European Journal of Human Genetics (2004) 12, 584–590

www.nature.com/ejhg

ARTICLE

Are common disease susceptibility alleles the same in outbred and founder populations?

Dina L Newman*[,1,5], Sabine Hoffjan[1], Catherine Bourgain[1,6], Mark Abney[1], Raluca I Nicolae[1], Elle T Profits[1], Michael A Grow[2], Karen Walker[2], Lori Steiner[2], Rodney Parry[3], Rebecca Reynolds[2,7], Mary Sara McPeek[1,4], Suzanne Cheng[2] and Carole Ober[1]

[1]*Department of Human Genetics, University of Chicago, Chicago, IL, USA;* [2]*Roche Molecular Systems, Alameda, CA, USA;* [3]*Department of Medicine, University of South Dakota, Sioux Falls, SD, USA;* [4]*Department of Statistics, University of Chicago, Chicago, IL, USA;* [5]*Department of Biological Sciences, Rochester Institute of Technology, Rochester, NY;* [6]*INSERM U535, Villejuif, France;* [7]*Bayer Corporation, E Walpole, MA, USA*

Founder populations have been the subjects of complex disease studies because of their decreased genetic heterogeneity, increased linkage disequilibrium and more homogeneous environmental exposures. However, it is possible that disease alleles identified in founder populations may not contribute significantly to susceptibility in outbred populations. In this study we examine the Hutterites, a founder population of European descent, for 103 polymorphisms in 66 genes that are candidates for cardiovascular or inflammatory diseases. We compare the frequencies of alleles at these loci in the Hutterites to their frequencies in outbred European-American populations and test for associations with cardiovascular disease-associated phenotypes in the Hutterites. We show that alleles at these loci are found at similar frequencies in the Hutterites and in outbred populations. In addition, we report associations between 39 alleles or haplotypes and cardiovascular disease phenotypes ($P<0.05$), with five loci remaining significant after adjusting for multiple comparisons. These data indicate that this founder population is informative and offers considerable advantages for genetic studies of common complex diseases.
European Journal of Human Genetics (2004) **12,** 584–590. doi:10.1038/sj.ejhg.5201191
Published online 21 April 2004

Keywords: founder population; complex traits; candidate genes; cardiovascular disease; inflammatory disease; association tests

Introduction

Many founder populations are currently the subjects of genetic studies of common diseases. The advantages of these populations are well known.[1–4] As many of the diseases under investigation in founder populations are major public health concerns, the primary rationale for these studies is to identify genetic factors that are also important in the general (outbred) population. However, it is possible that susceptibility alleles present in founder populations may not contribute to susceptibility in outbred individuals, as is the case for many Mendelian disorders.[5–8] Although identifying mutations associated with common diseases only in founder populations could identify pathways important for disease and possibly new therapeutic approaches, there would be considerably less enthusiasm for gene discovery in founder populations if their susceptibility alleles were population-specific.

In order to assess the utility of founder populations for identifying alleles that are associated with susceptibility to common diseases in outbred populations, we conducted a survey of polymorphisms in 66 candidate genes for cardiovascular disease-related phenotypes in the Hutterites

*Correspondence: Dr DL Newman, Department of Biological Sciences, Rochester Institute of Technology, 85 Lomb Memorial Dr., Rochester, NY 14623, USA. Tel: +1 585 475 4482; Fax: +1 585 475 5766;
E-mail: dnewman@mail.rit.edu
Received 4 September 2003; revised 16 January 2004; accepted 18 February 2004

and compared the results to published studies of the same variants in outbred populations. The Hutterites are particularly well suited for this study because the more than 35 000 extant Hutterites are derived from fewer than 90 ancestors who were born in Europe in the early 17th to early 18th century.[9] The Hutterites of South Dakota, the subjects of our study, are descendants of only 64 of these 90 ancestors.[10] The small number of Hutterite founders increases the likelihood that rare alleles could have risen to modest frequencies due to drift, making it possible that alleles that are very rare in outbred populations contribute significantly to disease risk in the Hutterites. Conversely, if rare variants contribute significantly to common diseases in outbred populations,[11] these variants may not be present in the Hutterites because either they were not carried by one of the founders or were lost due to drift.

In this investigation, we asked three questions: (1) Are variants thought to be associated with cardiovascular disease-related phenotypes in outbred populations present in the Hutterites? (2) Are allele frequencies at these loci similar in the Hutterites and outbred populations? (3) Are the alleles with evidence for association with disease in the Hutterites the same as in outbred populations? Our results indicate that founder populations are indeed informative for genetic studies of common diseases.

Materials and methods

Founder and outbred population samples

Measurements of blood pressure and serum lipids were determined as part of a larger study of complex trait genetics in the Hutterites; the details of these studies were described previously. [4] Briefly, phenotype information and blood samples for DNA extraction were collected from all individuals age 6 years or older during field trips to nine Hutterite colonies in 1993–1994 and 1996–1997. The 813 South Dakota Hutterites in our studies are related to each other in a 13-generation, 1623-person pedigree[12] and have been the subjects of genome-screens for asthma and atopy,[10,13,14] fasting serum insulin,[15] and serum triglyceride[16] susceptibility loci.

We used two published data sets to assess allele frequencies in outbred populations: a cohort of 142 Caucasian individuals at high risk for cardiovascular disease recruited from the San Francisco Bay area (UCSF)[17] and a cohort of 207 Caucasian children at high risk for developing asthma or atopy (COAST).[18]

Genotyping

Genotyping was performed with two linear array panels developed by Roche Molecular Systems, Inc (Alameda, CA, USA). Genotyping accuracy by this assay is estimated at $>99\%$ (S. Cheng *et al*., personal communication). The first panel, hereafter referred to as the 'CVD' set, consisted of 65 biallelic polymorphisms in 36 genes. These polymorphisms were selected as candidate markers for cardiovascular disease based on published reports in outbred populations. An earlier version of this panel with 35 polymorphisms in 15 genes, 26 of them overlapping with our panel, was previously described.[17] Four single-nucleotide polymorphisms (SNPs) in two genes (*CETP* intron 14 +1, +3 and asp442gly,[19] and *TNF* -244[20]) were excluded because they were originally identified in non-European populations and were very rare ($<0.5\%$) in European populations (S. Cheng *et al*., unpublished). The second panel, hereafter referred to as the 'INF' set, included 50 biallelic polymorphisms in 35 genes. These polymorphisms were selected as candidates for inflammatory diseases. Although not all of the SNPs included in the INF panel had been studied in patients with cardiovascular disease or associated phenotypes, we considered them to be good candidates because of the important role of inflammation in cardiovascular disease (reviewed by Libby[21]). Eight SNPs in five genes were present in both sets. The final study set included 103 polymorphisms in 66 genes. In total, 721 Hutterites were genotyped for the CVD panel and 794 for the INF panel; 692 individuals were genotyped for both. Error checking was performed by comparing blind duplicates, utilizing the known pedigree structure to detect Mendelian errors and testing for Hardy–Weinberg equilibrium.

Statistical analyses

We compared the allele frequencies in the populations using a case–control (CC) association test that takes into account both the relatedness between individuals and inbreeding.[22] Instead of contrasting the frequency of an allele between a group of cases and a group of controls, we contrasted the frequency of the allele between a sample of Hutterites and a sample of outbred individuals. Because we did not have access to the raw data of the outbred samples, but only to their size and allele frequency, we created dummy samples of genotypes corresponding to these sizes and frequencies, assuming Hardy–Weinberg equilibrium. Thus, the data did not allow us to contrast genotype frequencies between the Hutterite sample and the outbred samples. We note however that there was no departure from Hardy–Weinberg equilibrium in the Hutterite sample once the pedigree structure was taken into account. Differences in the genotype frequencies between the two samples are thus due to the differences in allele frequencies and to inbreeding, which is the same for every locus.

We also compared allele frequencies in the populations by calculating F_{ST} with the program GENDIST in the PHYLIP software package.[23]

We tested for associations in the Hutterites using 89 polymorphic markers (multiple SNPs in the *APOE*, *GC* and *LTA* genes and the *CETP* promoter were analyzed as haplotypes) and six quantitative phenotypes associated with cardiovascular disease: systolic blood pressure (SBP),

diastolic blood pressure (DBP), low-density lipoprotein–cholesterol (LDL), high-density lipoprotein–cholesterol (HDL), triglycerides (TG), and lipoprotein (a) [Lp(a)]. The descriptions of these phenotypes in the Hutterites are shown in supplementary Table 1. To test for association, we used two approaches that take into account the relatedness between all pairs of individuals in our sample.[15,22] The first test, called the general two-allele model (GTAM), allows for a quantitative trait to follow any two-allele model (including dominant, recessive, and additive).[15] In these analyses, age and gender were included as covariates. In order to eliminate excess skewness and kurtosis, a transformation was applied to each trait, resulting in a phenotype that closely matched a normal distribution. Cube root was used for LDL and HDL, $\log_{10}$ was used for TG, Lp(a) and SBP, and square root was used for DBP. The second approach utilized a case–control design whereby the cases were individuals in our sample in the highest quartile for LDL, Lp(a), and TG and the lowest quartile for HDL, while the controls were the individuals in the lowest quartile for LDL, Lp(a), and TG and the highest quartile for HDL, after adjusting for age and gender (113, 93, 121, and 121 cases and an equivalent number of controls for each phenotype, respectively). For the HTN phenotype, 110 cases (adults taking antihypertensive medication or stage 1 or higher hypertension as defined by the World Health Organization-International Society of Hypertension;[24] children with high blood pressure as defined by Council on Cardiovascular Disease in the Young[25]) were compared with 84 controls (age and gender matched normotensive controls for all individuals under age 40 years, plus all normotensive adults over age 40 years). To test for association with these categorical phenotypes, we used two CC association tests (the quasi-likelihood score test and the corrected χ^2-test).[22]

Results

Frequencies of the minor alleles in the Hutterites are shown for all three populations in Supplementary Table II (Hutterite and COAST data are also on our websites). Ten polymorphisms were monomorphic in the Hutterites (supplementary Table 2; shown in bold). All of these SNPs had low minor allele frequencies (<0.07) or were monomorphic in the UCSF or COAST samples or in other published studies.[17,26–28] Thus, 93 of the 103 (90%) SNPs that were associated with disease or identified as candidates in outbred European and European–American populations were present in the Hutterites. Among the more common SNPs (minor allele frequencies >0.10) in the outbred population samples, all (58 of 58) were present in the Hutterites, whereas among SNPs with minor allele frequencies <0.10 in the outbred population samples, only 35 of 45 (78%) were present in the Hutterites. Thus, approximately 25% of the less common alleles (<0.10) were either not present in the Hutterite founders or were lost due to drift.

The correlation between minor allele frequencies in the Hutterites and the COAST and UCSF samples are shown in Figure 1a and b, respectively. Among the 50 polymorphisms in the INF panel, allele frequencies in the Hutterite and COAST samples were strongly correlated ($R=0.854$), as were the 26 polymorphisms from the CVD panel that could be compared between the Hutterite and UCSF samples ($R=0.939$). The average difference between minor allele frequencies in the Hutterites and outbred samples was 0.066 (range 0–0.210). Overall, however, among alleles present in the Hutterites, the frequencies are similar to those observed in outbred Caucasian populations. Only three of 75 comparisons (4%) were significantly different ($P<0.05$ for *ACE* intron 16 ins/del, *CTLA4* −318 C/T and *IL5RA* −80 G/A), as would be expected by chance. Additionally, in comparisons of Hutterite *vs* UCSF allele frequencies, $F_{ST}=0.0191$, and of

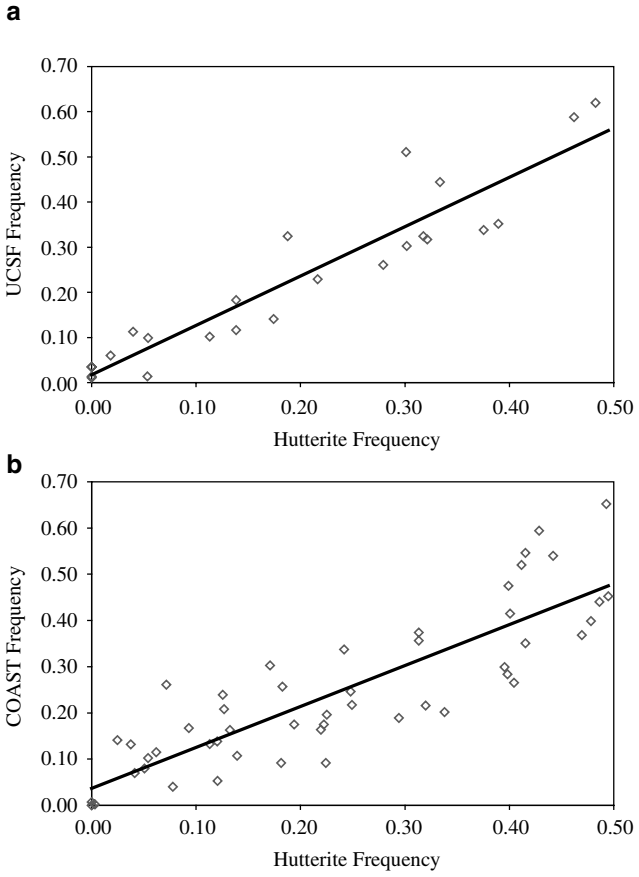

Figure 1 Comparison of allele frequencies in Hutterites and outbred populations. (**a**) Hutterites compared to UCSF for 26 biallelic polymorphisms from the CVD set. $R=0.939$. (**b**) Hutterites compared to COAST for 50 biallelic polymorphisms from the INF set. $R=0.854$.

Hutterite *vs* COAST, $F_{ST} = 0.0230$. These F_{ST} values are similar to those obtained in comparisons between European populations.[29,30] Thus, the Hutterites do not appear to have significantly diverged from other European-American population samples.

We found 39 significant associations ($P < 0.05$) of lipid levels or blood pressure with 29 different polymorphisms using the GTAM (supplementary Table 3). Four of these associations were highly significant ($P < 0.001$) and remained significant even after adjusting for 89 loci by a permutation test.[15] We found 56 significant associations ($P < 0.05$) of abnormal lipid levels or hypertension with 42 different polymorphisms using the CC tests (supplementary Table 4). The same four alleles that were highly significant by the GTAM plus one more were highly significantly associated by CC tests and remained significant after adjusting for testing of polymorphisms in 63 genes and two CC tests using a Bonferroni correction (adjusted critical *P*-value = 0.0004). These include the *APOE* ε2 allele with low LDL levels (GTAM $P = 1.0 \times 10^{-3}$; CC $P = 6.0 \times 10^{-5}$), the *LDLR Nco*I+ allele with high LDL levels (CC $P = 2.2 \times 10^{-4}$), the *CETP* −631C/−629A haplotype with high HDL levels (GTAM $P = 1.3 \times 10^{-5}$; CC $P = 3.9 \times 10^{-5}$), the *APOC3* 3175G allele with high TG levels (GTAM $P = 9.3 \times 10^{-5}$; CC $P = 1.6 \times 10^{-5}$), and the *LPA* +93T allele with high Lp(a) levels (GTAM $P = 2.9 \times 10^{-8}$; CC $P = 2.9 \times 10^{-4}$).

These five associated variants had frequencies ranging from 0.02 (*APOE*) to 0.56 (*CETP*) in the Hutterites. The average minor allele frequency for all 49 variants that showed association with one or more phenotype in the Hutterites was 0.24 (range 0.02–0.49), which was the same as the average allele frequency for the 41 loci that were not associated with these phenotypes in the Hutterites (average minor allele frequency 0.25, range 0.03–0.49).

Discussion

Although classical population genetic theory predicts that human founder populations will have allele frequencies on average similar to those in the ancestral population, to our knowledge this is the first study to provide empiric evidence of this prediction for both biallelic markers and loci selected because of their potential role as susceptibility alleles for common diseases. In this investigation, all of the variants identified in outbred populations, except for approximately one fourth of low frequency (<0.10) variants, were present in the Hutterites. These results are consistent with results of a previous analysis of microsatellite alleles in the Hutterites and CEPH families.[13] In that study of 164 microsatellite alleles, all alleles that were present in the CEPH families but absent in the Hutterites had frequencies <0.10 in the CEPH sample. Among those alleles that were present in the Hutterites, the frequencies were similar to those found in the CEPH families.[13] Likewise, in this study SNP allele frequencies were similar in Hutterite and outbred populations. Thus, common alleles (>0.10) that are identified and associated with diseases in outbred populations should be present in the Hutterites and will often show similar patterns of association.

Owing to the complex etiology of cardiovascular disease and associated phenotypes, we would not expect to replicate all associations in the Hutterites, particularly those reported only in non-Caucasian populations or in only a single sample. However, we would expect to find some associations with related phenotypes, particularly with those that have been replicated in multiple samples. All five of the highly significant associations in the Hutterites have been reported in other populations. The *APOC3* 3175 polymorphism (a.k.a. 'the *Sst*I polymorphism') is located in exon 4 in the 3′ untranslated region (3′UTR) of the gene encoding apolipoprotein C-III (apo C-III). Apo C-III is a component of triglyceride-rich lipoproteins, and numerous studies have demonstrated an association between high triglycerides levels and the rare (G) allele of this SNP (reviewed by Groenendijk *et al*.[31]), as reported in this study. Apolipoprotein E is the primary ligand for the LDL receptor, and the ε2 variant binds with significantly lower affinity to the receptor than either the ε3 or ε4 isoforms. It has been well established that the ε2 variant is associated with lower levels of cholesterol and LDL, and that carriers of the ε2 variant have a lower incidence of coronary heart disease (reviewed by Eichner *et al*.[32]). In the Hutterites, this variant was associated with significantly lower levels of LDL by the GTAM, whereas the ε4 variant was significantly associated with 'high LDL' in the CC study. More than 770 mutations have been discovered in the LDL receptor to date.[33,34] Mutations in LDLR have been associated with familial hypercholesterolemia, a disorder characterized by high levels of LDL, and variation in the gene also contributes significantly to LDL levels in the general population.[35–37] The *Nco*I site is a polymorphism in exon 18, where the '+' allele is on a haplotype that is associated with increased total and LDL-cholesterol,[38,39] consistent with our finding of an association with 'high LDL' in the Hutterites. Cholesteryl ester transfer protein (CETP) transfers cholesteryl esters from HDL to LDL and very low-density lipoprotein (VLDL), thus promoting the redistribution of lipids from anti-atherogenic lipoproteins to proatherogenic lipoproteins. Several polymorphisms in the coding region of CETP have been associated with CETP activity, HDL concentration, CHD and/or atherosclerosis (reviewed by Barter *et al*.[40]). In addition, the C allele at −629 in the promoter has been associated with high-CETP and low-HDL concentrations.[41,42] Here, we report significant associations between the −631C/−629A haplotype and high HDL by the GTAM and between the −631C/−629C haplotype and low HDL in the CC test. *LPA* encodes apolipoprotein(a), a protein

component of Lp(a), and variation in this gene is known to affect the concentration of Lp(a) in the blood. The +93 promoter polymorphism influences expression of *LPA*[43] and has been associated with serum Lp(a) levels in Japanese and Africans.[44,45] In the Hutterites, the +93T allele was very significantly associated with high Lp(a) levels by the GTAM and CC tests. Many other loci that have been associated with cardiovascular phenotypes in outbred populations were also associated with similar phenotypes in the Hutterites (eg, *AGTR1*, *AGT*, *LIPC*, *ACE*).

A number of novel associations with SNPs in the INF panel are also reported here, although none of these remained significant after adjusting for multiple comparisons and some may represent false positives. Nevertheless, alleles at some of these loci were associated with multiple phenotypes with $P<0.01$ (eg, *TGFB1*, *IL13*, *IL6*, *CTLA4*) making them particularly intriguing candidates that may contribute to the inflammatory and immune processes that underlie atherosclerosis. Overall, among the polymorphic markers tested, 30 of 51 (59%) in the CVD panel and 24 of 47 (51%) in the INF panel showed some association with blood pressure or lipid levels in the Hutterites, indicating that many common disease-associated variants that are present in outbred populations also show evidence for association with related phenotypes in the Hutterites.

One question that cannot be addressed directly with these data is whether disease-associated variants first detected in the Hutterites are also present and associated with disease in outbred populations. However, data from our laboratory suggest that this is likely to be the case. For example, all SNPs that we have identified in the Hutterites have also been detected in outbred populations,[46–48] although our strategy for SNP detection in the Hutterites would not detect very low-frequency SNPs (less than approximately 0.02). However, because we would have less power to detect susceptibility alleles in this very low-frequency range, the disease susceptibility alleles that we identify in the Hutterites will likely be higher frequency, and therefore should be present in the general population. On the other hand, we do not expect all disease associations detected in the Hutterites to be replicated in all outbred populations. In particular, susceptibility to common diseases involves gene–gene and gene–environment interactions. The frequencies of interacting alleles differ among populations, and the Hutterites' unique lifestyle (eg, prohibition of cigarette smoking and uniformly high-fat, high-salt diet) may not be replicated in other populations. In addition, linkage disequilibrium (LD) is increased in the Hutterites and other founder populations. This should result in longer ancestral haplotypes on which disease susceptibility alleles reside, and a greater likelihood that an associated allele detected in the Hutterites is merely a marker for the true susceptibility allele on the extended haplotype. Because the ancestral haplotype is not likely to extend as far in the outbred population, the association may not be replicated. It should be noted that characterizing LD among the SNPs was not the purpose of this study and indeed, we do not have the correct data or methods to assess this important question.

It is not possible at this time to predict whether most susceptibility alleles for common diseases can be identified in founder populations, because the proportional contributions of common *vs* rare variants to common diseases are still being debated.[11,49] Indeed, given the size of the Hutterite sample it is unlikely that we would have sufficient power to detect associations with alleles in the very low-frequency range, particularly if they have modest effects on susceptibility, as is expected for genes underlying complex phenotypes. However, our results indicate that populations like the Hutterites will be useful for identifying common variants that contribute to common diseases in the general (outbred) population and that interpretation of our results will not be limited to this unique population. On the other hand, the Hutterite's large and well-characterized genealogy, along with a naturally high fertility rate resulting in large family sizes, provide significant advantages for mapping complex trait genes compared with outbred populations. Further, the fact that association studies in young founder populations such as the Hutterites provide equivalent power with fewer markers and smaller sample sizes, and therefore lower costs, compared with outbred populations,[50] makes them well suited for identifying risk alleles for common diseases.

Acknowledgements

We thank Nancy Cox and Jonathan Pritchard for helpful discussions, Ken Weiss for comments on an earlier draft of this manuscript, Arkadiy Silbergleit for helping to develop the CVD panel, Daniel Schneider and Joonhee Park for technical assistance, and the Hutterites for their participation in this study. This work was funded by NIH Grants HL56399, HL66533, HL72414, and field studies were funded in part by a grant from Hoffmann-LaRoche, Inc.

Electronic-database information

The URLs for data in this article are: www. genes.uchicago.edu/hutterite/inflasnps (INF panel on Hutterites), www.genes.uchicago.edu/hutterite/cvdsnps (CVD panel on Hutterites), and www.genes.uchicago.edu/coast/inflasnps (INF panel on COAST). The rs numbers in Supplementary Table II are from dbSNP: www.ncbi.nlm.nih.gov/SNP/.

References

1 Kruglyak L: Genetic isolates: separate but equal? *Proc Natl Acad Sci USA* 1999; **96**: 1170–1172.
2 Lander ES, Schork NJ: Genetic dissection of complex traits. *Science* 1994; **265**: 2037–2048.

3 Peltonen L: Positional cloning of disease genes: advantages of genetic isolates. *Hum Hered* 2000; **50**: 66–75.
4 Ober C, Abney M, McPeek MS: The genetic dissection of complex traits in a founder population. *Am J Hum Genet* 2001; **69**: 1068–1079.
5 McKusick VA, Hostetler JA, Egeland JA, Eldridge R: The distribution of certain genes in the Old Order Amish. *Cold Spring Harbor Symp Quant Biol* 1964; **XXIX**: 99–114.
6 Bowen P: Workshop on genetic disorders in the Hutterites – Edmonton, Canada, October 12-13, 1983. *Am J Med Genet* 1985; **22**: 449–451.
7 Kalaydjieva L, Gresham D, Calafell F: Genetic studies of the Roma (Gypsies): a review. *BMC Med Genet* 2001; **2**: 5.
8 Sipila K, Aula P: Database for the mutations of the Finnish disease heritage. *Hum Mutat* 2002; **19**: 16–22.
9 Martin AO: The founder effect in a human isolate: evolutionary implications. *Am J Phys Anthropol* 1970; **32**: 351–368.
10 Ober C, Tsalenko A, Parry R, Cox NJ: A second-generation genomewide screen for asthma-susceptibility alleles in a founder population. *Am J Hum Genet* 2000; **67**: 1154–1162.
11 Pritchard JK: Are rare variants responsible for susceptibility to complex diseases? *Am J Hum Genet* 2001; **69**: 124–137.
12 Abney M, McPeek MS, Ober C: Estimation of variance components of quantitative traits in inbred populations. *Am J Hum Genet* 2000; **66**: 629–650.
13 Ober C, Cox NJ, Abney M *et al*: Genome-wide search for asthma susceptibility loci in a founder population. The Collaborative Study on the Genetics of Asthma. *Hum Mol Genet* 1998; **7**: 1393–1398.
14 Ober C, Tsalenko A, Willadsen S *et al*: Genome-wide screen for atopy susceptibility alleles in the Hutterites. *Clin Exp Allergy* 1999; **29** (Suppl 4): 11–15.
15 Abney M, Ober C, McPeek MS: Quantitative-trait homozygosity and association mapping and empirical genomewide significance in large, complex pedigrees: fasting serum-insulin level in the hutterites. *Am J Hum Genet* 2002; **70**: 920–934.
16 Newman DL, Abney M, Dytch H *et al*: Major loci influencing serum triglyceride levels on 2q14 and 9p21 localized by homozygosity-by-descent mapping in a large Hutterite pedigree. *Hum Mol Genet* 2003; **12**: 137–144.
17 Cheng S, Grow MA, Pallaud C *et al*: A multilocus genotyping assay for candidate markers of cardiovascular disease risk. *Genome Res* 1999; **9**: 936–949.
18 Hoffjan S, Nicolae D, Ostrovnaja I *et al*: Genetic variation in immunoregulatory pathways and atopic phenotypes in infancy. *J Allergy Clin Immunol* 2004; **113**: 511–518.
19 Inazu A, Jiang XC, Haraki T *et al*: Genetic cholesteryl ester transfer protein deficiency caused by two prevalent mutations as a major determinant of increased levels of high density lipoprotein cholesterol. *J Clin Invest* 1994; **94**: 1872–1882.
20 Zimmerman PA, Guderian RH, Nutman TB: A new TNFA promoter allele identified in South American Blacks. *Immunogenetics* 1996; **44**: 485–486.
21 Libby P: Inflammation in atherosclerosis. *Nature* 2002; **420**: 868–874.
22 Bourgain C, Hoffjan S, Nicolae R *et al*: Novel case–control test in a founder population identifies P-selectin as an atopy susceptibility locus. *Am J Hum Genet* 2003; **73**: 612–626.
23 Felsenstein J PHYLIP (Phylogeny Inference Package). In: version 3.5c. ed. *Department of Genetics*. University of Washington: Seattle, Distributed by the author: 1993.
24 World Health Organization-International Society of Hypertension: 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *Guidelines Subcommittee*. *J Hypertens* 1999; **17**: 151–183.
25 Williams CL, Hayman LL, Daniels SR *et al*: Cardiovascular health in childhood: a statement for health professionals from the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2002; **106**: 143–160.
26 von Eckardstein A, Funke H, Schulte M *et al*: Nonsynonymous polymorphic sites in the apolipoprotein (apo) A-IV gene are associated with changes in the concentration of apo B- and apo A-I- containing lipoproteins in a normal population. *Am J Hum Genet* 1992; **50**: 1115–1128.
27 Rosendaal FR, Siscovick DS, Schwartz SM *et al*: A common prothrombin variant (20210 G to A) increases the risk of myocardial infarction in young women. *Blood* 1997; **90**: 1747–1750.
28 Rubattu S, Ridker P, Stampfer MJ *et al*: The gene encoding atrial natriuretic peptide and the risk of human stroke. *Circulation* 1999; **100**: 1722–1726.
29 Cavalli-Sforza LL, Menozzi P, Piazza A: Analysis of classical markers in forty-two selected populations; In: *The history and geography of human genes*, Abridged paperback edition ed. Princeton, NJ: Princeton University Press,; 1993, pp. 73–77.
30 Nicholson G, Donnelly P: Assessing population differentiation and isolation from single-nucleotide polymorphism data. *J R Statist Soc B* 2002; **64**: 1–21.
31 Groenendijk M, Cantor RM, de Bruin TW, Dallinga-Thie GM: The apoAI-CIII-AIV gene cluster. *Atherosclerosis* 2001; **157**: 1–11.
32 Eichner JE, Dunn ST, Perveen G *et al*: Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol* 2002; **155**: 487–495.
33 Varret M, Rabes JP, Thiart R *et al*: LDLR Database (second edition): new additions to the database andvthe software, and results of the first molecular analysis. *Nucleic Acids Res* 1998; **26**: 248–252.
34 www.ucl.ac.uk/fh.
35 Schuster H, Humphries S, Rauh G *et al*: Association of DNA-haplotypes in the human LDL-receptor gene with normal serum cholesterol levels. *Clin Genet* 1990; **38**: 401–409.
36 Haviland MB, Ferrell RE, Sing CF: Association between common alleles of the low-density lipoprotein receptor gene region and interindividual variation in plasma lipid and apolipoprotein levels in a population-based sample from Rochester, Minnesota. *Hum Genet* 1997; **99**: 108–114.
37 Knoblauch H, Bauerfeind A, Krahenbuhl C *et al*: Common haplotypes in five genes influence genetic variance of LDL and HDL cholesterol in the general population. *Hum Mol Genet* 2002; **11**: 1477–1485.
38 Hansen PS, Defesche JC, Kastelein JJ *et al*: Phenotypic variation in patients heterozygous for familial defective apolipoprotein B (FDB) in three European countries. *Arterioscler Thromb Vasc Biol* 1997; **17**: 741–747.
39 Ahn YI, Kamboh MI, Aston CE *et al*.: Role of common genetic polymorphisms in the LDL receptor gene in affecting plasma cholesterol levels in the general population. *Arterioscler Thromb Vasc Biol* 1994; **14**: 663–670.
40 Barter PJ, Brewer HB Jr, Chapman MJ *et al*: Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler Thromb Vasc Biol* 2003; **23**: 160–167.
41 Dachet C, Poirier O, Cambien F *et al*: New functional promoter polymorphism, CETP/−629, in cholesteryl ester transfer protein (CETP) gene related to CETP mass and high density lipoprotein cholesterol levels: role of Sp1/Sp3 in transcriptional regulation. *Arterioscler Thromb Vasc Biol* 2000; **20**: 507–515.
42 Klerkx AH, Tanck MW, Kastelein JJ *et al*.: Haplotype analysis of the CETP gene: not TaqIB, but the closely linked −629C→A polymorphism and a novel promoter variant are independently associated with CETP concentration. *Hum Mol Genet* 2003; **12**: 111–123.
43 Suzuki K, Kuriyama M, Saito T, Ichinose A: Plasma lipoprotein(a) levels and expression of the apolipoprotein(a) gene are dependent on the nucleotide polymorphisms in its 5′-flanking region. *J Clin Invest* 1997; **99**: 1361–1366.
44 Ichinose A, Kuriyama M: Detection of polymorphisms in the 5′-flanking region of the gene for apolipoprotein(a). *Biochem Biophys Res Commun* 1995; **209**: 372–378.
45 Kraft HG, Windegger M, Menzel HJ, Utermann G: Significant impact of the +93 C/T polymorphism in the apolipoprotein(a)

gene on Lp(a) concentrations in Africans but not in Caucasians: confounding effect of linkage disequilibrium. *Hum Mol Genet* 1998; **7**: 257–264.
46 Ober C, Leavitt SA, Tsalenko A *et al*: Variation in the interleukin 4-receptor alpha gene confers susceptibility to asthma and atopy in ethnically diverse populations. *Am J Hum Genet* 2000; **66**: 517–526.
47 Donfack J, Kogut P, Forsythe S *et al*: Sequence variation in the promoter region of the cholinergic receptor muscarinic 3 gene and asthma and atopy. *J Allergy Clin Immunol* 2003; **111**: 527–532.
48 Ober C, Aldrich CL, Chervoneva I *et al*: Variation in the HLA-G promoter region influences miscarriage rates. *Am J Hum Genet* 2003; **72**: 1425–1435.
49 Lohmueller KE, Pearce CL, Pike M *et al*: Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet* 2003; **33**: 177–182.
50 Service SK, Sandkuijl LA, Freimer NB: Cost-effective designs for linkage disequilibrium mapping of complex traits. *Am J Hum Genet* 2003; **72**: 1213–1220.
51 McPeek MS, Wu X, Ober C: Bestlinear unbiased allele-frequency estimation in complex pedigrees. *Biometrics* 2004; **60**: in press.

Supplementary information accompanies the paper on European Journal of Human Genetics website (http://www.nature.com/ejhg)

Supplementary Table 1. Characteristics of the Hutterites. Total cholesterol, LDL, HDL, TG and Lp(a) are given in mg/dl. Blood pressure is given in mm Hg. Age and BMI are listed separately for the set of subjects with lipid data and the set of subjects with blood pressure data. Individuals used in the GTAM analyses were included in this table; 37 subjects were excluded from analyses of lipid levels because they were taking hypercholesterolemia medication or exogenous estrogens, and 58 subjects were excluded from analyses of SBP and DBP because they were on antihypertensive medication. The 485 individuals included in the lipid analyses were 49% male and 51% female, and the 623 individuals included in the blood pressure analyses were 47% male and 53% female. All were non-smokers.

Phenotype[a]	N	Mean	Std. Dev.	Range
Lipids				
Age (years)	485	34.5	15.8	14-89
BMI (kg/m^2)	477	26.1	5.5	14-52
Total Cholesterol	485	201.3	43.0	110-452
LDL	452[b]	128.2	39.0	46-386
HDL	485	47.3	13.8	8-105
TG	485	134.8	92.3	16-714
Lp(a)	374	2.88	3.64	0.10-22.53
Blood Pressure				
Age (years)	623	27.8	16.2	5-89
BMI (kg/m^2)	611	23.9	5.9	12-52
SBP	623	122.4	14.4	76-180
DBP	623	79.6	10.0	48-110

[a]BMI = body mass index, LDL = low density lipoprotein-cholesterol, HDL = high density lipoprotein-cholesterol, TG = triglycerides, Lp(a) = lipoprotein(a), SBP = systolic blood pressure, DBP = diastolic blood pressure.
[b]LDL could not be calculated accurately for 33 people with TG > 300 mg/dl and were excluded.

Supplementary Table 2. Allele frequencies in the Hutterite, COAST and UCSF samples. Only a subset of the CVD panel was genotyped in the UCSF sample.[17] Polymorphisms are shown with the common allele in the Hutterites listed first. COAST data from ref.[18]; UCSF data from ref.[17]. Hutterite allele frequencies are based on best-linear unbiased estimates that take into account the relatedness between individuals.[51] Allele frequencies are given with 95% confidence intervals. SNPs that were not polymorphic in the Hutterites are in bold and were not included in association studies. Allele frequencies that were significantly different (P <0.05) between Hutterite and outbred samples are indicated with an asterisk (see Methods).

Gene	Polymorphism	rs#	Location	Panel	Hutterites	UCSF	COAST
ACE	intron 16 ins/del	1799752	17q23	CVD	0.30 ±0.17*	0.51 ±0.06*	
ADD1	gly460trp	4961	4p16.3	CVD	0.13 ±0.13		
ADRB2	gly16arg	1042713	5q32	CVD/INF	0.31 ±0.18		0.36 ±0.05
	gln27glu	1042714	5q32	CVD/INF	0.49 ±0.19		0.44 ±0.05
	thr164ile	1800888	5q32	INF	0		0.01 ±0.01
ADRB3	trp64arg	4994	8p11.22	CVD	0.03 ±0.06		
AGT	thr235met	699	1q42.13	CVD	0.46 ±0.19	0.59 ±0.06	
AGTR1	1166 A/C	5186	3q24	CVD	0.30 ±0.17	0.30 ±0.05	
APOA4	thr347ser	675	11q23.3	CVD	0.35 ±0.18		
	gln360his	5110	11q23.3	CVD	0		
APOB	thr71ile	1367117	2p24	CVD	0.19 ±0.15	0.32 ±0.05	
	arg3500gln	5742904	2p24	CVD	0	0.01 ±0.01	
APOC3	-641 C/A	2542052	11q23.3	CVD	0.48 ±0.19		
	-482 C/T	2854117	11q23.3	CVD	0.28 ±0.17	0.26 ±0.05	
	-455 T/C	2854116	11q23.3	CVD	0.48 ±0.19	0.62 ±0.06	
	1100 C/T	4520	11q23.3	CVD	0.32 ±0.18	0.32 ±0.05	
	3175 C/G	5128	11q23.3	CVD	0.14 ±0.13	0.12 ±0.04	
	3206 T/G	4225	11q23.3	CVD	0.33 ±0.18	0.44 ±0.06	
APOE[a]	cys112arg	429358	19q13	CVD	0.14 ±0.13	0.18 ±0.04	
	arg158cys	7412	19q13	CVD	0.02 ±0.05	0.06 ±0.03	
C3	arg102gly	2230199	19p13	INF	0.29 ±0.18		0.19 ±0.04
C5	val802ile	17611	9q34.1	INF	0.49 ±0.19		0.45 ±0.05
CBS	ile278thr,68-bp ins	5742905[b]	21q22.3	CVD	0.04 ±0.07	0.11 ±0.04	
CCR2	val62ile	1799864	3p21	INF	0.05 ±0.08		0.08 ±0.03
CCR3	pro39leu	5742906	3p21.3	INF	<0.01		<0.01
CCR5	-2454 A/G	1799987	3p21	INF	0.40 ±0.19		0.48 ±0.05
	32bp del	333	3p21	INF	0.14 ±0.13		0.11 ±0.03
CD14	-260 T/C	2569190	5q31.1	INF	0.41 ±0.19		0.52 ±0.05

CETP	-631 C/A[c]	1800776	16q21	CVD	0.01 ±0.03		
	-629 A/C[c]	1800775	16q21	CVD	0.43 ±0.20		
	ile405val	5882	16q21	CVD	0.38 ±0.18	0.34 ±0.06	
CSF2	ile117thr	25882	5q31.1	INF	0.19 ±0.15		0.18 ±0.04
CTLA4	-318 C/T	5742909	2q33	INF	0.22 ±0.16*		0.09 ±0.03*
	thr17ala	231775	2q33	INF	0.31 ±0.18		0.37 ±0.05
F2	**20210 G/A**	1799963	11p11.1	CVD	0		
F5	arg506gln	6025	1q23	CVD	0.05 ±0.09	0.01 ±0.01	
F7	-323 del/ins	5742910	13q34	CVD	0.27 ±0.17		
	arg353gln	6046	13q34	CVD	0.27 ±0.17		
FCER1B	glu237gly	569108	11q13	INF	0.08 ±0.10		0.04 ±0.02
FGB	-455 G/A	1800790	4q28	CVD	0.22 ±0.16	0.23 ±0.05	
GC	glu416asp[c]	7041	4q12	INF	0.40 ±0.19		0.42 ±0.05
	thr420lys[c]	4588	4q12	INF	0.25 ±0.16		0.25 ±0.04
GNB3	825 C/T	5443	12p13	CVD	0.30 ±0.17		
ICAM1	gly214arg	1799969	19p13	CVD/INF	0.11 ±0.12		0.13 ±0.03
	lys56met	5491	19p13	INF	0		0
IL1A	-889 C/T	1800587	2q14	INF	0.40 ±0.19		0.30 ±0.04
IL1B	-1418 C/T	16944	2q14	INF	0.24 ±0.16		0.34 ±0.05
	phe105 (C/T)	1143634	2q14	INF	0.32 ±0.18		0.22 ±0.04
IL4	-589 C/T	2243250	5q31.1	INF	0.12 ±0.12		0.14 ±0.03
IL4RA	val50ile	1805010	16p12	INF	0.42 ±0.19		0.55 ±0.05
	ser478pro	1805015	16p12	INF	0.22 ±0.16		0.16 ±0.04
	gln551arg	1801275	16p12	INF	0.23 ±0.16		0.20 ±0.04
IL5RA	-80 G/A	2290608	3p26	INF	0.07 ±0.10*		0.26 ±0.04*
IL6	-174 C/G	1800795	7p21	INF	0.44 ±0.19		0.54 ±0.05
	-572 G/C	1800796	7p21	INF	0.04 ±0.08		0.07 ±0.02
IL9	thr113met	2069885	5q31.1	INF	0.04 ±0.07		0.13 ±0.03
IL10	-571 C/A	1800872	1q31	INF	0.40 ±0.19		0.26 ±0.04
IL13	intron 3 C/T	1295686	5q31	INF	0.13 ±0.13		0.24 ±0.04
ITGA2	873 G/A	1062535	5q11.2	CVD	0.45 ±0.19		
ITGB3	leu33pro	5918	17q21	CVD	0.17 ±0.14	0.14 ±0.04	
LDLR	NcoI+/-	5742911	19p13.2	CVD	0.30 ±0.17		
LIPC	-480 C/T	1800588	5q21	CVD	0.20 ±0.15		
LPA	93 C/T	1652503	6q27	CVD	0.12 ±0.13		
	121 G/A	1800769	6q27	CVD	0.12 ±0.12		
LPL	**-93 T/G**	1800590	8p22	CVD	0	0.04 ±0.02	
	asp9asn	1801177	8p22	CVD	0	0.04 ±0.02	
	asn291ser	268	8p22	CVD	0	0.01 ±0.01	
	ser447term	328	8p22	CVD	0.11 ±0.12	0.10 ±0.04	
LTA[a]	intron A A/G	909253	6p21.3	INF	0.17 ±0.14		0.30 ±0.04
	thr26asn	1041981	6p21.3	CVD	0.17 ±0.14		
LTC4S	-444 A/C	730012	5q35	INF	0.18 ±0.15		0.26 ±0.04
MMP3	-1171 A_5/A_6	3025058	11q22	CVD	0.33 ±0.18		
MTHFR	677 C/T	1801133	1p36.3	CVD	0.39 ±0.19	0.35 ±0.06	
NOS2A	asp346 (C/T)	1137933	17q11	INF	0.25 ±0.16		0.22 ±0.04

NOS3	-922 A/G	1800779	7q36	CVD/INF	0.47 ±0.19		0.37 ±0.05
	-690 C/T	3918226	7q36	CVD	0.08 ±0.10		
	asp298glu	1799983	7q36	CVD/INF	0.49 ±0.19		0.35 ±0.05
NPPA	**664 G/A**	5063	1p36.2	CVD	0		
	2238 T/C	5065	1p36.2	CVD	0.06 ±0.09		
PAI1	-675 G_5/G_4	1799768	7q22	CVD	0.37 ±0.18		
	11053 T/G	7242	7q22	CVD	0.31 ±0.18		
PON1	leu55met	3202100	7q21	CVD	0.25 ±0.17		
	gln192arg	662	7q21	CVD	0.32 ±0.18	0.32 ±0.05	
PON2	ser311cys	7493	7q21	CVD	0.22 ±0.16		
PPARG	pro12ala	1801282	3p25	CVD	0.14 ±0.13		
SCNN1A	trp493arg	5742912	12p13	CVD	0.06 ±0.09		
	ala663thr	2228576	12p13	CVD	0.33 ±0.18		
SCYA11	-1328G/A	4795895	17q21	INF	0.22 ±0.16		0.18 ±0.04
	ala23thr	3744508	17q21	INF	0.13 ±0.13		0.21 ±0.04
SDF1	800 G/A	1801157	10q11.1	INF	0.34 ±0.18		0.20 ±0.04
SELE	ser128arg	5361	1q23	CVD/INF	0.05 ±0.09	0.10 ±0.03	0.10 ±0.03
	leu554phe	5355	1q23	CVD	0	0.04 ±0.02	
SELP	ser330asn	6131	1q23	INF	0.13 ±0.13		0.16 ±0.04
	val640leu	6133	1q23	INF	0.18 ±0.15		0.09 ±0.03
TCF7	pro19thr	5742913	5q31.1	INF	0.06 ±0.09		0.12 ±0.03
TGFB1	-509 C/T	1800469	19q13.1	INF	0.40 ±0.19		0.28 ±0.04
TNF	-376 G/A	1800750	6p21.3	CVD	0.03 ±0.06		
	-308 G/A	1800629	6p21.3	CVD/INF	0.02 ±0.06		0.14 ±0.03
	-238 G/A[c]	361525	6p21.3	CVD/INF	0.12 ±0.12		0.05 ±0.02
UGB	38 G/A	3741240	11q12	INF	0.42 ±0.19		0.35 ±0.05
VCAM1	-1594 T/C	1041163	1p32	INF	0.09 ±0.11		0.17 ±0.04
VDR	thr1met	2228570	12q13	INF	0.48 ±0.19		0.40 ±0.05
	intron 8 A/G	1544410	12q13	INF	0.43 ±0.19		0.59 ±0.05

[a]The amino acid 112 and 158 polymorphisms of *APOE* were combined into a haplotype with the standard ε2/ε3/ε4 designation for analysis, and the *LTA* 26 and intron a polymorphisms were combined in a two-locus haplotype for analysis.

[b]Linear array assay cannot distinguish between heterozygous and homozygous carriers of the insertion.

[c]*CETP* –631 and –629 were genotyped as two-locus haplotypes in the CVD panel; *TNF* –238 was genotyped as a two locus haplotype with –244 G/A, which was excluded from this study (see text); *GC* glu416asp and thr420lys were genotyped as a two-locus haplotype in the INF panel.

Supplementary Table 3. Twenty-nine polymorphisms accounted for 39 associations with lipid levels and/or blood pressure in the Hutterites by the GTAM (P <0.05). Direction of association indicates whether the allele is associated with high or low phenotypic values. Associations that remain significant after correction for testing of 89 loci (see ref.[15]) are shown in bold.

Phenotype	Gene	Associated Allele or Haplotype	Direction of Association	P-value
LDL				
	AGTR1	1166C	negative	0.0064
	APOE	**ε2**	**negative**	**0.0010**
HDL				
	APOC3	-641A	negative	0.023
		-455C	positive	0.027
	CETP	**-631C/-629A**	**positive**	**1.3×10^{-5}**
	SELE	arg128	negative	0.041
TG				
	APOC3	-641A	positive	0.010
		-482C	negative	0.016
		-455T	negative	0.013
		3175G	**positive**	**9.3×10^{-5}**
		3206G	positive	0.047
	CCR2	ile62	positive	0.039
	CETP	-631C/-629A	negative	0.045
	CTLA4	-318C	negative	0.041
	ICAM1	arg214	positive	0.032
	IL4	-589T	negative	0.014
	IL6	-572C	positive	0.013
	SCNN1A	ala663	positive	0.048
	SCYA11	thr23	negative	0.029
Lp(a)				
	APOB	thr71	negative	0.019
	C5	ile802	negative	0.018
	CCR2	val62	positive	0.041
	CETP	val405	positive	0.048
	FGB	-455A	negative	0.043
	LPA	**+93T**	**positive**	**2.9×10^{-8}**
	SELE	ser128	positive	0.038
SBP				
	ACE	intron 16 ins	positive	0.0026

	AGT	met235	negative	0.027
	C5	val802	positive	0.0098
	FGB	-455G	positive	0.015
	IL5RA	-80A	negative	0.025
	TGFB1	-509C	positive	0.0078
DBP				
	AGT	met235	negative	0.037
	C5	val802	positive	0.0091
	IL13	intron 3 C	positive	0.0038
	IL1B	-1418T	negative	0.024
	IL4RA	val50	positive	0.042
	LIPC	-480T	positive	0.0022
	TGFB1	-509C	positive	0.0040

Supplementary Table 4. Forty-two polymorphisms accounted for 56 associations with lipid levels and/or hypertension in Hutterites by two CC tests (P <0.05). The test with the more significant result is shown. Associations that remain significant after correction for testing of 63 genes and two CC tests are indicated in bold.

Phenotype	Gene	Associated Allele or Haplotype	Case-Control Test[a]	*P*-value
LDL				
	AGTR1	1166A	Corr χ^2	0.0025
	APOC3	1100C	Corr χ^2	0.042
		3206T	Corr χ^2	0.026
	APOE	**ε4**	**QL**	**6.0×10^{-5}**
	FGB	-455A	QL	0.025
	GC	glu416/thr420	Corr χ^2	0.026
	IL4	-589C	Corr χ^2	0.047
	IL4R	arg551	QL	0.025
	IL6	-572C	QL	0.043
		-174G	Corr χ^2	0.0038
	IL13	intron 3 C	Corr χ^2	0.0080
	LDLR	**NcoI+**	**QL**	**0.00022**
	LTA	intron A/thr26	QL	0.0015
	NPPA	2238T	Corr χ^2	0.038
HDL				
	AGTR1	1166A	Corr χ^2	0.032
	APOC3	3175G	QL	0.042
	CCR2	ile62	QL	0.034
	CETP	**-631C/-629C**	**QL**	**3.9×10^{-5}**
	CTLA4	-318T	Corr χ^2	0.0071
		thr17	Corr χ^2	0.040
	ICAM1	arg214	Corr χ^2	0.0056
	IL1B	-1418C	Corr χ^2	0.015
	IL5R	-80G	QL	0.038
	PON2	ser311	Corr χ^2	0.0091
	SCNN1A	arg493	Corr χ^2	0.021
	SDF1	800G	Corr χ^2	0.0052
	SELE	arg128	QL	0.019
	TGFB1	-509T	QL	0.010
TG				
	APOC3	-482T	Corr χ^2	0.040
		1100T	QL	0.036
		3175G	**QL**	**1.6×10^{-5}**
		3206G	QL	0.0065

	C3	arg102	QL	0.0078
	CCR2	ile62	QL	0.038
	CTLA4	-318T	Corr χ^2	0.0065
	ICAM1	arg214	Corr χ^2	0.0054
	IL4	-589C	Corr χ^2	0.010
	IL6	-572C	QL	0.012
	PON2	ser311	Corr χ^2	0.042
	SELP	val640	QL	0.031
Lp(a)				
	APOB	ile71	QL	0.026
	C5	val802	QL	0.0079
	F7	-323 ins	Corr χ^2	0.0037
		gln353	Corr χ^2	0.012
	FGB	-455G	Corr χ^2	0.013
	ITGB3	pro33	Corr χ^2	0.011
	LPA	**+93T**	**QL**	**0.00029**
	NOS3	-690C	Corr χ^2	0.038
	SELE	arg128	Corr χ^2	0.027
	SELP	val640	Corr χ^2	0.017
	TGFB1	-509C	QL	0.023
HTN				
	AGT	thr235	Corr χ^2	0.0096
	APOA4	ser347	QL	0.033
	FGB	-455G	Corr χ^2	0.029
	IL13	intron 3	QL	0.048
	IL5R	-80G	QL	0.014
	LIPC	-480T	Corr χ^2	0.0045
	TNF	-308A	QL	0.0089

[a]Corr χ^2 = corrected chi-square test; QL = quasi-likelihood chi square test (see ref.[22]).