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Association of Common DNA Sequence Variants at Thirty-three Genetic Loci with Blood Lipids in Individuals of African Ancestry from Jamaica

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Abstract

The relevance of loci associated with blood lipids recently identified in European populations in individuals of African ancestry is unknown. We tested association between lipid traits and 36 previously described single nucleotide polymorphisms (SNPs) in 1,466 individuals of African ancestry from Spanish Town, Jamaica. For the same allele and effect direction as observed in individuals of European ancestry, SNPs at three loci (1p13, 2p21, and 19p13) showed statistically significant association ($p < 0.05$) with LDL, two loci (11q12, and 20q13) showed association with HDL cholesterol, and two loci (11q12 and 2p24) showed association with triglycerides. The most significant association was between a SNP at 1p13 and LDL cholesterol ($p = 4.6 \times 10^{-8}$). This SNP is in a linkage disequilibrium region containing four genes (CELSR2, PSRC1, MYBPHL, and SORT1) and was recently shown to relate to risk for myocardial infarction. Overall, the results of this study suggest that much of the genetic variation which influences blood lipids is shared across ethnic groups.

Introduction

Plasma levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol are associated with cardiovascular disease. It has been estimated that over 50% of variation in LDL and HDL cholesterol levels is heritable. (Kathiresan et al. 2007) Several of the genetic loci responsible for this heritability have been identified in genome-wide association (GWA) studies. We and others have recently shown association between 36 loci

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¹Notes: LDL = Total chol – (triglycerides $\times$ 0.46 + HDL)

³Diabetes mellitus: self-report of doctor diagnosis, or fasting glucose ≥ 7.1 mmol/l or 2 hr post-challenge glucose ≥ 11.1 mmol/l

⁴These participants are not significantly different from participants who were not genotyped in terms of age, proportion of men, BMI, total cholesterol, LDL cholesterol, and prevalence of diabetes mellitus. The genotyped participants were, however, significantly different ($P < 0.05$) from those not genotyped for HDL cholesterol (higher), triglycerides (lower), and systolic blood pressure (higher).

and blood lipids, 12 of which were newly identified. (Aulchenko et al. 2009; Kathiresan et al. 2009; Sabatti et al. 2009) These studies, however, were conducted in populations of European ancestry. The relevance of these findings to individuals of non-European ancestry remains unclear. (Adeyemo and Rotimi 2010)

Several recent studies have sought to determine whether the single-nucleotide polymorphisms (SNPs) identified thus far show similar association in racially diverse cohorts. Many SNPs showed association with lipids in a cross-sectional study of Malay participants in Singapore. (Muallem et al. 2007; Tai et al. 2009) In a cohort of primarily non-Hispanic blacks, Mexican Americans and non-Hispanic whites in the United States, several loci showed statistically significant association. (Keebler et al. 2009) Other reports, however, have found systematically lower effect sizes in the risk variants discovered in European populations when they were examined in persons of African ancestry. (Deo et al. 2009)

The purpose of this study was to attempt to replicate the previously reported genetic associations with hyperlipidemia in an African-descent population. Here we present the results of a similar validation study in a population sample from Jamaica.

Materials and Methods

Participants

Participants were recruited from Spanish Town, a stable, residential urban area neighboring the capital city of Kingston, Jamaica as part of the International Collaborative Study of Hypertension in Blacks (ICSHIB); recruitment and measurement procedures have been described in detail previously. (Ataman et al. 1996; Cooper et al. 1997) Briefly, a stratified random sampling scheme was used to recruit adult males and females aged 25 – 74 years from the general population; the participation rate was 60%. Spanish Town was chosen because its demographic make-up was broadly representative of Jamaica as a whole. Anthropometric and blood pressure measurements were performed by trained observers according to a standardized protocol. Serum lipid measurements were carried out on serum samples collected after an overnight fast and were performed on an Alcyon 300i autoanalyser (Abbott Laboratories, Abbott Park, IL, USA). The study protocol was reviewed and approved by the University Hospital of the West Indies/University of the West Indies/ Faculty of Medical Sciences Ethics Committee, Mona, Kingston, Jamaica, and the Institutional Review Board at Loyola University Medical Center, Maywood, IL. Written informed consent was obtained from all participants. Among 2,096 participants enrolled between 1993 and 1998, DNA and data from 1,466 participants were available; no other criteria (e.g. clinical or demographic) were used to select participants for the present study.

Phenotype Modeling

None of the participants were taking lipid-lowering medications, so lipid values were treated as continuously distributed traits. LDL-C was calculated according to Friedewald's formula: $LDL-C = total - (HDL-C + 1/5TG)$. If a triglyceride value was > 400 mg/dL, LDL-C was treated as a missing value. Triglyceride values were log(10)-transformed. Sex-specific phenotype residuals were constructed after accounting for age and age². Each set of residuals was standardized to a mean of zero and a standard deviation of one. The standardized residual served as the phenotype in genotype-phenotype association analyses. Generation of residuals was performed with the R statistical package (The R Foundation for Statistical Computing, Vienna, Austria).

²LDL and HDL units = mmol/l. One can multiply these values by 38.7 to convert to mg/dl.

SNP Selection and Genetic Analysis

We selected 36 SNPs that exceeded genome-wide statistical significance ($P < 5 \times 10^{-8}$) in 3 recently published GWA studies for LDL-C, HDL-C, and triglycerides (Aulchenko et al. 2009; Kathiresan et al. 2009; Sabatti et al. 2009). The full list of genotyped SNPs are summarized, with their associated loci, in Table Two.

Genotyping was performed with the Sequenom platform, which uses matrix-assisted laser-desorption ionization time-of-flight mass spectrometry as described previously (Gabriel and Ziaugra 2004).

Of the 36 genotyped SNPs, 33 met quality control standards with genotyping $> 90\%$ in the samples, Hardy-Weinberg $p > 1 \times 10^{-6}$ for SNPs, and 1 or less concordance errors among replicates. Average genotyping for the 33 SNPs in the Spanish Town panel was 98.5% and concordance among replicates $> 99.5\%$.

Association Testing

For each of the three traits, we used linear regression to test SNP-phenotype associations assuming an additive genetic model. These association analyses were performed in PLINK. We considered $P < 0.05$ to be the threshold for statistical significance. Power calculations were conducted with QUANTO software (University of Southern California, Los Angeles).

Results and Discussion

Participant characteristics

Participant characteristics are summarized in Table One.

Associations of Genotypes with Lipid Traits

In this study we examined the associations of thirty-three recently discovered dyslipidemia loci in a population of African descent from Jamaica. Despite the fact that these SNPs were originally derived via genome-wide association studies in a primarily Caucasian population, a number of the variants showed replicable association with lipid phenotype in this primarily African population.

Nine Loci Showed Significant Association with Lipid Traits—The genetic associations of blood lipids in the Spanish Town cohort with all tested SNPs identified through GWA are shown in Table 2. Given that several index SNPs were associated with more than one lipid trait in the original studies, we evaluated a total of 36 SNP-lipid trait associations, defining significance as an unadjusted p-value of less than 0.05, with effect in the same direction as the original study.

At this threshold, 7 index SNPs were significant. The strongest association was between rs12740374 (at 1p13 near CELSR2/PSRC1/SORT1) and LDL-C ($p = 4.6 \times 10^{-8}$). Among the six significant SNPs there were no notable differences in effect size. In fact, for the two loci with the best association with lipid traits (rs1274037 and rs6544713), the effect size was nearly identical to that seen in the much larger European population in which the original GWA was conducted.

Though replication of association at these 7 loci suggests that these loci influence blood lipid phenotypes in an African-descent population, it is not necessarily the case that the remaining 27 loci do not influence lipid phenotypes in this population. Given the modest effect sizes of the individual genetic variants for complex traits, the available sample sizes for many of the lipid traits were too small. To obtain a power of 80% for a SNP with a

MAF=0.20 and $p=0.05$, the SNP will need an effect size (β) of 2.6 mg/dl. Among the seven statistically significant SNPs in our study the average effect size was 0.26 mg/dl.

An alternative explanation for the null findings is that although the loci discovered in whites may be relevant in other ethnicities, the specific polymorphisms associated with lipids may differ across ethnicities because of differences in linkage disequilibrium structure; African populations, from which the individuals in this study have descended, have a more complex linkage disequilibrium structure than found in European whites. A final possibility to consider is that genetic variants influencing lipid traits in individuals of African ancestry may truly be different from those observed in whites. New variant discovery through additional GWA studies in non-white populations would be necessary to uncover these variants.

Majority of SNPs showed concordant direction of effect size—With regard to the latter two explanations for the occurrence of null results in this study, the observation of concordant direction of effect suggests that sample size may, in fact, be the critical factor. Of the thirty-six tested SNP-trait associations, effect sizes (β) were calculated for 35 in both Caucasian and Jamaican populations. The number of concordant SNPs in regards to effect size and direction of effect was 23 out of the 35 (0.74) which yields a $p=0.04$ when tested against random chance (50%) using a two-tailed exact binomial test. Though sample size may have limited our ability to replicate each SNP in the Jamaican cohort, the significant proportion of concordant SNPs suggests that these loci do influence lipid phenotypes in the Jamaican population.

In conclusion, we evaluated 36 SNPs in 33 loci from recent GWA studies for blood lipids in a population of individuals of African descent from Jamaica. We found that at 6 loci, the exact same SNP identified in whites was associated with lipids in Jamaicans. Though many of the SNPs did not replicate in this population for the reasons discussed above, the six loci that did replicate show the importance of these loci in a population of African ancestry.

The importance of these studies goes beyond determining relevant genetic polymorphisms in new populations. An oft-cited problem with GWAS is the failure to replicate. (Hirschhorn et al. 2002) If common diseases are associated with common risks, then replication across populations would be expected. However, if common diseases are associated with population-specific risks, then failure to replicate across populations would be expected. The replication of these SNPs in the Jamaican population and the concordance between previous reports and the direction of effect for the majority of the other SNPs in this study suggest that these are common risk alleles that are shared between populations.

These results further illustrate the importance of conducting functional analysis and fine mapping of these SNPs in individuals of African ancestry in addition to the European populations in which they were first described.

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Table One
Descriptive characteristics by sex for participants in the Spanish Town Study

	Men (609)		Women (857)		Total (1466)	
	N		N		N	
Age (years)	598	45.9 ± 14.2	844	39.9 ± 8.0	1442	45.9 ± 13.7
Body mass index (kg/m ²) ^{**}	602	23.8 ± 4.4	856	27.9 ± 6.5	1458	26.2 ± 6.1
Total cholesterol (mmol/l) ^{**}	511	4.61 ± 1.06	790	4.88 ± 1.12	1301	4.77 ± 1.10
HDL-C (mmol/l)	372	1.28 ± 0.325	607	1.32 ± 0.306	979	1.30 ± 0.310
LDL-C (mmol/l) [*]	362	2.97 ± 1.01	595	3.24 ± 1.07	957	3.14 ± 1.05
Triglycerides (mmol/l)	517	0.82 ± 0.43	790	0.81 ± 0.37	1307	0.81 ± 0.40
Systolic BP (mm Hg)	609	122.1 ± 21.0	856	121.5 ± 22.3	1465	121.8 ± 21.8
Diabetes mellitus (%) ^{**}	–	10.3	–	16.9	–	14.2
Antihypertensive medication use (%) [*]	–	7.2	–	15.4	–	12.0

^{*} P < 0.001

^{**} P < 0.0001

Table Two

Associations of Genotypes with Lipid Traits

Locus	Chr	SNP	Trait ^a	Allele 1, Allele 2 ^b	Allele 1 Freq (whites)	Allele 1 Freq (Jam.)	β (whites) ^d s.e.m	β (Jam.) ^e s.e.m	P (Jam.)	N (Jam.)
CELSR2, PSRC1, SORT1	1p13	rs12740374	LDL	G, T	0.21	0.26	-0.23 (0.02)	-0.25 (0.05)	4.6×10^{-8}	1132
ABCG8	2p21	rs6544713	LDL	C, T	0.32	0.16	0.15 (0.02)	0.19 (0.05)	2.4×10^{-4}	1140
LDLR	19p13	rs6511720	LDL	G, T	0.10	0.14	-0.26 (0.04)	-0.17 (0.06)	1.5×10^{-3}	1128
FADS1-FADS2-FADS3	11q12	rs174547	HDL	T, C	0.33	0.04	-0.09 (0.02)	-0.24 (0.11)	0.01	1205
FADS1-FADS2-FADS3	11q12	rs174547	TG	T, C	0.33	0.04	0.06 (0.02)	0.21 (0.10)	0.02	1345
HNF4A	20q13	rs1800961	HDL	C, T	0.03	0.003	-0.19 (0.05)	-0.68 (0.36)	0.03	1206
APOB	2p24	rs7557067	TG	A, G	0.22	0.14	-0.08 (0.02)	-0.10 (0.06)	0.03	1332
APOB	2p24	rs515135	LDL	C, T	0.20	0.52	-0.16 (0.02)	0.07 (0.04)	0.04	1140
ABCA1	9q31	rs1883025	HDL	C, T	0.26	0.64	-0.08 (0.02)	0.11 (0.04)	4.5×10^{-3}	1204
NR1H3	11	rs2167079	TG	A, G	0.42	0.40	0.04 (0.007)	0.07 (0.04)	0.05	1332
ANGPTL3	1p31	rs10889353	TG	A, C	0.33	0.39	-0.05 (0.02)	-0.06 (0.04)	0.06	1350
GCKR	2p23	rs1260326	TG	C, T	0.45	0.12	0.12 (0.02)	0.09 (0.06)	0.06	1333
HMGCR	5q13	rs3846663	LDL	C, T	0.38	0.23	0.07 (0.02)	0.07 (0.05)	0.07	1140
PLTP	20q13	rs7679	HDL	T, C	0.19	0.02	-0.07 (0.02)	-0.21 (0.16)	0.09	1204
TM64-HAVCR1	5q23	rs1501908	LDL	C, G	0.37	0.65	-0.07 (0.02)	-0.05 (0.04)	0.10	1130
APOA1-C3-A4-A5	11q23	rs964184	HDL	C, G	0.14	0.20	-0.17 (0.03)	0.06 (0.05)	0.11	1200
LPL	8p21	rs12678919	TG	A, G	0.10	0.11	-0.25 (0.03)	-0.07 (0.06)	0.13	1349
LPL	8p21	rs12678919	HDL	A, G	0.10	0.11	0.23 (0.03)	0.07 (0.07)	0.15	1206
GALNT2	1q42	rs4846914	HDL	A, G	0.40	0.90	-0.05 (0.02)	0.06 (0.07)	0.18	1206
ANGPTL4	19p13	rs2967605	HDL	C, T	0.16	0.23	-0.12 (0.04)	0.04 (0.05)	0.19	1205
LIPG	18q21	rs4939883	HDL	C, T	0.17	0.49	-0.14 (0.02)	-0.04 (0.04)	0.21	1203
TMEM57	1	rs10903129	TCho	A, G	0.46	0.29		-0.04 (0.04)	0.21	1345
CSPG3, CILP2, PBX4	19p13	rs10401969	LDL	T, C	0.06	0.18	-0.05 (0.04)	0.04 (0.05)	0.22	1141
DNAH11 ^d	7	rs12670798	LDL	A, G	0.24	0.33	0.09	-0.03 (0.04)	0.24	1128
MMAB, MVK	12q24	rs2338104	HDL	G, C	0.45	0.25	-0.07 (0.02)	-0.03 (0.05)	0.25	1188

Locus	Chr	SNP	Trait ^a	Allele 1, Allele 2 ^b	Allele 1 Freq (whites)	Allele 1 Freq (Jam.)	β (whites) ^d s.e.m	P (whites) ^c	β (Jam.) ^e s.e.m	P (Jam.)	N (Jam.)
MLXIPL	7q11	rs714052	TG	A, G	0.12	0.04	-0.16 (0.03)	3×10^{-15}	-0.06 (0.11)	0.30	1333
LIPC	15q22	rs10468017	HDL	C, T	0.30	0.16	0.10 (0.02)	8×10^{-23}	0.03 (0.05)	0.31	1203
CSPG3, CILP2, PBX4	19p13	rs17216525	TG	C, T	0.07	0.04	-0.11 (0.03)	4×10^{-11}	-0.05 (0.10)	0.33	1350
APOE-C1-C4-C2	19q13	rs4420638	LDL	A, G	0.16	0.22	0.29 (0.06)	4×10^{-27}	-0.02 (0.05)	0.34	1139
TRIB1	8q24	rs2954029	TG	A, T	0.44	0.31	-0.11 (0.02)	3×10^{-19}	0.01 (0.04)	0.36	1333
TCF1	12q24	rs2650000	LDL	C, A	0.36	0.11	0.07 (0.02)	2×10^{-8}	0.02 (0.06)	0.37	1134
MAFB	20q12	rs6102059	LDL	C, T	0.32	0.43	-0.06 (0.02)	4×10^{-9}	0.01 (0.04)	0.39	1124
TTC39B	9p22	rs471364	HDL	T, C	0.12	0.19	-0.08 (0.03)	3×10^{-10}	0.01 (0.05)	0.42	1191
PCSK9	1p32	rs11206510	LDL	T, C	0.19	0.13	-0.09 (0.02)	4×10^{-8}	-0.01 (0.06)	0.43	1118
PLTP	20q13	rs7679	TG	T, C	0.19	0.02	0.07 (0.02)	7×10^{-11}	-0.01 (0.14)	0.47	1345
APOA1-C3-A4-A5	11q23	rs964184	TG	C, G	0.14	0.20	0.30 (0.03)	4×10^{-62}	0.003 (0.05)	0.47	1343
LCAT	16q22	rs2271293	HDL	G, A	0.11		0.07 (0.03)	9×10^{-13}	Not Tested		1184
CETP	16q13	rs173539	HDL	C, T	0.32		0.25 (0.02)	4×10^{-75}	Not Tested		1184
XKR6-AMAC1L2	8p23	rs7819412	TG	A, G	0.48		-0.04 (0.02)	3×10^{-8}	Not Tested		1330

^aLipid trait for which SNP showed statistically significant association in Caucasian population

^bAllele 1 refers to minor allele in Caucasian population

^cAssociation in Caucasians demonstrated in previous publications (Aulchenko et al. 2009; Kathiresan et al. 2009; Sabatti et al. 2009)

^dBeta values calculated for Allele