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SHORT REPORT

Association of common DNA sequence variants at 33 genetic loci with blood lipids in individuals of African ancestry from Jamaica

R. Gupta · K. Ejebe · J. Butler · G. Lettre · H. Lyon · C. Guiducci · R. Wilks · F. Bennett · T. Forrester · B. Tayo · K. Musunuru · J. Hirschhorn · S. Kathiresan · R. S. Cooper · C. A. McKenzie

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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.

R. Gupta · K. Ejebe · K. Musunuru · S. Kathiresan
Cardiovascular Research Center and Center for Human Genetic Research, Massachusetts General Hospital, Boston, USA

R. Gupta · K. Ejebe · J. Butler · G. Lettre · C. Guiducci · K. Musunuru · J. Hirschhorn · S. Kathiresan
Program in Medical and Population Genetics, Broad Institute, Cambridge, USA

G. Lettre
Université de Montréal and Montreal Heart Institute, Montreal, Quebec, Canada

J. Butler · H. Lyon · J. Hirschhorn
Department of Genetics,
Children's Hospital Boston, Boston, USA

R. Wilks
Epidemiology Research Unit,
Tropical Medicine Research Institute,
University of the West Indies, Mona, Kingston 7, Jamaica

B. Tayo · R. S. Cooper
Preventive Medicine and Epidemiology,
Loyola University Medical Center, Maywood, USA

F. Bennett · T. Forrester · C. A. McKenzie (✉)
Tropical Metabolism Research Unit,
Tropical Medicine Research Institute,
University of the West Indies, Mona, Kingston 7, Jamaica
e-mail: colin.mckenzie02@uwimona.edu.jm

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 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, USA. 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 was 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. 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).

SNP selection and genetic analysis

We selected 36 SNPs that exceeded genome-wide statistical significance ($p < 5 \times 10^{-8}$) in three 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 is summarized, with their associated loci in Table 2.

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 fewer 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 using genetic power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/).

Results and discussion

Participant characteristics

Participant characteristics are summarized in Table 1.

Associations of genotypes with lipid traits

In this study, we examined the associations of 33 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

Table 1 Descriptive characteristics by sex for participants in the Spanish Town Study

	Men (609)	*N*	Women (857)	*N*	Total (1,466)	*N*
Age (years)	45.9 ± 14.2	598	39.9 ± 8.0	844	45.9 ± 13.7	1,442
Body mass index (kg/m^2)**	23.8 ± 4.4	602	27.9 ± 6.5	856	26.2 ± 6.1	1,458
Total cholesterol (mmol/l)**	4.61 ± 1.06	511	4.88 ± 1.12	790	4.77 ± 1.10	1,301
HDL-C (mmol/l)	1.28 ± 0.325	372	1.32 ± 0.306	607	1.30 ± 0.310	979
LDL-C (mmol/l)*	2.97 ± 1.01	362	3.24 ± 1.07	595	3.14 ± 1.05	957
Triglycerides (mmol/l)	0.82 ± 0.43	517	0.81 ± 0.37	790	0.81 ± 0.40	1,307
Systolic BP (mm Hg)	122.1 ± 21.0	609	121.5 ± 22.3	856	121.8 ± 21.8	1,465
Diabetes mellitus (%)**	10.3	–	16.9	–	14.2	–
Antihypertensive medication use (%)*	7.2	–	15.4	–	12.0	–

LDL = Total cholesterol − (triglycerides × 0.46 + HDL)

Unit of LDL and HDL is mmol/l. One can multiply these values by 38.7 to convert to mg/dl

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

These 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)

* $p < 0.001$

** $p < 0.0001$

variants showed replicable association with lipid phenotype in this primarily African population.

Six 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, seven 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 significant SNPs there were no notable differences in effect size. In fact, for the two loci with the best association with lipid traits (rs12740374 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 six loci suggests that the 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 $p = 0.05$ in 1466 individuals, the SNP must explain ~0.5% of overall trait variance. For most of the GWAS SNPs studied in this report, the proportion of the variance explained by the SNP is less than 0.5%.

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 36 tested SNP-trait associations, effect sizes (β) were calculated for 35 both in Caucasian and in Jamaican populations. The number of concordant SNPs regarding 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

Table 2 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	P (whites)[c]	β (Jam.)[d] s.e.m	P (Jam.)	N (Jam.)
CELSR2, PSRC1, SORT1	**1p13**	**rs12740374**	**LDL**	**G, T**	**0.21**	**0.26**	**−0.23 (0.02)**	**2×10^{-42}**	**−0.25 (0.05)**	**4.6×10^{-8}**	**1,132**
ABCG8	**2p21**	**rs6544713**	**LDL**	**C, T**	**0.32**	**0.16**	**0.15 (0.02)**	**2×10^{-20}**	**0.19 (0.05)**	**2.4×10^{-4}**	**1,140**
LDLR	**19p13**	**rs6511720**	**LDL**	**G, T**	**0.10**	**0.14**	**−0.26 (0.04)**	**2×10^{-26}**	**−0.17 (0.06)**	**1.5×10^{-3}**	**1,128**
FADS1-FADS2-FADS3	**11q12**	**rs174547**	**HDL**	**T, C**	**0.33**	**0.04**	**−0.09 (0.02)**	**2×10^{-12}**	**−0.24 (0.11)**	**0.01**	**1,205**
FADS1-FADS2-FADS3	**11q12**	**rs174547**	**TG**	**T, C**	**0.33**	**0.04**	**0.06 (0.02)**	**2×10^{-14}**	**0.21 (0.10)**	**0.02**	**1,345**
HNF4A	**20q13**	**rs1800961**	**HDL**	**C, T**	**0.03**	**0.003**	**−0.19 (0.05)**	**8×10^{-10}**	**− 0.68 (0.36)**	**0.03**	**1,206**
APOB	**2p24**	**rs7557067**	**TG**	**A, G**	**0.22**	**0.14**	**−0.08 (0.02)**	**9×10^{-12}**	**−0.10 (0.06)**	**0.03**	**1,332**
ABCA1	9q31	rs1883025	HDL	C, T	0.26	0.64	−0.08 (0.02)	1×10^{-9}	0.11 (0.04)	4.5×10^{-3}	1,204
APOB	2p24	rs515135	LDL	C, T	0.20	0.52	−0.16 (0.02)	5×10^{-29}	0.07 (0.04)	0.04	1,140
NR1H3	11	rs2167079	TG	A, G	0.42	0.40	0.04 (0.007)	5×10^{-8}	0.07 (0.04)	0.05	1,332
ANGPTL3	1p31	rs10889353	TG	A, C	0.33	0.39	−0.05 (0.02)	3×10^{-7}	−0.06 (0.04)	0.06	1,350
GCKR	2p23	rs1260326	TG	C, T	0.45	0.12	0.12 (0.02)	2×10^{-31}	0.09 (0.06)	0.06	1,333
HMGCR	5q13	rs3846663	LDL	C, T	0.38	0.23	0.07 (0.02)	8×10^{-12}	0.07 (0.05)	0.07	1,140
PLTP	20q13	rs7679	HDL	T, C	0.19	0.02	−0.07 (0.02)	4×10^{-9}	−0.21 (0.16)	0.09	1,204
TIMD4-HAVCR1	5q23	rs1501908	LDL	C, G	0.37	0.65	−0.07 (0.02	1×10^{-11}	−0.05 (0.04)	0.10	1,130
APOA1-C3-A4-A5	11q23	rs964184	HDL	C, G	0.14	0.20	−0.17 (0.03)	1×10^{-12}	0.06 (0.05)	0.11	1,200
LPL	8p21	rs12678919	TG	A, G	0.10	0.11	−0.25 (0.03)	2×10^{-41}	−0.07 (0.06)	0.13	1,349
LPL	8p21	rs12678919	HDL	A, G	0.10	0.11	0.23 (0.03)	2×10^{-34}	0.07 (0.07)	0.15	1,206
GALNT2	1q42	rs4846914	HDL	A, G	0.40	0.90	−0.05 (0.02)	4×10^{-8}	0.06 (0.07)	0.18	1,206
ANGPTL4	19p13	rs2967605	HDL	C, T	0.16	0.23	−0.12 (0.04)	1×10^{-8}	0.04 (0.05)	0.19	1,205
LIPG	18q21	rs4939883	HDL	C, T	0.17	0.49	−0.14 (0.02)	7×10^{-15}	−0.04 (0.04)	0.21	1,203
TMEM57	1	rs10903129	TCho	A, G	0.46	0.29	N/A	N/A	−0.04 (0.04)	0.21	1,345
CSPG3, CILP2, PBX4	19p13	rs10401969	LDL	T, C	0.06	0.18	−0.05 (0.04)	2×10^{-8}	0.04 (0.05)	0.22	1,141
DNAH11[d]	7	rs12670798	LDL	A, G	0.24	0.33	0.09/ N/A	6×10^{-9}	−0.03 (0.04)	0.24	1,128
MMAB, MVK	12q24	rs2338104	HDL	G, C	0.45	0.25	−0.07 (0.02)	1×10^{-10}	−0.03 (0.05)	0.25	1,188
MLXIPL	7q11	rs714052	TG	A, G	0.12	0.04	−0.16 (0.03)	3×10^{-15}	−0.06 (0.11)	0.30	1,333
LIPC	15q22	rs10468017	HDL	C, T	0.30	0.16	0.10 (0.02)	8×10^{-23}	0.03 (0.05)	0.31	1,203
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	1,350
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	1,139
TRIB1	8q24	rs2954029	TG	A, T	0.44	0.31	−0.11 (0.02)	3×10^{-19}	0.01 (0.04)	0.36	1,333
TCF1	12q24	rs2650000	LDL	C, A	0.36	0.11	0.07 (0.02)	2×10^{-8}	0.02 (0.06)	0.37	1,134
MAFB	20q12	rs6102059	LDL	C, T	0.32	0.43	−0.06 (0.02)	4×10^{-9}	0.01 (0.04)	0.39	1,124
TTC39B	9p22	rs471364	HDL	T, C	0.12	0.19	−0.08 (0.03)	3×10^{-10}	0.01 (0.05)	0.42	1,191
PCSK9	1p32	rs11206510	LDL	T, C	0.19	0.13	−0.09 (0.02)	4×10^{-8}	−0.01 (0.06)	0.43	1,118
PLTP	20q13	rs7679	TG	T, C	0.19	0.02	0.07 (0.02)	7×10^{-11}	−0.01 (0.14)	0.47	1,345
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	1,343
LCAT	16q22	rs2271293	HDL	G, A	0.11		0.07 (0.03)	9×10^{-13}	Not tested		1,184
CETP	16q13	rs173539	HDL	C, T	0.32		0.25 (0.02)	4×10^{-75}	Not tested		1,184
XKR6-AMAC1L2	8p23	rs7819412	TG	A, G	0.48		−0.04 (0.02)	3×10^{-8}	Not tested		1,330

Bold values indicate statistically significant results

[a] Lipid trait for which SNP showed statistically significant association in Caucasian population

[b] Allele 1 refers to minor allele in Caucasian population

[c] Association in Caucasians demonstrated in previous publications (Aulchenko et al. 2009; Kathiresan et al. 2009; Sabatti et al. 2009)

[d] Beta values calculated for Allele 1

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 often-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 in concordance with 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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