difficulty of attempting to replicate GWAS findings from Caucasians across other ethnic groups. When MAF of a candidate SNP is lower in African Americans, for example, than Caucasians, larger sample sizes are needed to detect an association of similar magnitude to that reported in Caucasians. These problems are exacerbated when non-Caucasian study samples are relatively small.

We also explored identifying both the SNP with the smallest p-value and with the largest β coefficient from regression for each region *across ethnic groups* to see if we found any interesting SNPs for further study. We thought, given our low power in non-Caucasian MESA ethnic groups, and the consistent measurement of glucose across the four ethnicities in MESA, SNPs that were detected repeatedly across ethnic groups using these two parameters might provide interesting information to aid in the search for causal variants in the region. In fact, two of the four SNPs we identified this way were previously highlighted in the literature. SNP rs1799884 in *GCK*, was previously hypothesized [Weedon, et al. 2006] to be a SNP causally related to fasting glucose based on high sequence homology, a promoter location, and a comprehensive tag SNP study. When we meta-analyzed this SNP across the four ethnic groups in MESA, the p-value for the association of the SNP with fasting glucose was 1.3 E −6. SNP rs3821117 was one of the SNPs in the *G6PC2* region most significantly associated with plasma glucose in a Caucasian GWAS of fasting glucose published by Bouatia-Naji et al., and remained associated at the level of p = .05 when the association was adjusted for SNP rs560887, the SNP most significantly associated with fasting glucose in the region in the Bouatia-Naji GWAS [Bouatia-Naji, et al. 2008]. According to the Hap Map project [2003], SNP rs3821117 is in high LD with SNP rs2232328 in Caucasian, Asian, and Hispanic populations (although not, interestingly, in African Americans) (r^2 for CEPH = 1.0, r^2 for MEX = .923, r^2 for JPT/CHB = 1.0, r^2 for AFA = .24). SNP rs2232328 is a missense SNP in *G6PC2*, encoding the Ser342Cys amino acid change, and was the SNP most significantly (p = .06) associated with fasting glucose in our *G6PC2* region in African Americans. However, this SNP itself was not associated at the p< .05 level with fasting glucose in any of the four MESA ethnic sub-groups and neither SNP rs3821117 or rs2232328 was even nominally associated (p < .05) with fasting glucose in the meta-analysis of all four groups in MESA. (Of note, SNPs rs1799884, rs3821117, and rs2232328 were all typed (not imputed) in the MESA cohort.) Based on our findings as well as others [Bouatia-Naji, et al. 2008; Weedon, et al. 2006], we believe these SNPs should be further examined as others attempt to investigate the common causal genetic variants for fasting glucose variation.

The primary strength of this study was the availability of GWAS data and consistent measurements of fasting glucose across four ethnic groups in a single study. This allowed the easy comparison of effect sizes for SNP associations across the four ethnic groups. A weakness of the analysis was the limited power for GWAS analysis (and even individual SNP associations) in each of the ethnic subgroups. Unfortunately, given both the large sample sizes required for GWAS, and the potential for SNPs discovered in Caucasian populations to have smaller minor allele frequencies in other ethnic groups, it is likely that SNP association studies attempting to replicate fasting glucose associations from Caucasian GWAS in other ethnic groups will be underpowered. It is imperative then that power calculations be included in replication studies of these SNPs, so that false negative associations in other ethnic groups are not reported due to lack of power.

In summary, we performed a GWAS of fasting glucose in four ethnic groups in the MESA study. Analysis of three regions identified in previous Caucasian GWAS analysis demonstrated that the associations of SNP rs10830963 in *MTNR1B* and rs4607517 in *GCK* are of similar magnitude in the four ethnic groups in the MESA study, although there was

limited power to detect even nominally significant associations with these SNPs in some of the ethnic samples.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of non-diabetic participants included in fasting glucose and fasting insulin GWAS analyses, by race/ethnicity, MESA

	European Americans (CAU) (n=2349)	Chinese (CHN) (n= 664)	African American (AFA) (n= 1366)	Hispanic (HIS)(n=1171)
Age (years)	62.5 (10.3)	61.7 (10.4)	61.8 (10.2)	60.7 (10.3)
BMI (mg/kg/m^2)	27.5 (4.9)	23.8 (3.3)	29.8 (5.6)	29.0 (4.8)
Fasting glucose (mg/dl)	87.7 (9.9)	91.5 (10.0)	90.2 (10.6)	90.9 (10.7)
% female	53.2	51.4	54.9	52.0
Recruitment site				
% Winston-Salem, NC	21.6	0	26.1	0.3
% New York NY	8.3	0.3	17.8	33.6
%Baltimore, MD	20.2	0	30.7	0
%Minneapolis, MN	23.5	0	0	31.2
% Chicago, IL	21.1	36.1	16.3	0
% Los Angeles, CA	5.3	63.5	9.2	35.0

Mean (sd)

Table 2

Association of fasting glucose index SNPs with baseline fasting glucose by race/ethnicity, MESA

Gene(SNP)		CAU (n=2349)	CHN (n=664)	AFA (n=1366)	HIS (n=1171)
MTNR1B (rs10830963)	β* (SE)	1.43 (.32)	1.22 (.56)	1.66 (.73)	1.31 (.55)
	p-value	8.3 E −6	.03	.02	.02
	MAF (minor allele / major allele)	.27 (G/C)	.44 (G/C)	.08 (G/C)	.20 (G/C)
	Power†	.96	.58	.37	.57
	Imputation quality score††	NA	NA	NA	NA
G6PC2 (rs560887)	β* (SE)	−1.64 (.31)	0.50 (1.79)	0.13 (.82)	−1.60 (.61)
	p-value	1.8 E −7	.77	.87	.009
	MAF(minor allele / major allele)	.28 (T/C)	.03 (T/C)	.07 (T/C)	.14 (T/C)
	Power†	.99	.12	.38	.57
	Imputation quality score††	NA	NA	NA	NA
GCK (rs4607517)	β* (SE)	−1.19 (.36)	−1.10 (.76)	−1.06 (.72)	−1.19 (.56)
	p-value	.001	.16	.14	.03
	MAF(minor allele / major allele)	.17 (G/A)	.18 (G/A)	.11 (G/A)	.24 (G/A)
	Power†	.83	.34	.40	.57
	Imputation quality score††	.99	.91	.84	.86

β and p-value are for regression of fasting glucose on SNP, adjusted for age, gender, study center and ethnic-specific PCs

*Difference in fasting glucose (mg/dl) per 1 increase in the minor allele (additive model)

†Power to detect association with FG for p < .05, based on effect sizes from the Dupuis et al. GWAS meta-analysis [Dupuis, et al. 2010]--(β rs10830963 = 1.21 mg/dl, β rs560887 = −1.35 mg/dl, β rs4607517 = −1.12 mg/dl).

††oevar_imp from MACH [Li, et al. 2009], SNPs that were genotyped have score listed as NA

Table 3

Most significant and largest (effect size) SNP associations in candidate analysis regions by ethnic group, MESA

		CAU (n=2349)		CHN (n=664)		AFA (n=1366)		HIS (n=1171)	
		Most significant	**Largest β**	**Most significant**	**Largest β**	**Most significant**	**Largest β**	**Most significant**	**Largest β**
	rs#	rs10830963	rs10830963	rs1597023	rs3781637	rs10830963	rs10830964	rs10830963	rs3781637
MTNR1B	β*(SE)	1.43 (.32)	1.43 (.32)	−1.61 (.59)	2.44(1.18)	1.64 (.73)	−1.73(1.08)	1.31(.55)	2.84 (1.43)
	p	8.3 E −6	8.3 E −6	.0067	.039	.024	.11	.02	.05
	MAF (minor allele / major allele)	.27 (G/C)	.27 (G/C)	.33 (G/A)	.13 (T/C)	.08 (G/C)	.04 (G/C)	.20 (G/C)	.04 (T/C)
	Imputation score††	NA	NA	.99	.51	NA	NA	NA	.49
	rs#	rs3757840	rs1799884	rs2300587	rs741036	rs2908290	rs2268569	rs1799884	rs2268569
GCK	β*(SE)	1.07 (.30)	1.24 (.36)	1.98(.67)	2.19 (1.01)	−1.53(.43)	1.73 (.63)	1.54(.54)	−2.18 (1.07)
	p	.00035	.00055	.0029	.03	.00045	.0065	.0047	.043
	MAF (minor allele / major allele)	.47 (T/G)	.17 (T/C)	.23 (T/C)	.08 (G/A)	.48 (G/A)	.21 (T/G)	.21 (T/C)	.11 (T/G)
	Imputation score††	.87	NA	.96	NA	.99	.62	NA	.44
	rs#	rs560887	rs13430620	rs10497347	rs3821117	rs2232328	rs3821117	rs1402837	rs13431683
G6PC2	β*(SE)	−1.64(.31)	−2.63(1.06)	−1.18 (.59)	−2.31(1.88)	−0.76 (.41)	.85 (.46)	1.64 (.55)	−5.17 (1.88)
	p	1.8 E −7	.013	.045	.22	.06	.06	.0029	.0059
	MAF (minor allele / major allele)	.28 (T/C)	.04 (C/A)	.30 (T/C)	.023 (T/C)	.49 (G/C)	.27 (T/C)	.22 (T/C)	.013 (G/C)
	Imputation score††	NA	.40	NA	NA	NA	NA	.93	NA

β, SE, and p-value are for regression of fasting glucose on SNP, adjusted for age, gender, study center and ethnic-specific PCs

*Difference in fasting glucose (mg/dl) per 1 increase in the minor allele(additive model)

††oevar_imp from MACH [Li, et al. 2009], SNPs that were genotyped have score listed as NA