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NHLBI GO Exome Sequencing Project

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[21]Acute Lung Injury (ALI), [22]Atherosclerosis Risk in Communities (ARIC), [23]Cardiovascular Health Study (CHS), [24]Chronic Obstructive Pulmonary Disease (COPDGene), [25]Coronary Artery Risk Development in Young Adults (CARDIA), [26]Cystic Fibrosis (CF), [27]Early Pseudomonas Infection Control (EPIC), [28]Framingham Heart Study (FHS), [29]Jackson Heart Study (JHS), [30]Lung Health Study (LHS), [31]Multi-Ethnic Study of Atherosclerosis (MESA), [32]Pulmonary Arterial Hypertension (PAH), [33]Severe Asthma Research Program (SARP), [34]Women's Health Initiative (WHI)

Cardiovascular Health Study:
This research was supported by contracts HHSN268201200036C, N01HC85239, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/PI.htm.

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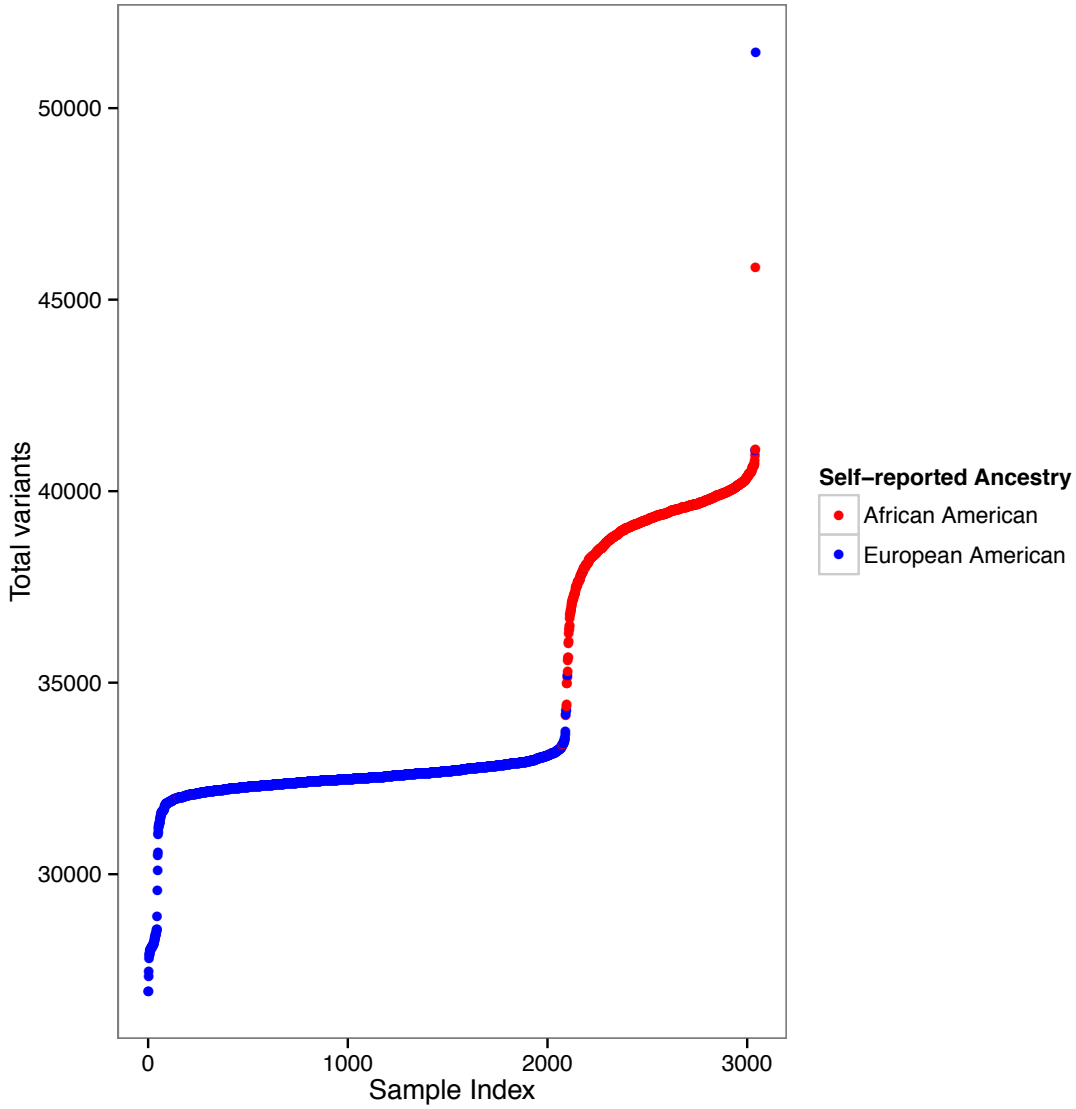
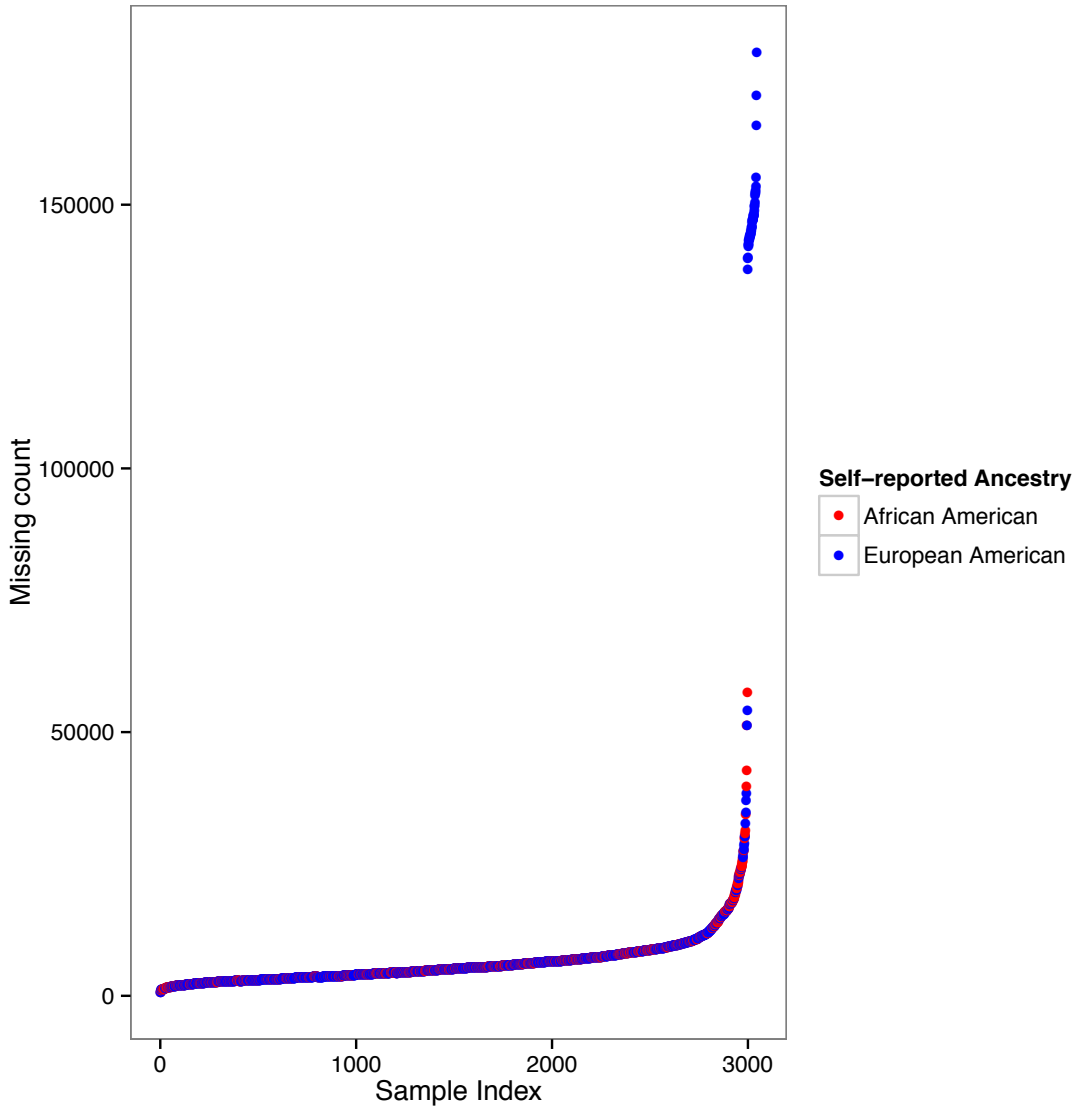
Supplementary Figure 1. Total number of single nucleotide variants per sample



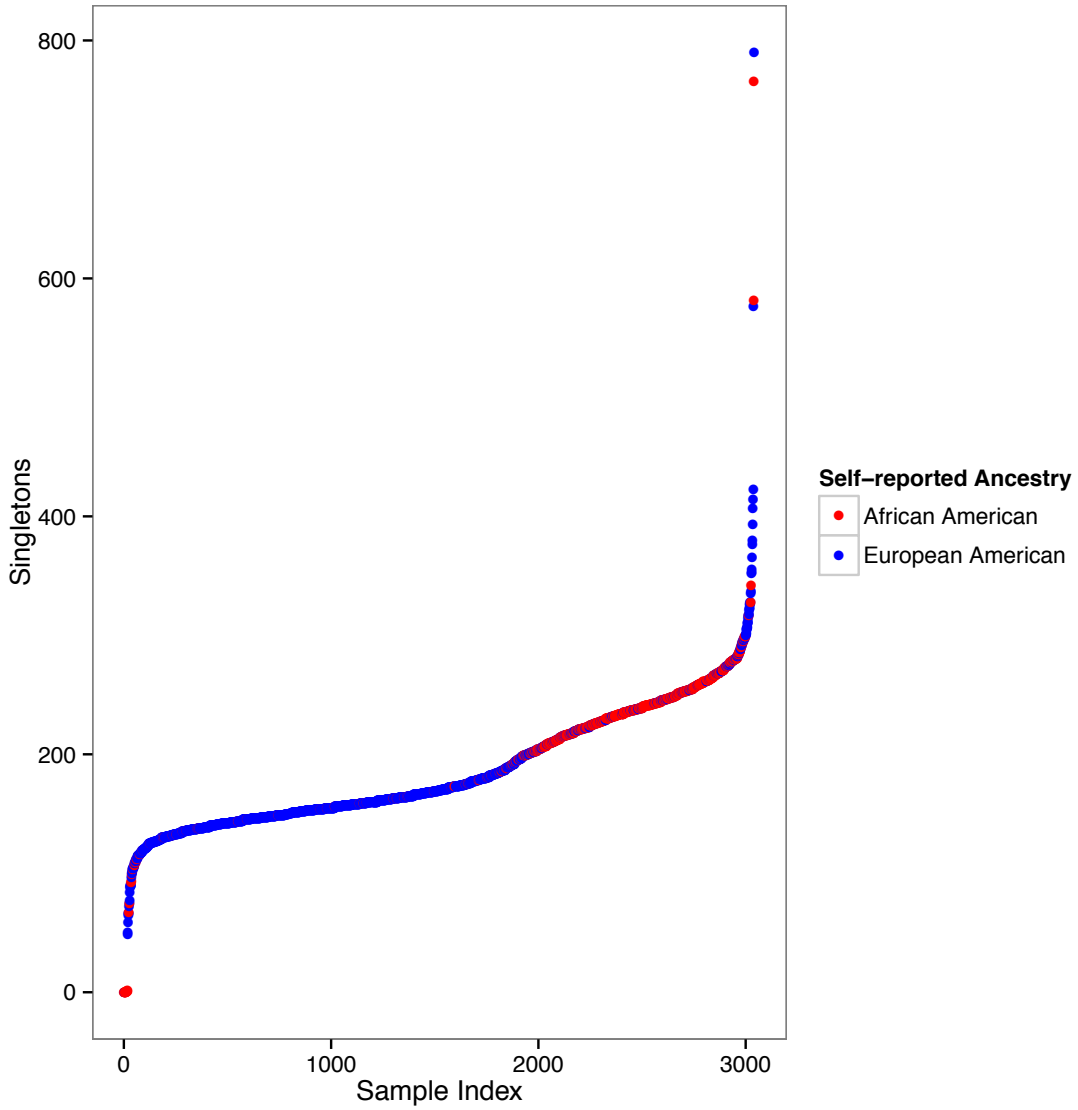
Examining the total number of single nucleotide variants discovered through sequencing can identify samples with possible contamination or low-quality DNA. Samples that were statistical outliers (those with greater than 44,000 variants) were removed from further analysis. The cluster of samples with a smaller number of variants (below 30,000) was sequenced with a smaller exome capture definition and has fewer variants, as expected. The higher and lower modes (plateaus around 32,500 and 40,000) reflect samples of African (red) and European (blue) ancestry, respectively.

Supplementary Figure 2. Missing rate per sample



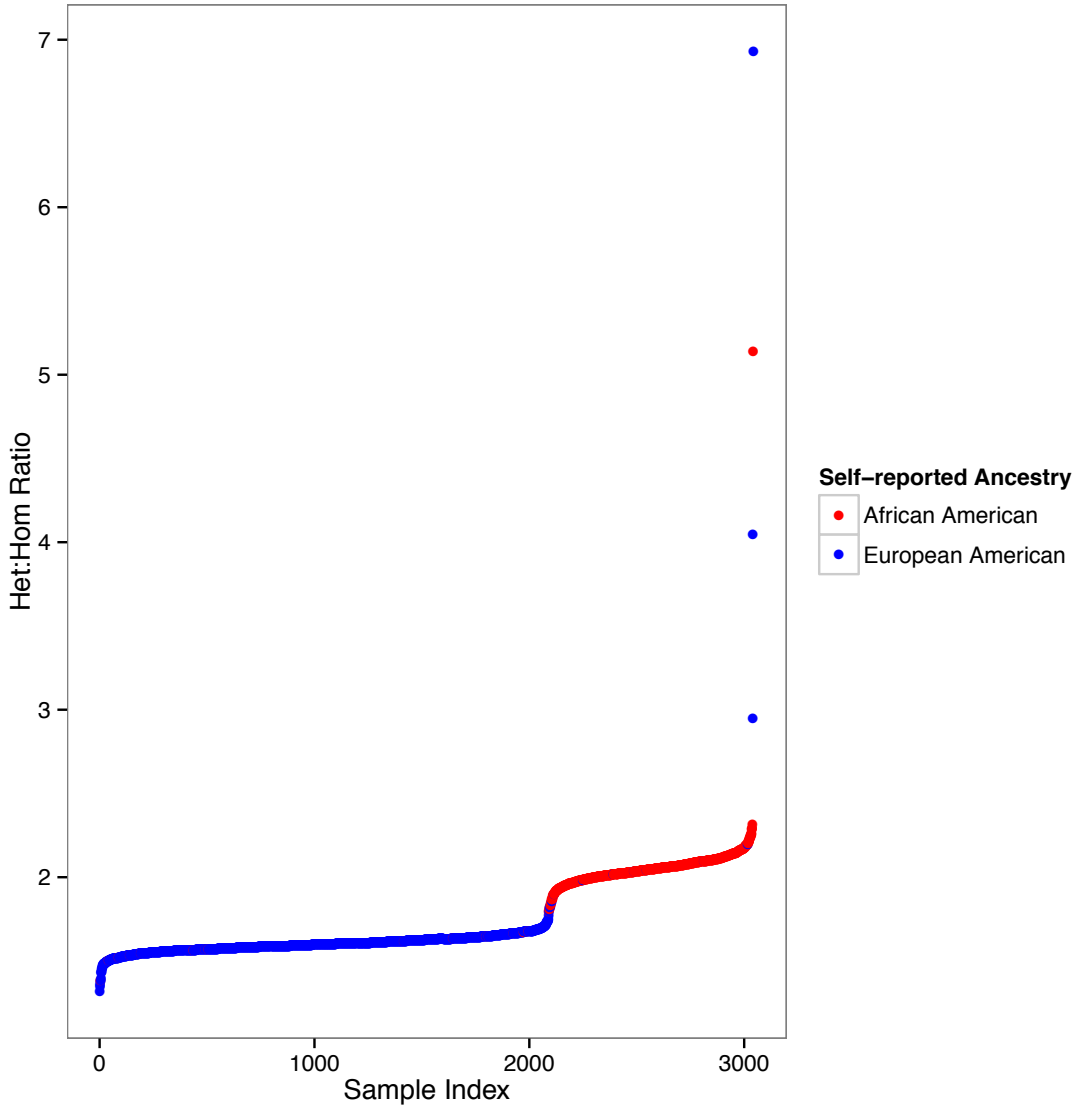
An excess of missing genotypes can reflect poor quality DNA or other technical problems. Samples that were outliers (those with more than 50,000 missing genotypes) were removed from further analysis. Red dots and blue dots represent samples of African and European ancestry, respectively.

Supplementary Figure 3. Number of singleton variants per sample



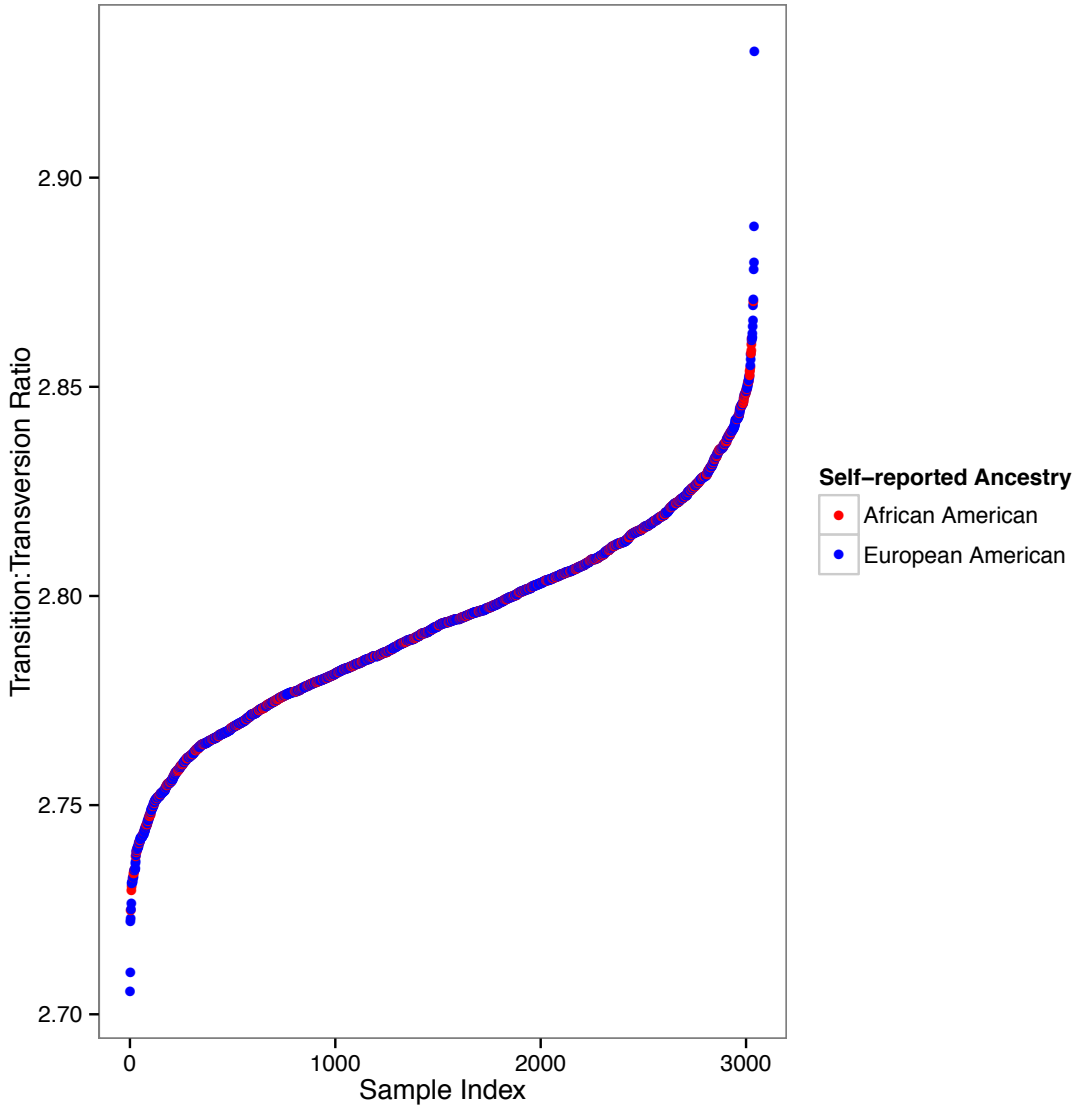
An excess number of singletons (defined as a variant present in only one sample) can reflect poor quality sequencing (if many spurious genotypes are identified, for example) while a very low number of singletons can reflect contamination, closely related individuals or duplicate samples. Samples with an excess (above 500) or lack (less than 50) of singletons were removed from further analysis. The higher and lower modes (plateaus around 150 and 300) reflect samples of African (red) and European (blue) ancestry, respectively.

Supplementary Figure 4. Number of heterozygous genotypes per sample



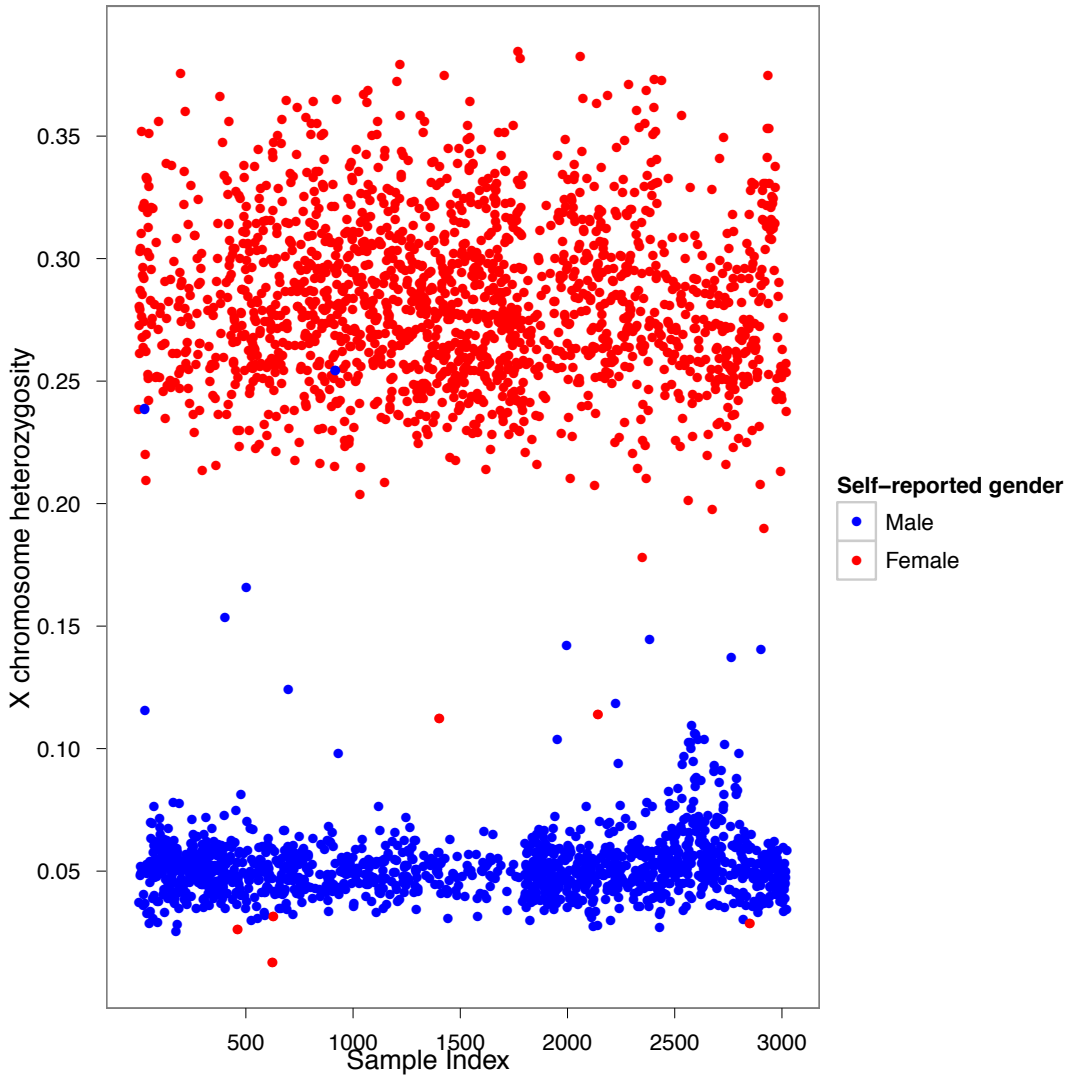
The number of heterozygous genotypes per individual (normalized by the number of homozygous non-reference genotypes) can be useful in identifying closely related or possibly contaminated samples. Samples with an excess of heterozygous genotypes (heterozygous to homozygous non-reference ratio of greater than 2.75) were removed from further analysis. The upper and lower modes reflect samples from African (red) and European (blue) ancestry, respectively.

Supplementary Figure 5. Transition-transversion per sample



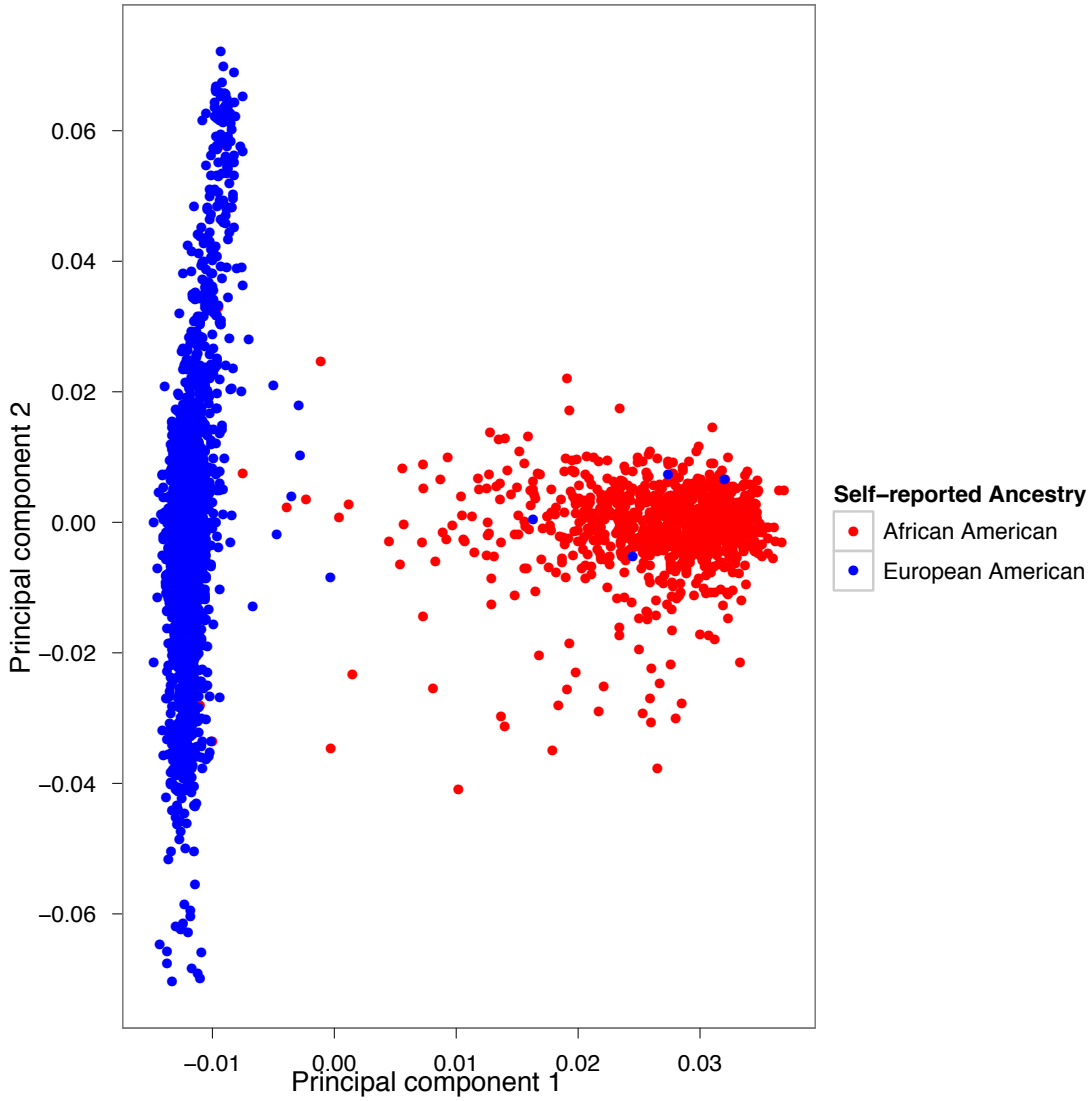
The transition-transversion ratio across all exome variants can be useful in identifying poorly genotyped samples. None of these samples were statistical outliers for this metric. Red dots and blue dots represent samples of African and European ancestry, respectively.

Supplementary Figure 6. X chromosome heterozygosity per sample



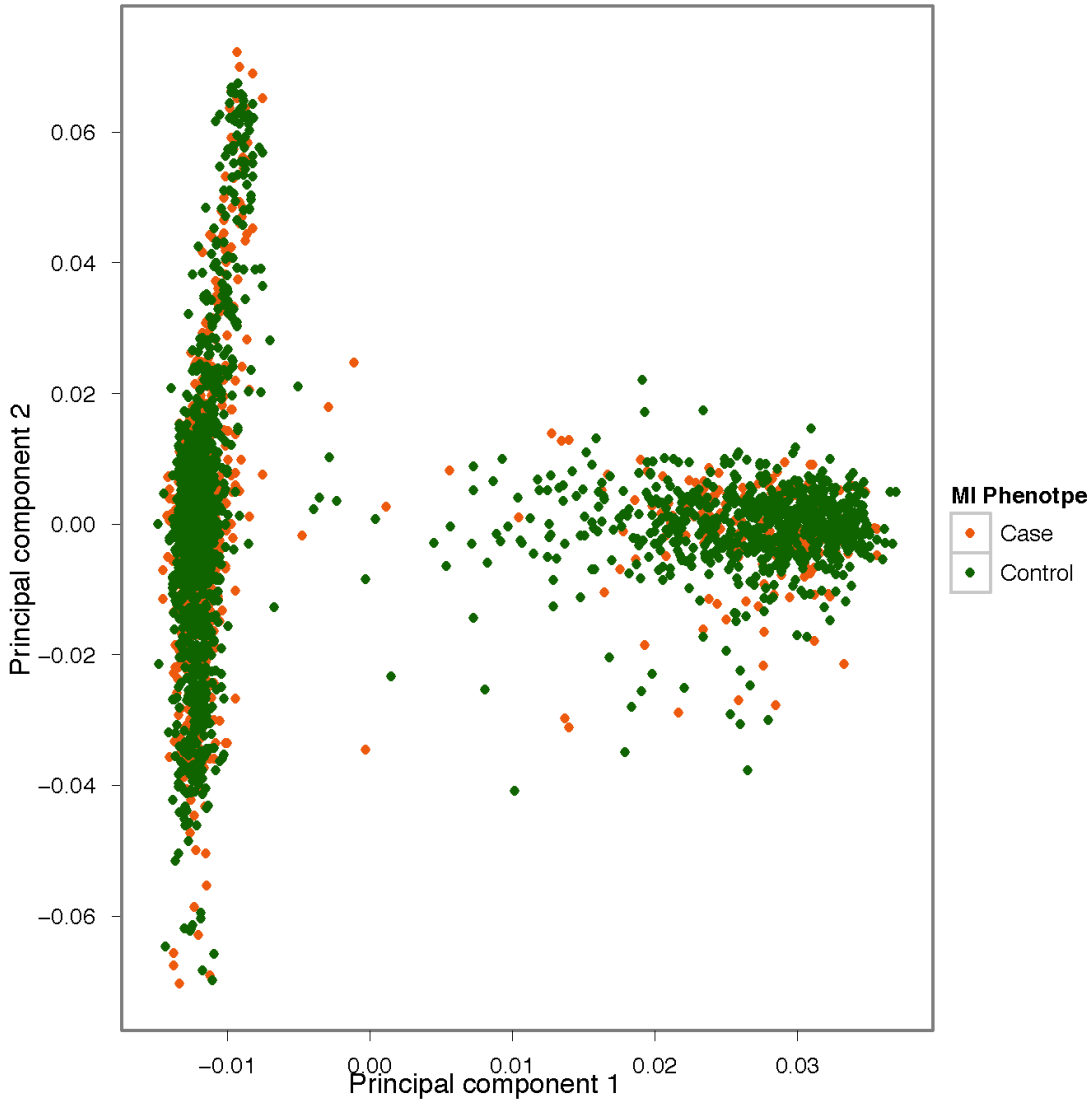
The percentage of non-missing heterozygous genotypes on the X chromosome can be used to identify samples with discordant genetic and reported gender. Self-identified male samples with X heterozygosity > 0.20 and self-identified female samples with X heterozygosity < 0.15 were removed from further analysis.

Supplementary Figure 7. Global ancestry per sample



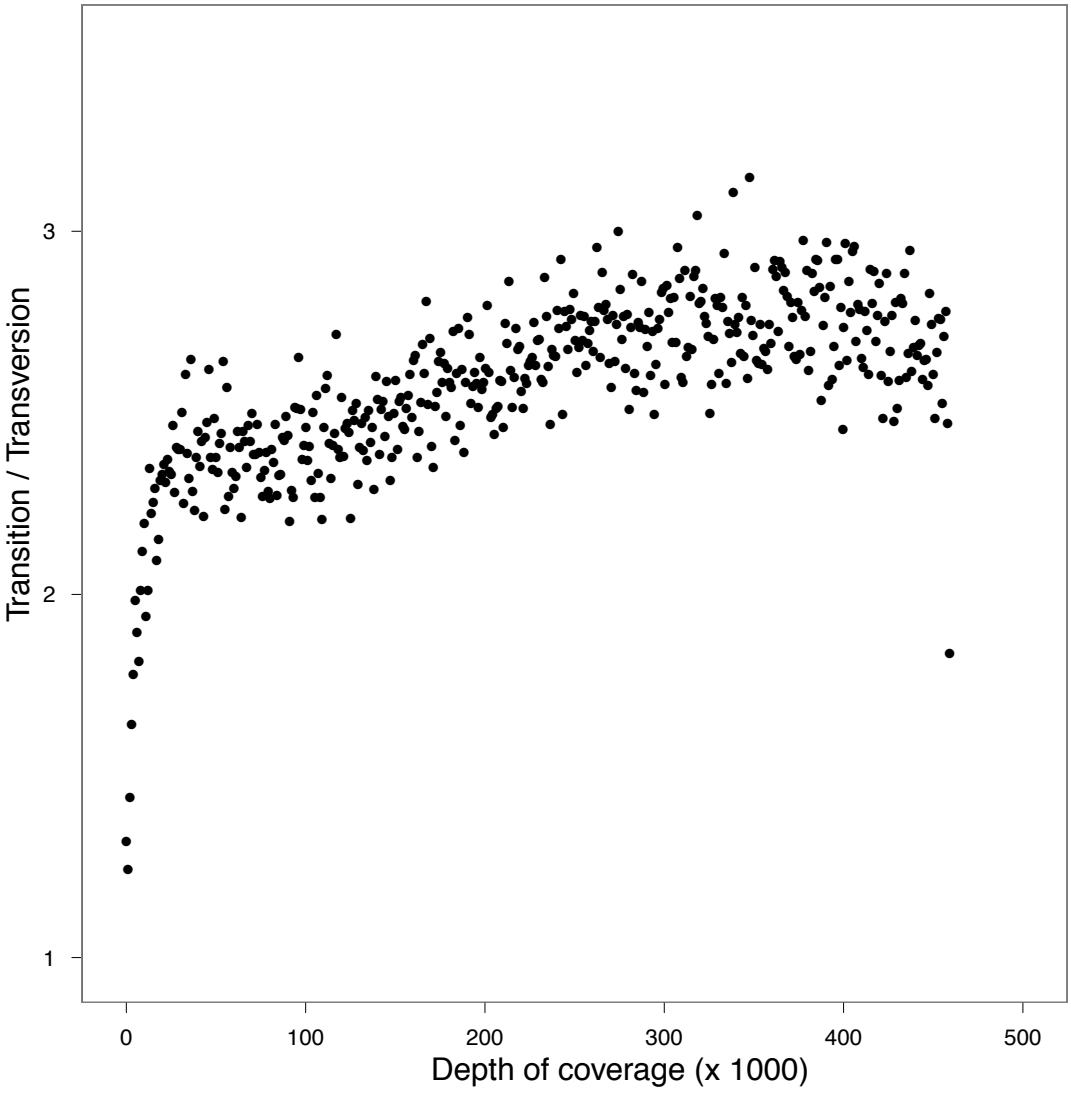
Principal component analysis was performed using Eigenstrat on a frequency and linkage disequilibrium-pruned set of genotypes to cluster samples by genetic ancestry. Ten principal components were calculated. Self-identified European-American samples with the first principal component (PC1) > 0.01 and self-identified African-American samples with PC1 < 0 were removed from further analysis.

Supplementary Figure 8. Global ancestry per sample clustered by phenotype



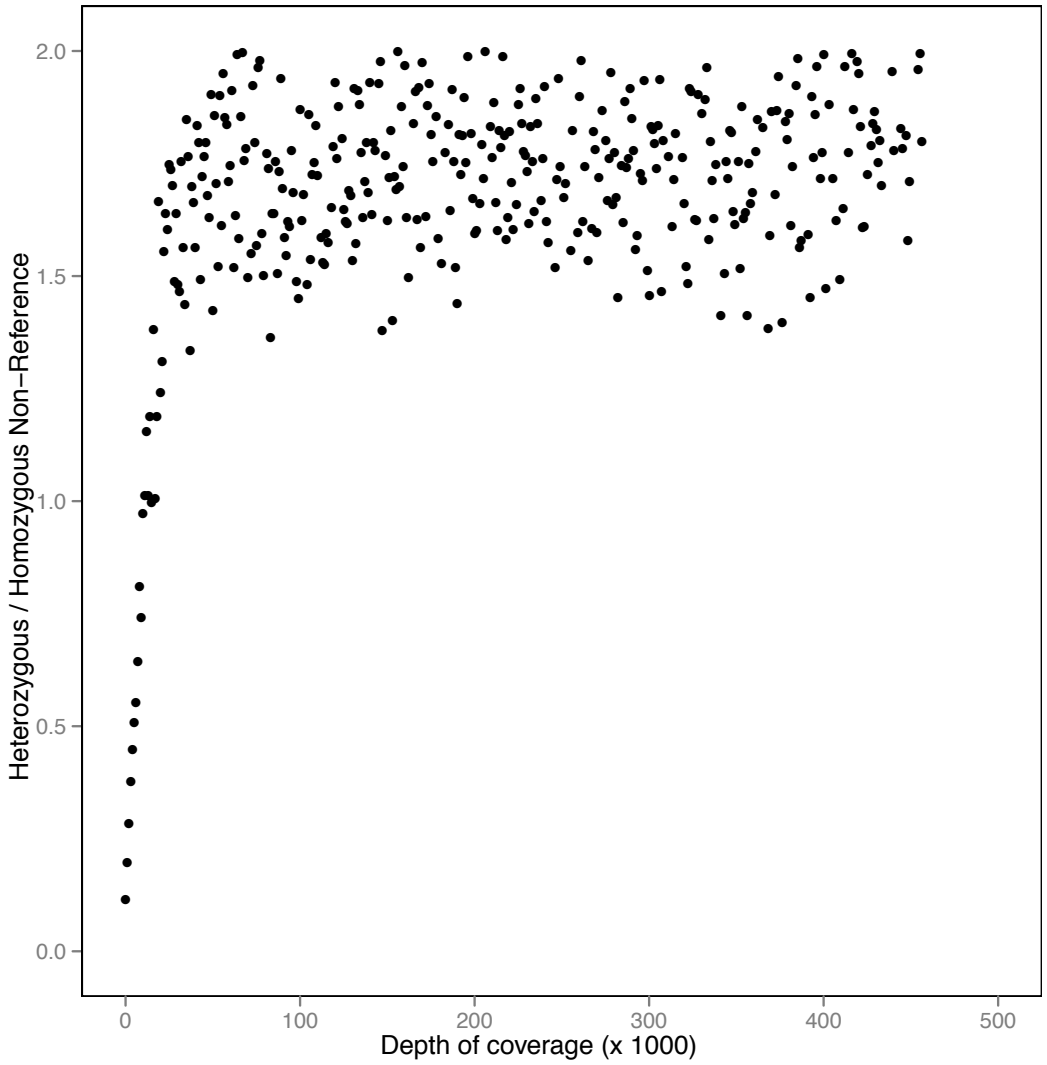
To ensure that population stratification was not confounding our analysis, we plotted the first two principal components according to phenotypic classification. No significant *P*-values were identified when testing for differences of the first 10 principal components between cases and controls.

Supplementary Figure 9. Transition-transversion ratio as a function of depth of coverage



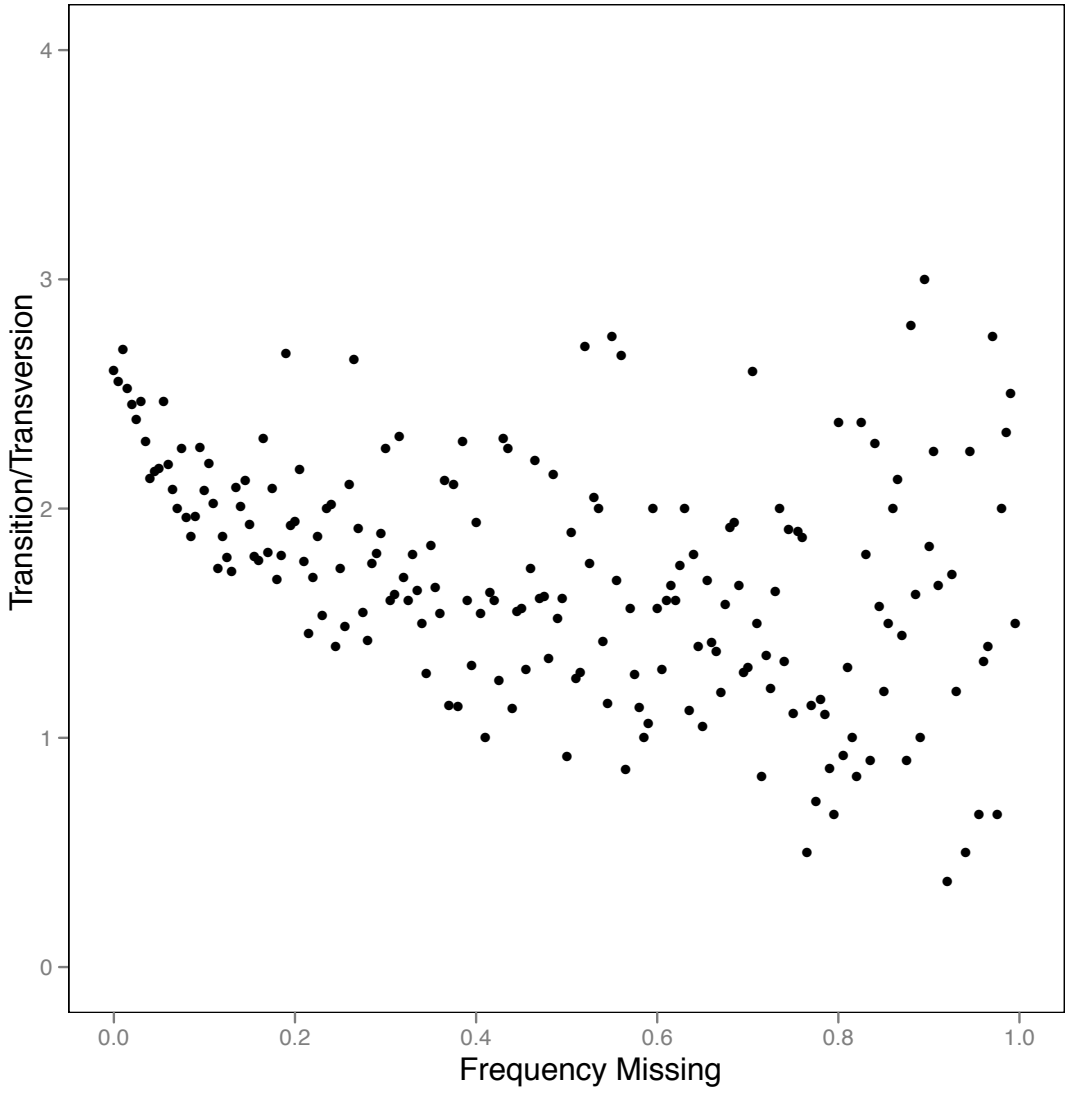
The transition-transversion ratio (TS-TV) of single nucleotide variants (SNVs) within bins of depth of coverage of 1,000 total reads across all samples was calculated. We observed that the TS-TV plateaus around 25,000 reads, or approximately eight reads per sample. SNVs with greater than eight reads per sample are considered more likely to be true SNVs.

Supplementary Figure 10. Heterozygosity as a function of depth of coverage



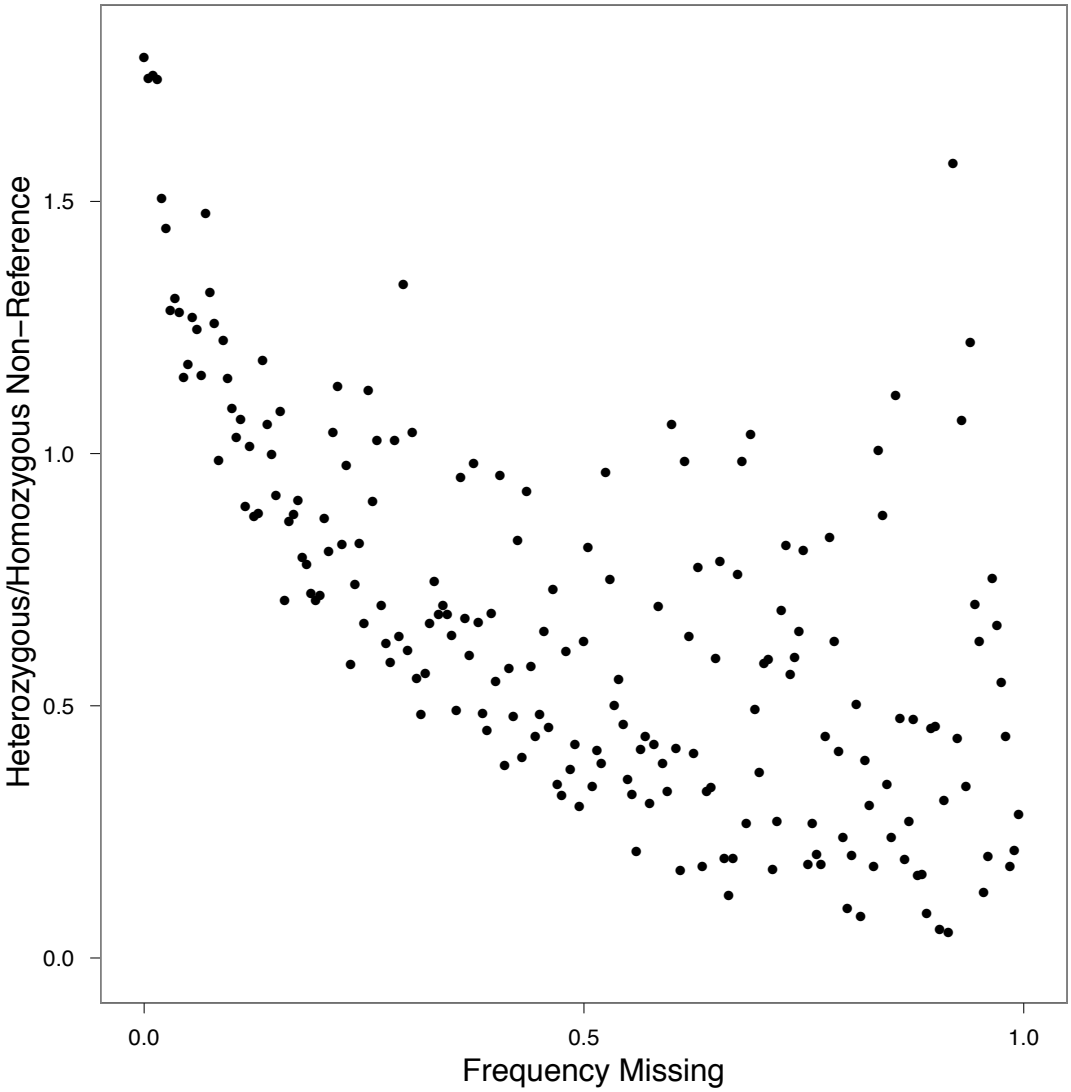
The heterozygous-homozygous non-reference ratio of single nucleotide variants (SNVs) within bins of depth of coverage of 1,000 reads was calculated. We observed that the heterozygous to homozygous non-reference ratio plateaus around 25,000 reads, or approximately 8 reads per sample. SNVs with greater than 8 reads per sample are considered more likely to be true SNVs.

Supplementary Figure 11. Transition-transversion ratio as a function of frequency of missingness



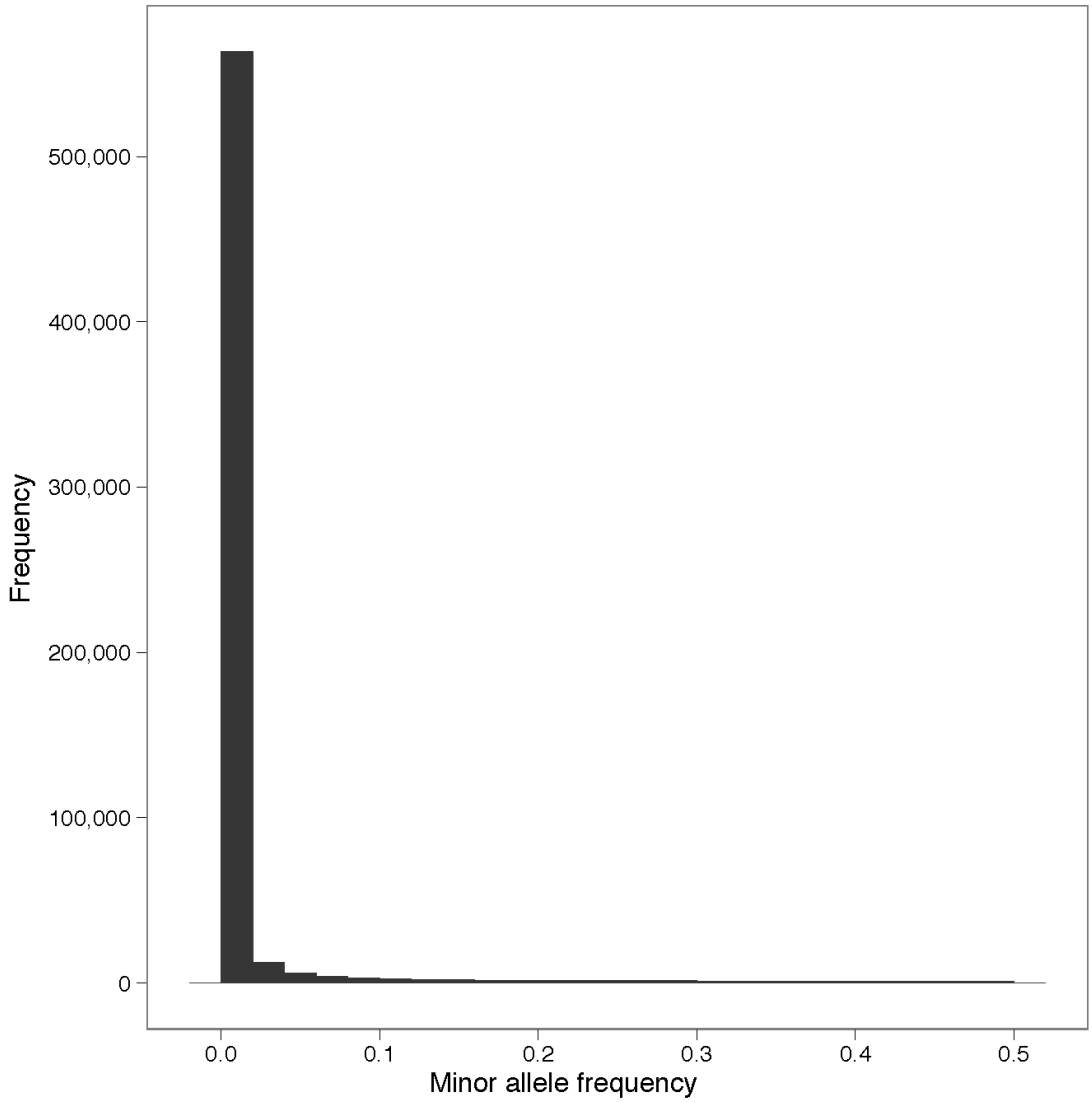
The transition-transversion ratio (TS-TV) of single nucleotide variants (SNVs) within bins of frequency of missingness was calculated. We observed that the TS-TV decreases as the frequency of missingness increases for SNVs.

Supplementary Figure 12. Heterozygosity as a function of frequency of missingness



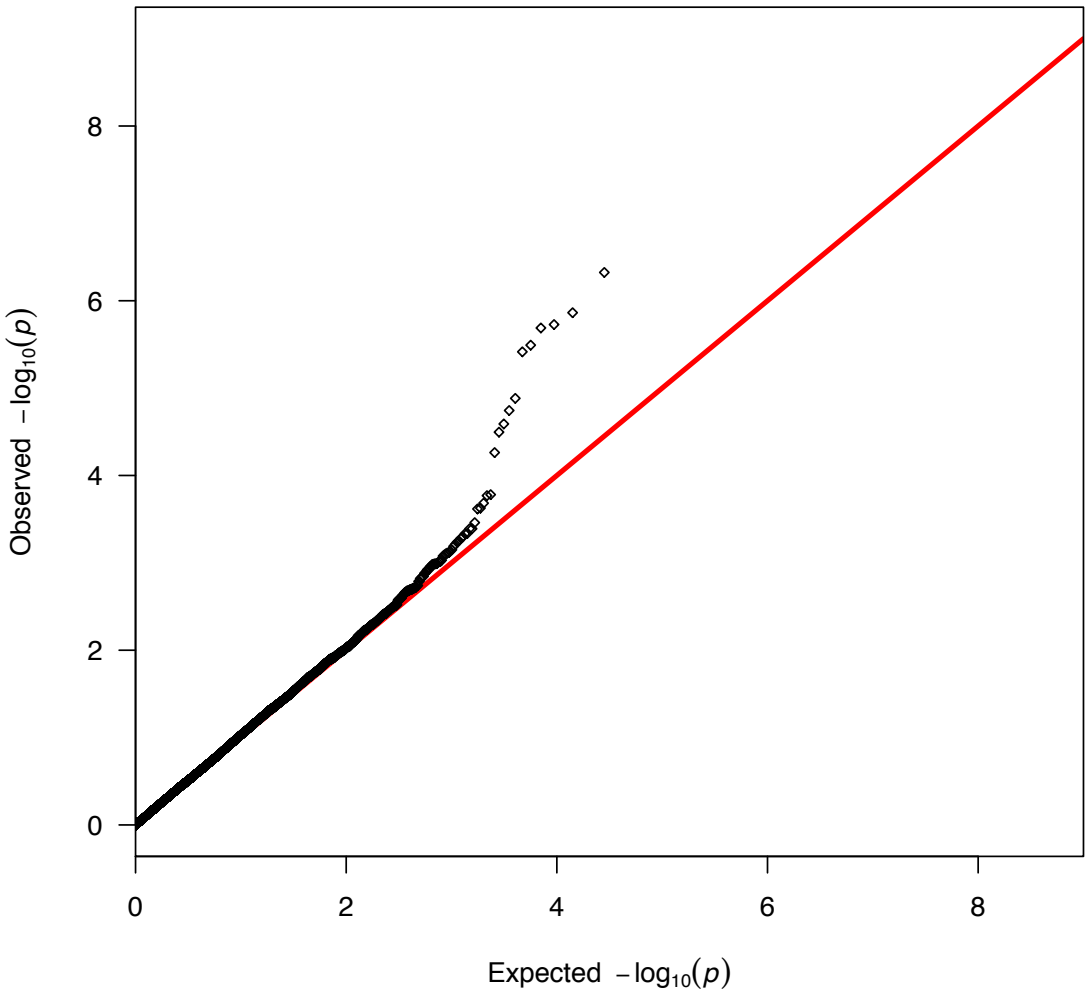
The heterozygous-homozygous non-reference ratio of single nucleotide variants within bins of frequency of missingness was calculated. We observed that the heterozygous-homozygous non-reference ratio decreases as the frequency of missingness increases.

Supplementary Figure 13. Distribution of allele frequencies of single nucleotide variants for the ESP EOMI study



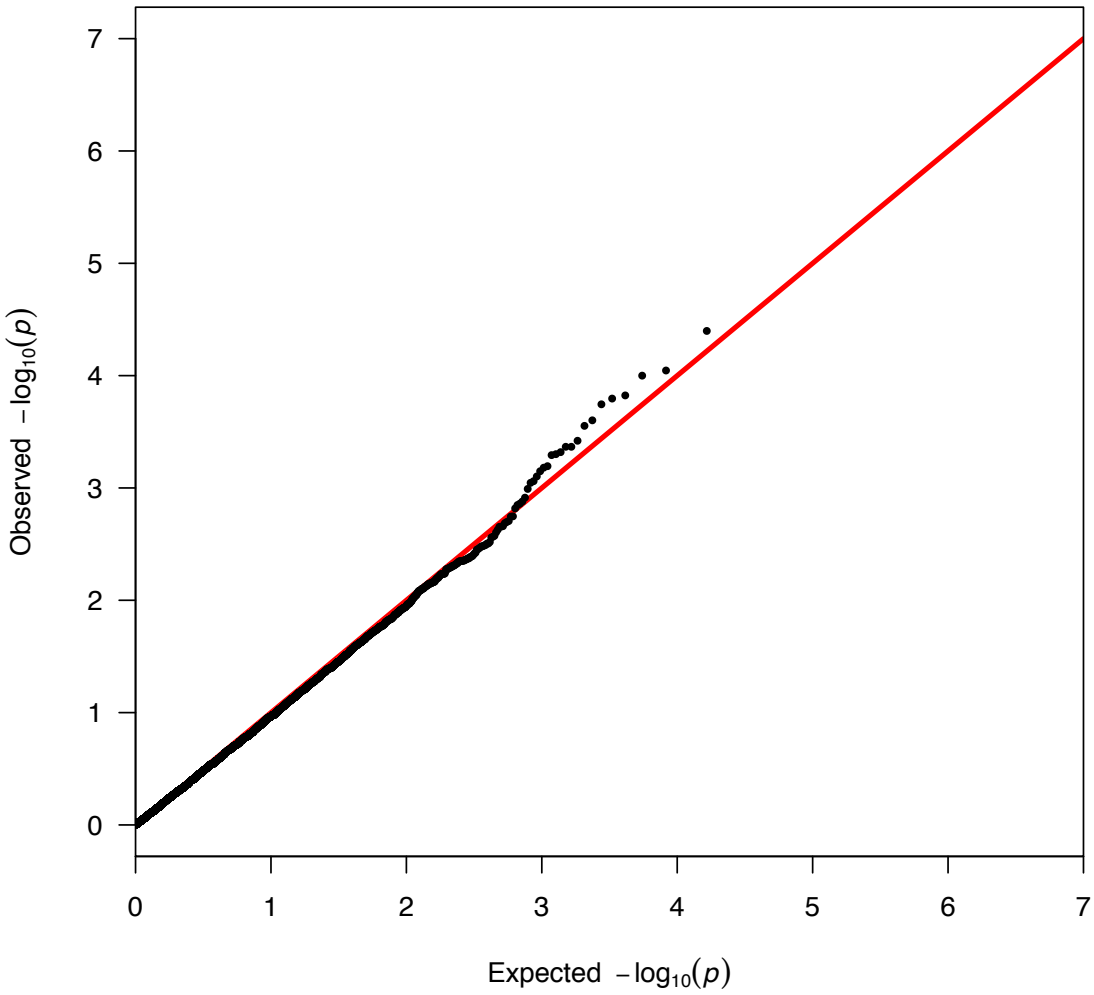
The allele frequency distribution of all single nucleotide variants (SNVs) in the exome is shown. The majority of SNVs are rare in frequency.

Supplementary Figure 14. Quantile-quantile plot of single nucleotide variant association results for the ESP EOMI study



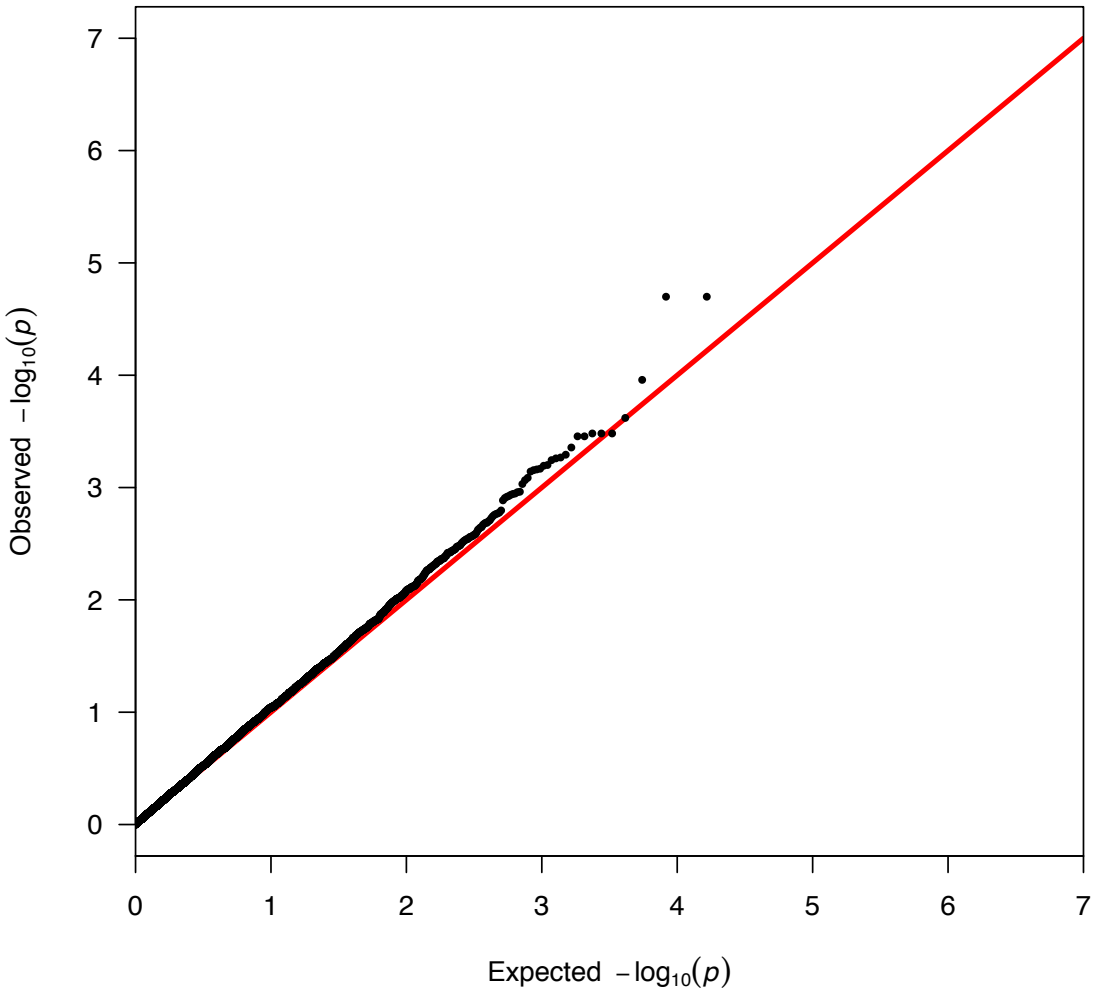
The plot shows that no single nucleotide variant exceeded a genome-wide significance level of $P < 5 \times 10^{-8}$.

Supplementary Figure 15. Quantile-quantile plot of association results for the T1 risk test for all non-synonymous single nucleotide variants and insertions/deletions



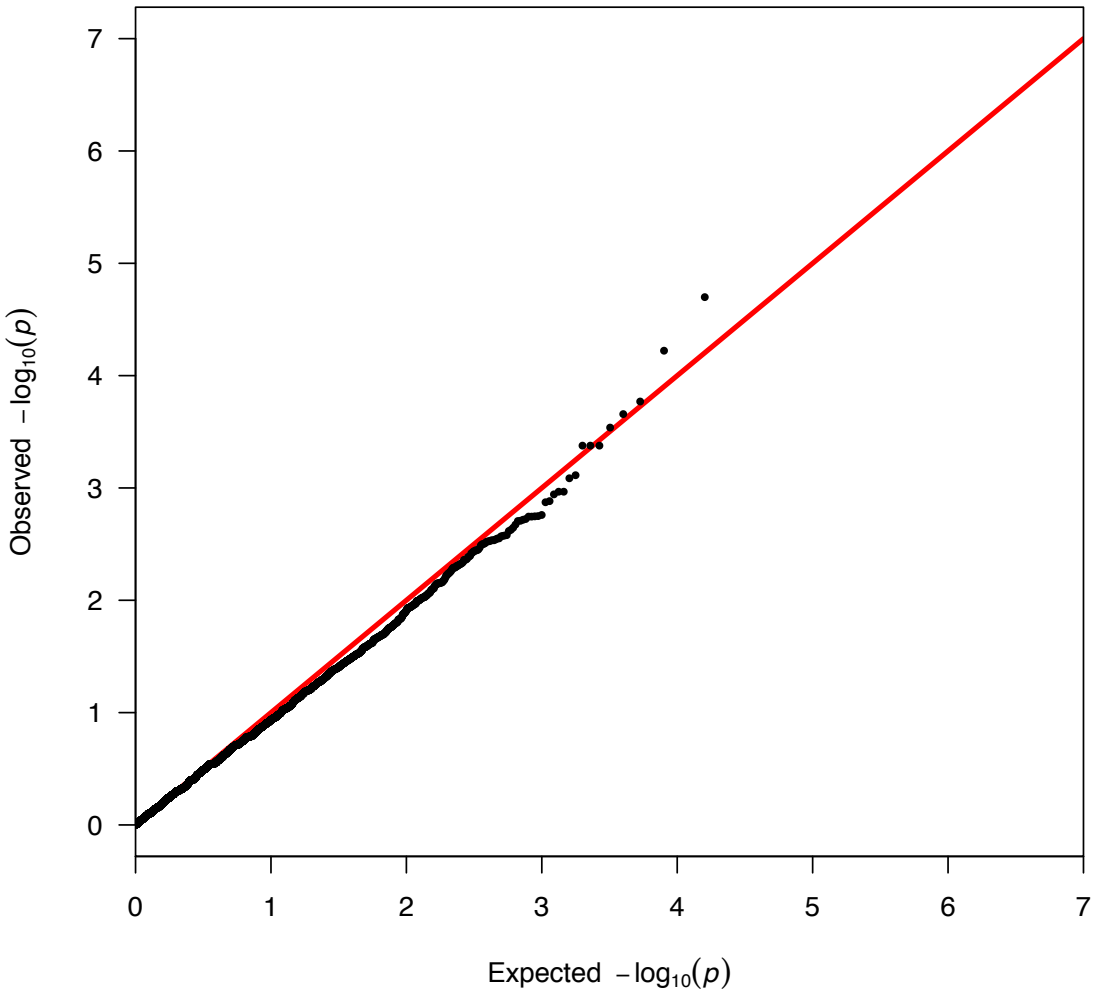
The T1 risk test includes all non-synonymous single nucleotide variants with frequency < 1% only. The risk test tests for a greater proportion of mutations in cases compared to controls. The quantile-quantile plot shows that no gene deviated significantly from the expected null distribution.

Supplementary Figure 16. Quantile-quantile plot of association results for the T1 protective test for all non-synonymous single nucleotide variants and insertions/deletions



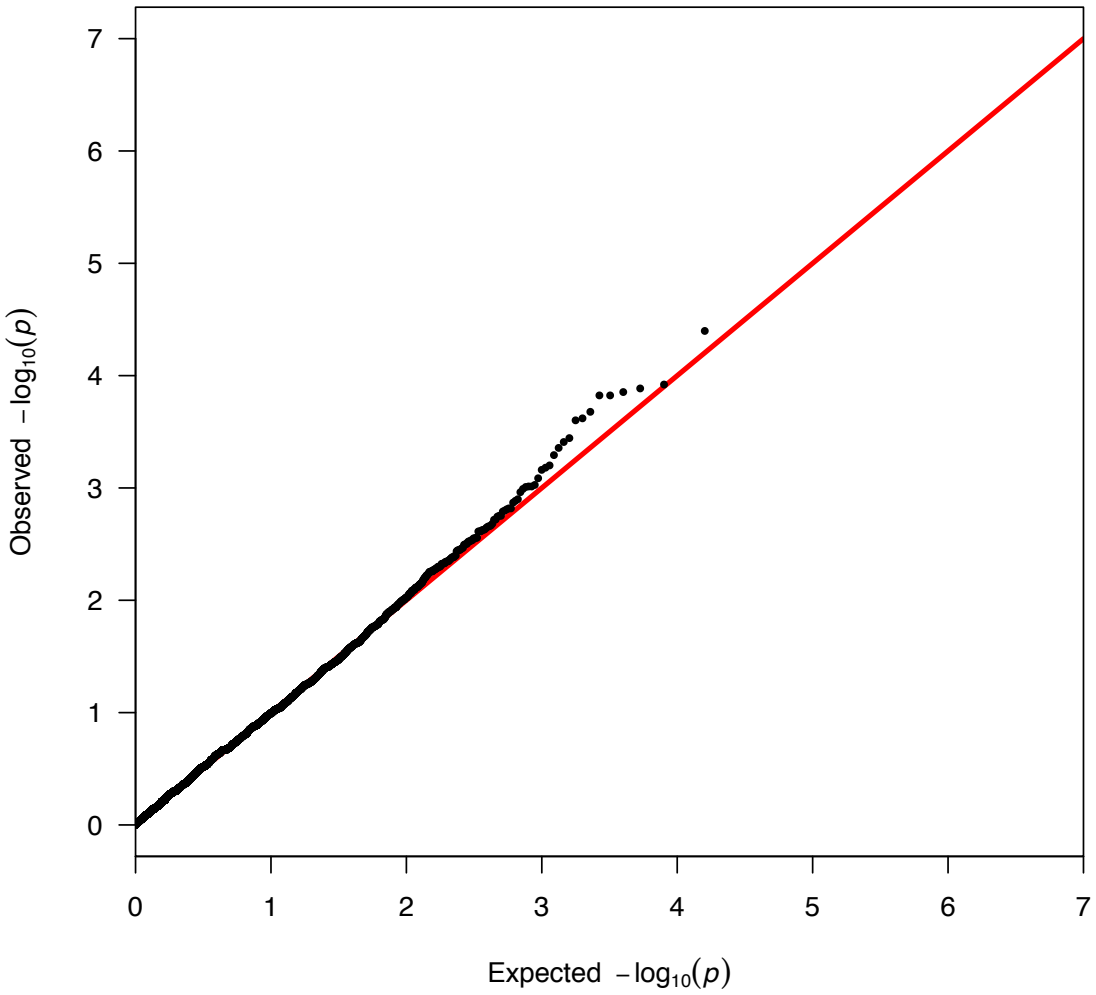
The T1 protective test includes all non-synonymous single nucleotide variants with frequency < 1% only. The protective test tests for a greater proportion of mutations in controls compared to cases. The quantile-quantile plot shows that no gene deviated significantly from the expected null distribution.

Supplementary Figure 17. Quantile-quantile plot of association results for the T1 risk test for deleterious single nucleotide variants and insertions/deletions



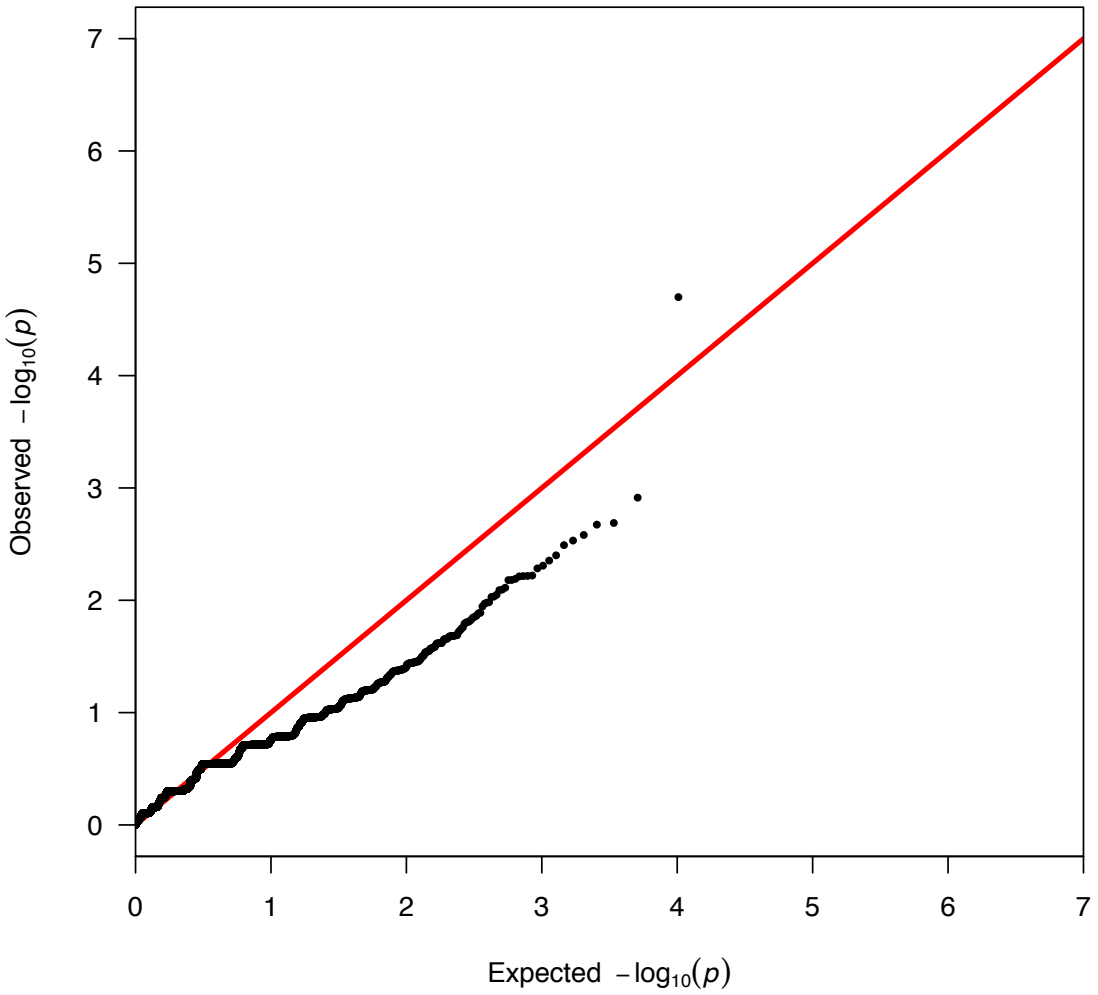
The T1 risk test includes all deleterious single nucleotide variants (SNVs) with frequency < 1% only. Deleterious SNVs are nonsense, splice-site, indel frameshift, "possibly damaging" or "probably damaging" SNVs as predicted from PolyPhen-2 HumDiv. The risk test tests for a greater proportion of mutations in cases compared to controls. The quantile-quantile plot shows that no gene deviated significantly from the expected null distribution.

Supplementary Figure 18. Quantile-quantile plot of association results for the T1 protective test for deleterious single nucleotide variants and insertions/deletions



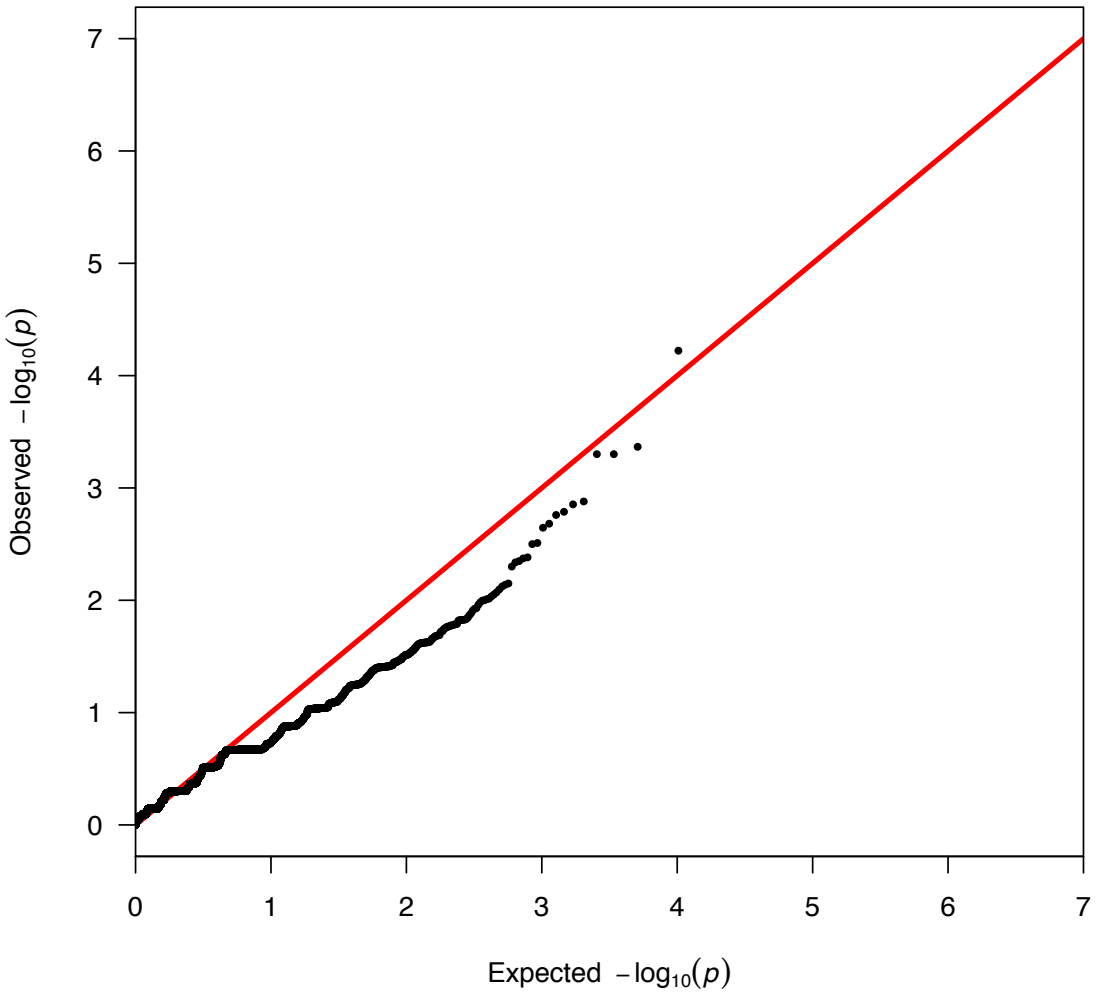
The T1 protective test includes all deleterious single nucleotide variants (SNVs) with frequency < 1% only. Deleterious SNVs are nonsense, splice-site, indel frameshift, "possibly damaging" or "probably damaging" SNVs as predicted from PolyPhen-2 HumDiv. The protective test tests for a greater proportion of mutations in controls compared to cases. The quantile-quantile plot shows that no gene deviated significantly from the expected null distribution.

Supplementary Figure 19. Quantile-quantile plot of association results for the T1 risk test for disruptive single nucleotide variants and insertions/deletions



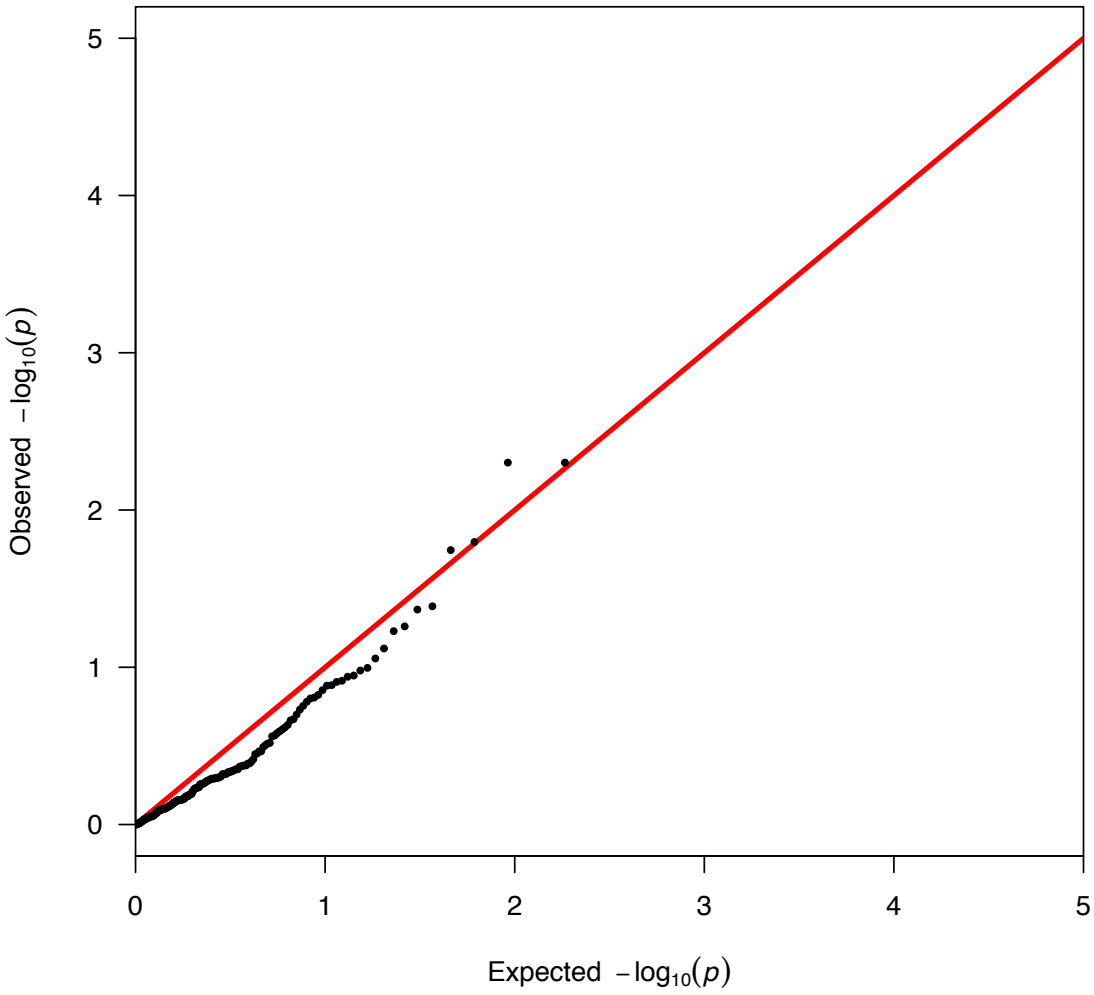
The T1 risk test includes all disruptive single nucleotide variants (SNVs) and indels with frequency < 1% only. Disruptive variants were defined as nonsense, splice-site or indel frameshift. The risk test tests for a greater proportion of mutations in cases compared to controls. The quantile-quantile plot shows deflation due to a much lower number of SNVs and indels than in the analysis involving all non-synonymous SNVs. The quantile-quantile plot shows that no gene deviated significantly from the expected null distribution.

Supplementary Figure 20. Quantile-quantile plot of association results for the T1 protective test for disruptive single nucleotide variants and insertions/deletions



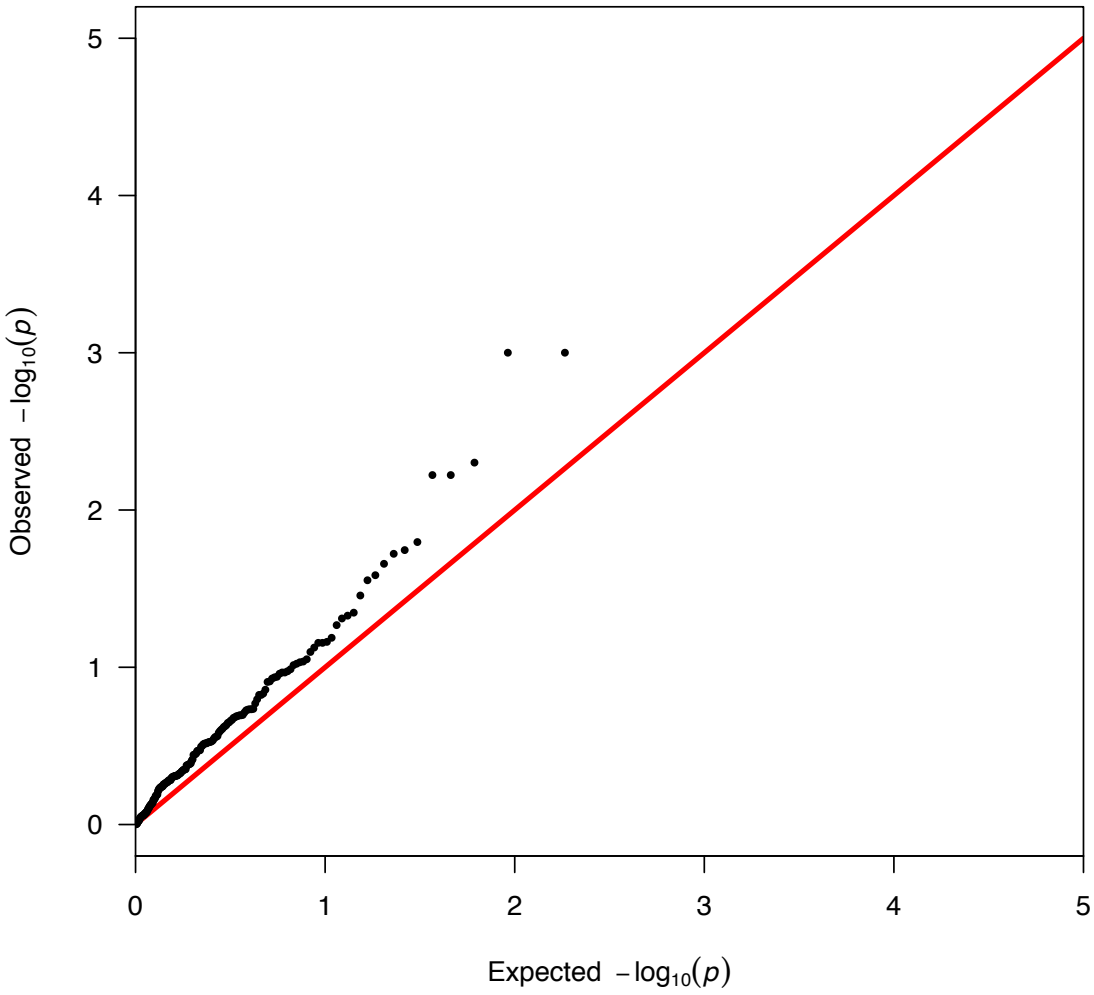
The T1 protective test includes all disruptive single nucleotide variants (SNVs) and indels with frequency < 1% only. Disruptive variants were defined as nonsense, splice-site or indel frameshift. The protective test tests for a greater proportion of mutations in controls compared to cases. The quantile-quantile plot shows deflation due to a much lower number of SNVs and indels than in the analysis involving all non-synonymous SNVs. The quantile-quantile plot shows that no gene deviated significantly from the expected null distribution.

Supplementary Figure 21. Quantile-quantile plot of association results for the T1 risk test for all non-synonymous single nucleotide variants and insertions/deletions for pathways in the KEGG database



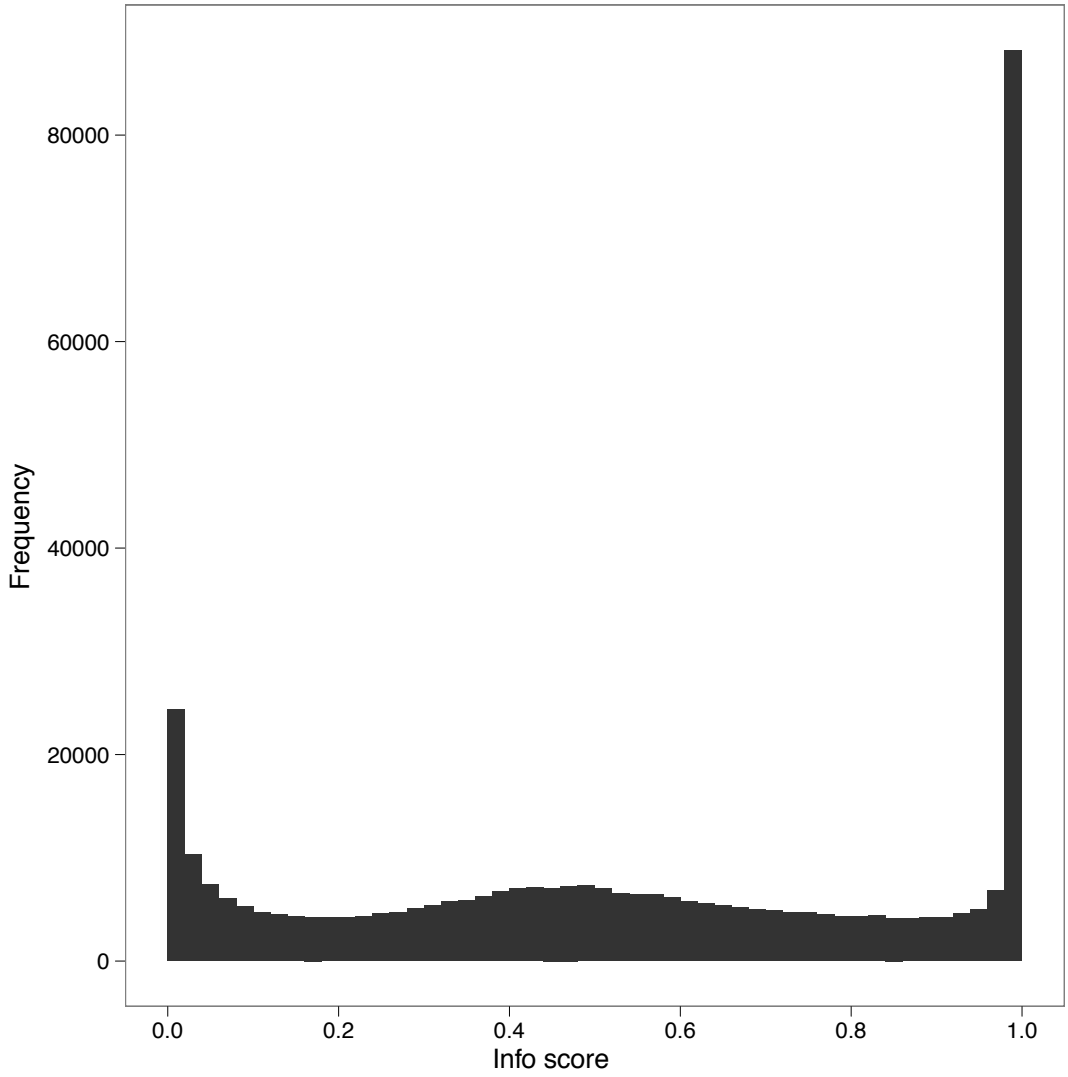
The T1 risk test includes all non-synonymous single nucleotide variants and indels with frequency < 1% only for pathways in the KEGG database. The risk test tests for a greater proportion of mutations in cases compared to controls. The quantile-quantile plot shows that no pathway deviated significantly from the expected null distribution.

Supplementary Figure 22. Quantile-quantile plot of association results for the T1 protective test for all non-synonymous single nucleotide variants and insertions/deletions for pathways in the KEGG database



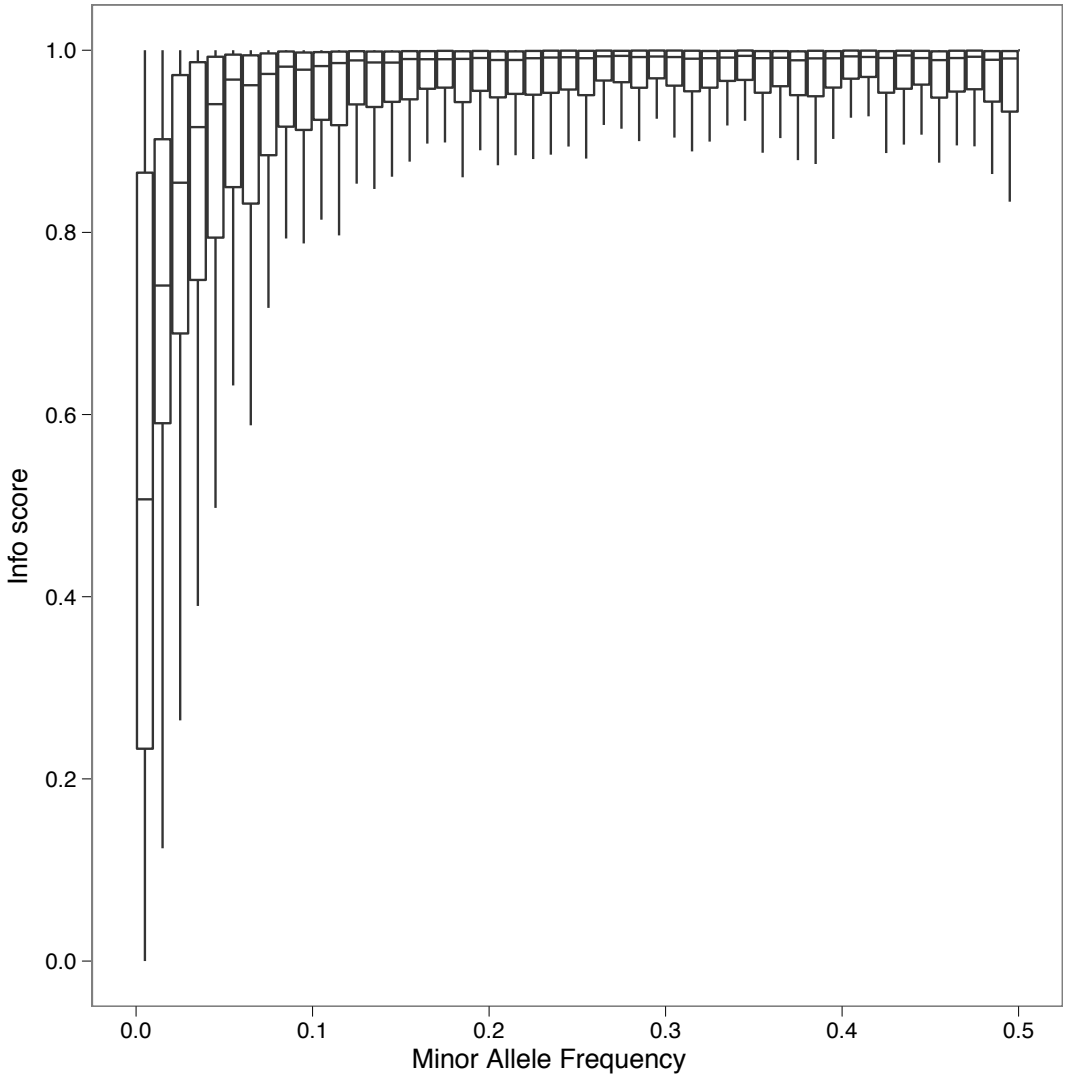
The T1 protective test includes all non-synonymous single nucleotide variants and indels with frequency < 1% only for pathways in the KEGG database. The protective test tests for a greater proportion of mutations in controls compared to cases. The quantile-quantile plot shows that no pathway deviated significantly from the expected null distribution.

Supplementary Figure 23. Distribution of imputation quality



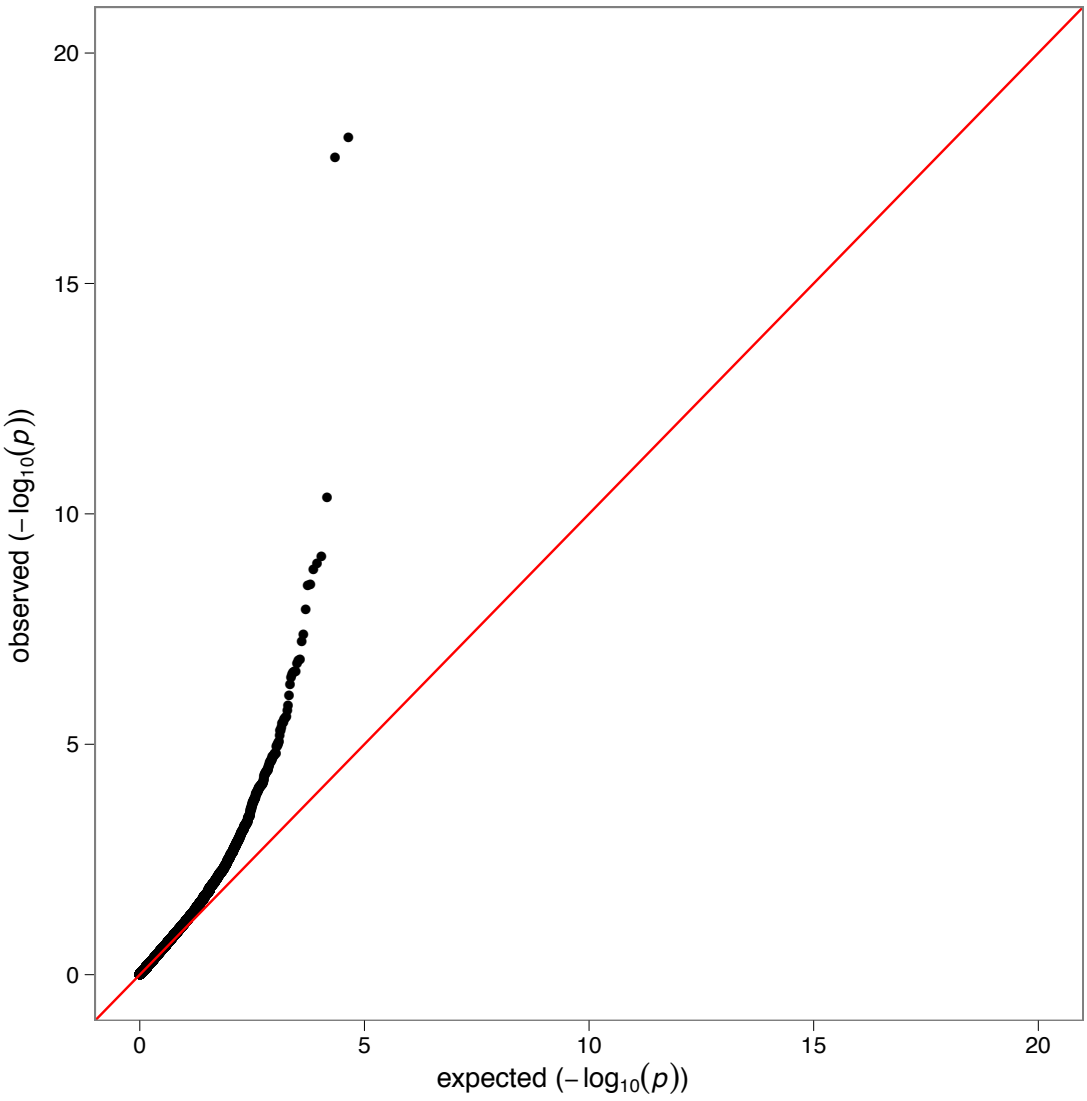
The distribution of INFO scores, a measure of imputation quality, for the MIGen study is shown. The plot shows that a large number of single nucleotide variants are either imputed very well (INFO ~ 1.0) or very poorly (INFO ~ 0.0).

Supplementary Figure 24. Distribution of INFO scores by minor allele frequency



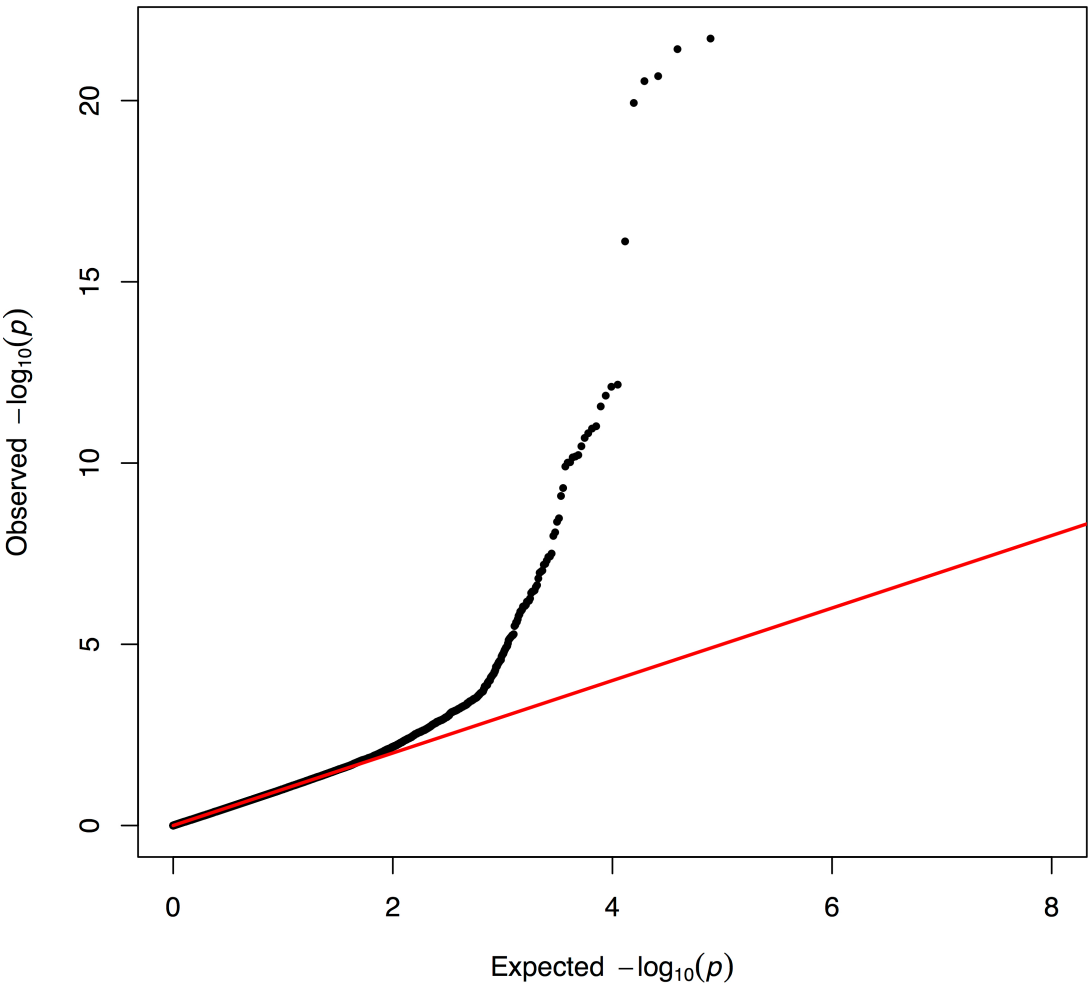
The distribution of INFO scores, a measure of imputation quality, for the MIGen study is shown. The plot shows that single nucleotide variants with frequency < 0.05 have lower INFO scores than those with frequency > 0.05.

Supplementary Figure 25. Quantile-quantile plot of association results from the follow-up imputation analysis



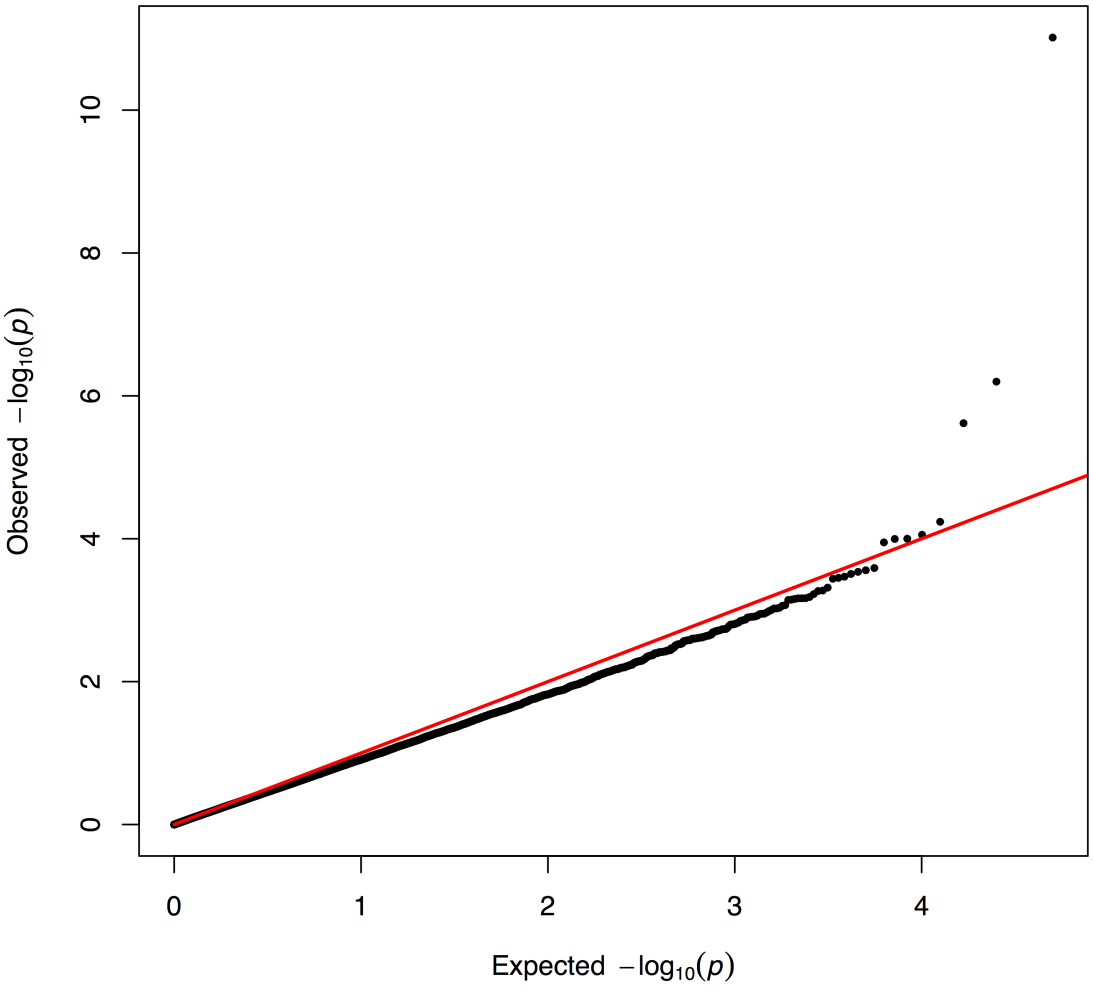
Several association signals deviate from what we expect by chance in the follow-up imputation analysis. All variants exceeding genome-wide significance level ($P < 5 \times 10^{-8}$) were previously discovered.

Supplementary Figure 26. Quantile-quantile plot of association results for all single nucleotide variants from follow-up array-based genotyping



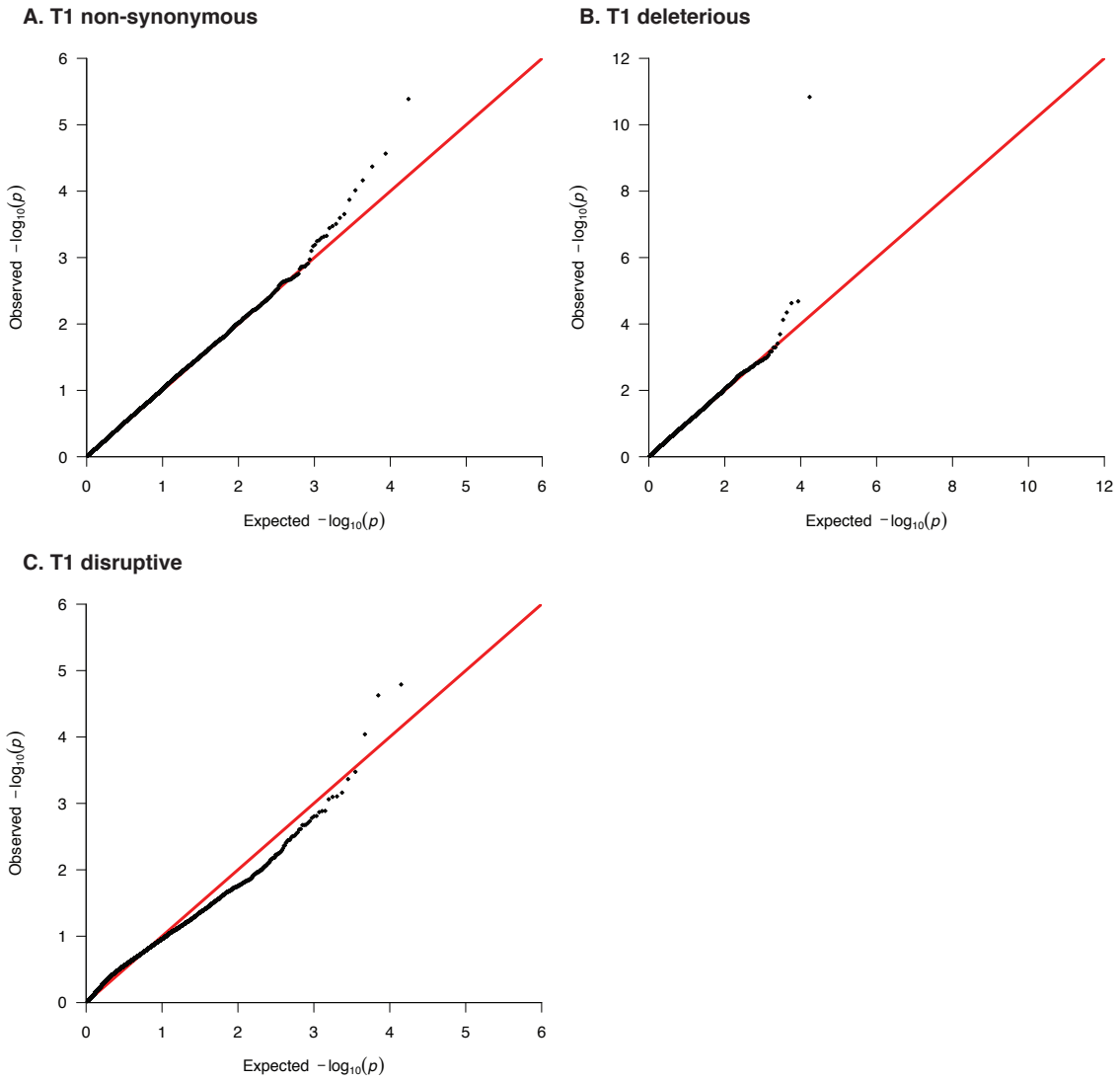
Several association signals deviate from what we expect by chance in the follow-up array-based analysis. All variants exceeding genome-wide significance level ($P < 5 \times 10^{-8}$) were previously discovered.

Supplementary Figure 27. Quantile-quantile plot of association results for single nucleotide variants with minor allele frequency (MAF) < 5% from follow-up array-based genotyping



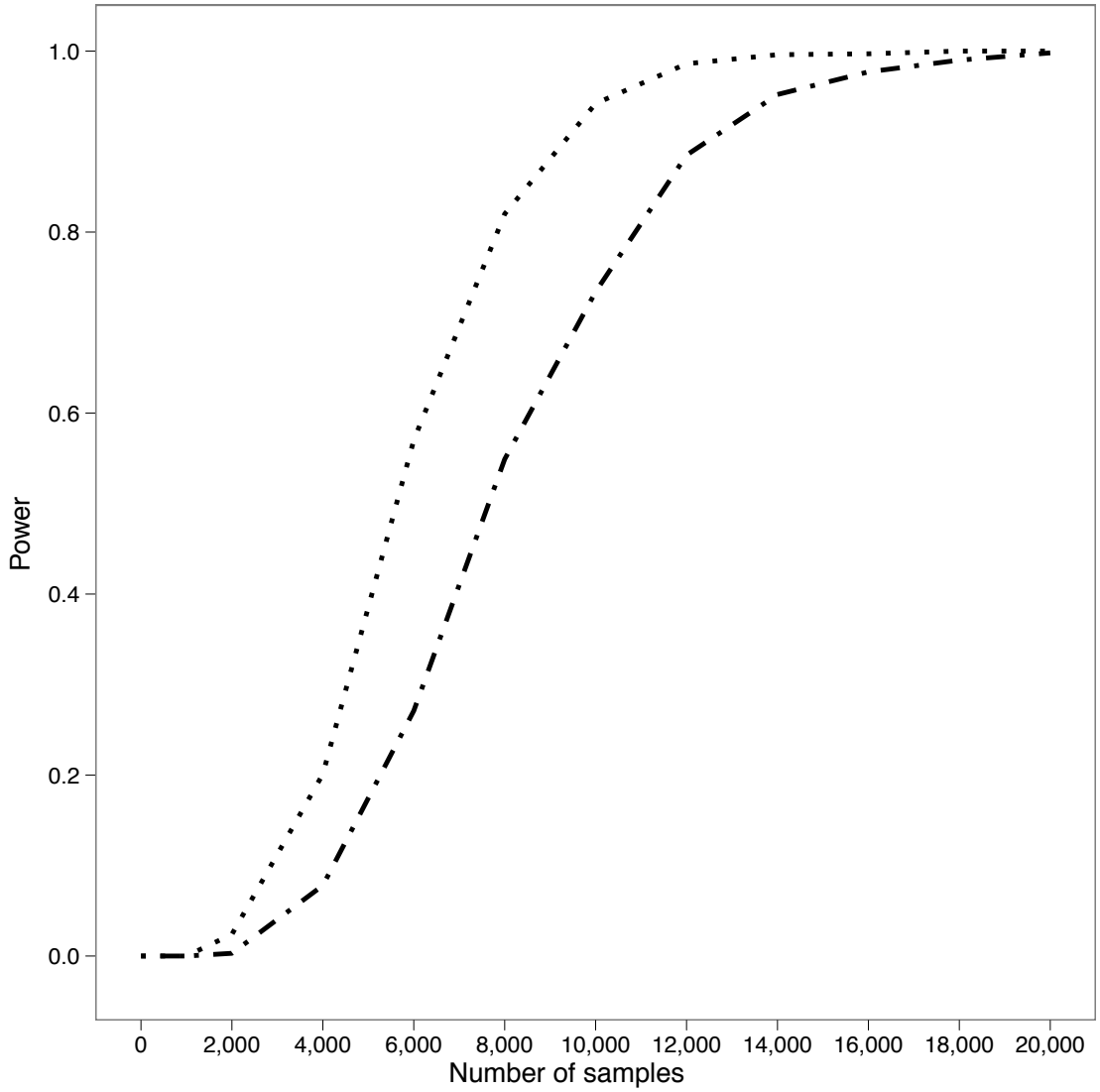
One association signal deviates from what we expect by chance in the follow-up array-based analysis of single nucleotide variants with MAF < 5%. All variants exceeding genome-wide significance level ($P < 5 \times 10^{-8}$) were previously discovered.

Supplementary Figure 28. Quantile-quantile plots of association results from follow-up exome sequencing



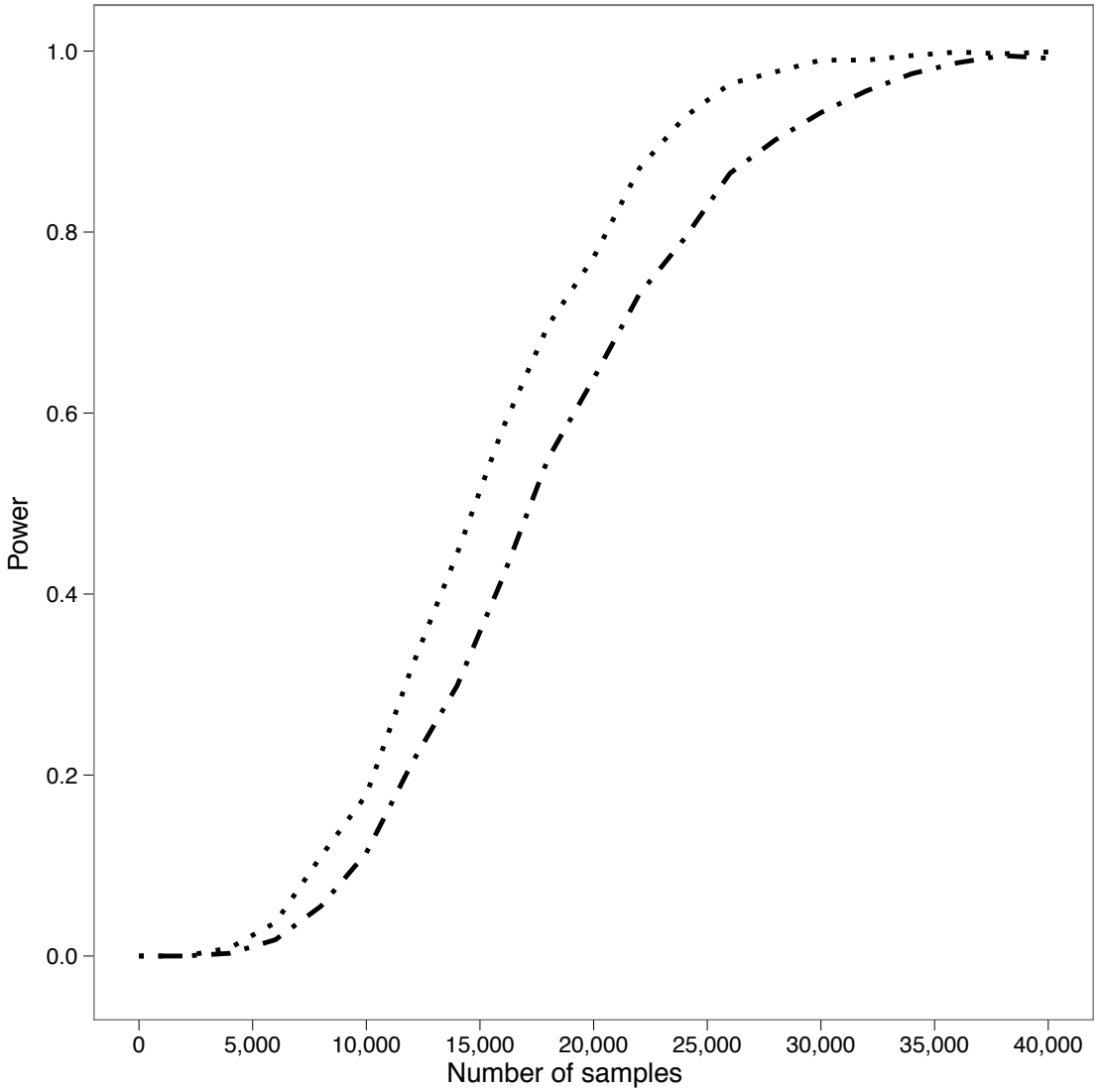
Statistical association results for the T1 burden test based on exome sequence data in 4,703 cases and 5,090 controls are compared with what is expected under a null hypothesis of no association. In each subpanel, $-\log_{10}$ of the association *P*-value is plotted as a function of the expected *P*-value. The red line represents what is expected under the null model. Each black dot represents the association signal for a gene. **A**. Association results after including only non-synonymous mutations. **B**. Association results after including only mutations annotated as deleterious (nonsense, splice-site, indel frameshift, "possibly damaging" and "probably damaging" as predicted using PolyPhen-2 HumDiv). **C**. Association results after including only mutations annotated as disruptive (nonsense, splice-site, indel frameshift).

Supplementary Figure 29. Power calculations for a gene with a median number of single nucleotide variants and insertions/deletions



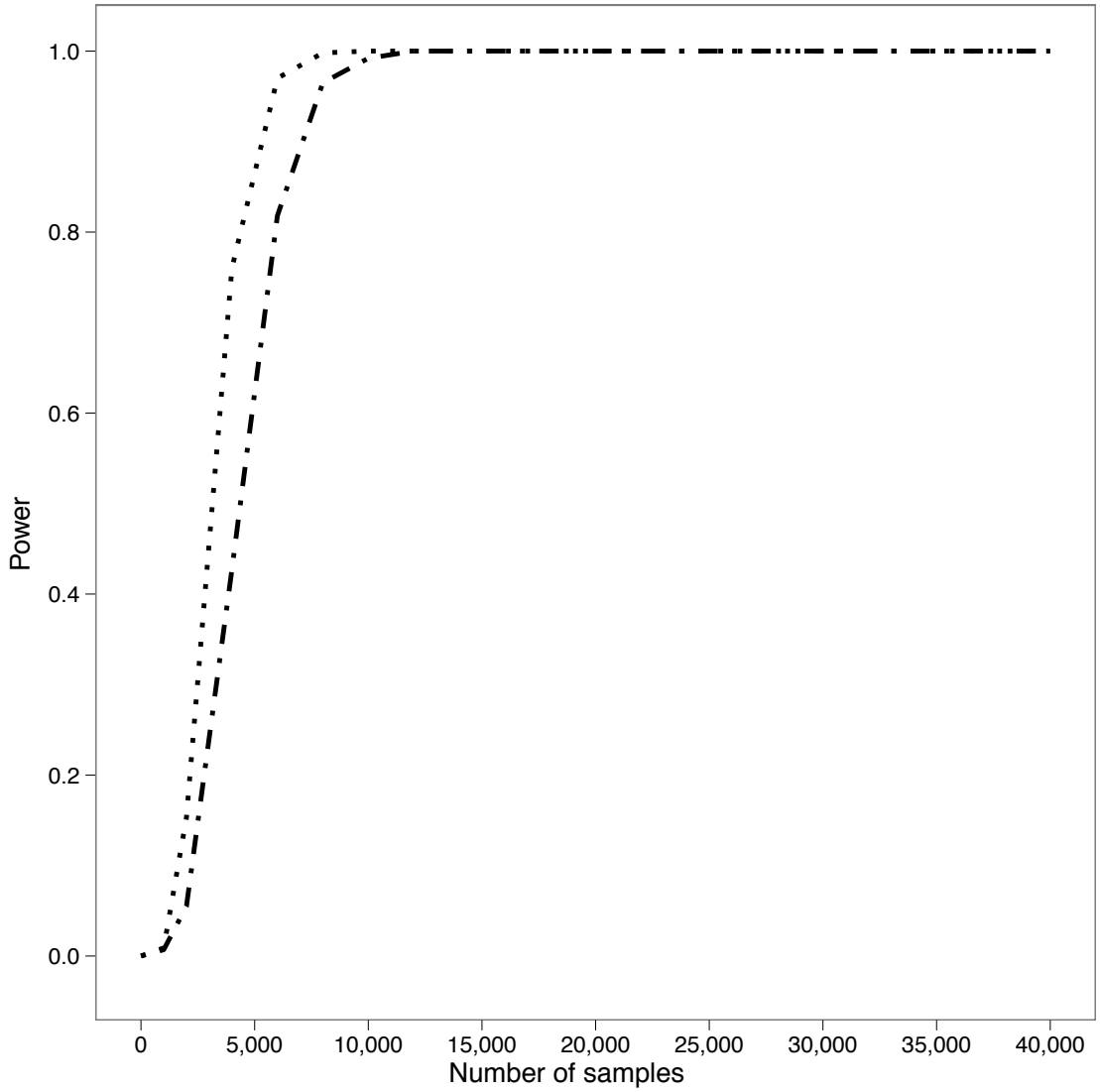
Power calculations were performed for a gene with the median number of mutation carriers (median number calculated across all genes available in the exome). Prevalence of disease was assumed to be 0.05. The relative risk of a mutation carrier was assumed to be 2.0 (i.e., the effect size observed for *APOA5* signal). We set alpha at P=2.5 x 10^{-6} to account for the testing of ~20,000 genes. The dotted-dashed line represents a conservative estimate and the dotted line represents a liberal estimate. Power calculations show that more than 10,000 samples are needed to reach 80% power for a gene of median size.

Supplementary Figure 30. Power calculations for a gene with a small number of single nucleotide variants and insertions/deletions



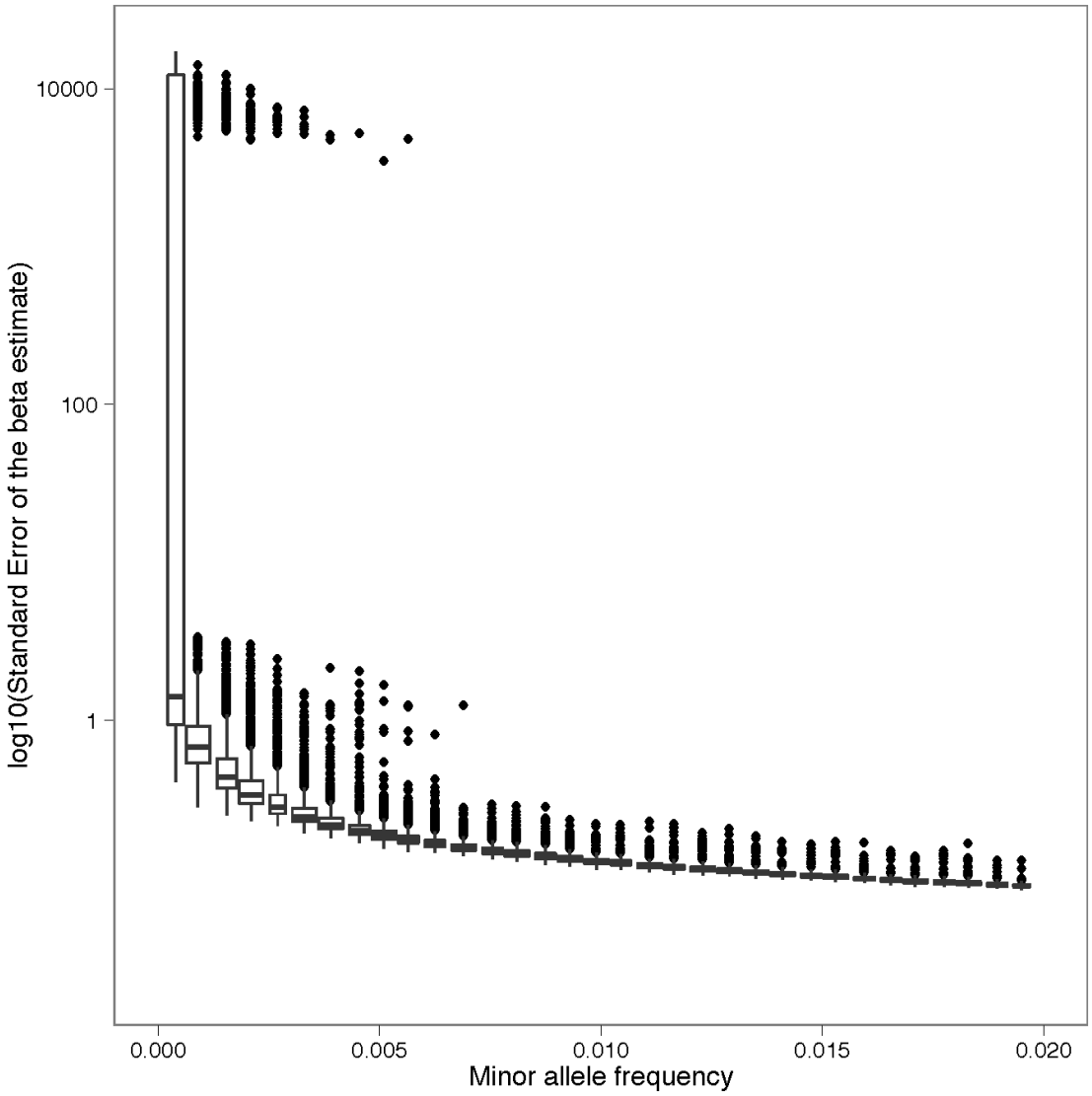
Power calculations were performed for a gene with a small number of single nucleotide variants (25th percentile) after performing sample size extrapolations based on the observed exome data. A prevalence rate of disease was assumed to be 0.05. The relative risk of a mutation carrier was assumed to be 2.0. The dotted-dashed line represents a conservative estimate and the dotted line represents a liberal estimate.

Supplementary Figure 31. Power calculations for a gene with a large number of single nucleotide variants and insertions/deletions



Power calculations were performed for a gene with a high number of single nucleotide variants (75th percentile) after performing sample size extrapolations based on the observed exome data. A prevalence rate of disease was assumed to be 0.05. The relative risk of a mutation carrier was assumed to be 2.0. The dotted-dashed line represents a conservative estimate and the dotted line represents a liberal estimate.

Supplementary Figure 32. Stability of logistic regression across allele frequencies in follow-up genotyping



A boxplot of the standard error of the beta estimate from logistic regression for the follow-up genotyping analysis is plotted for variants grouped by minor allele frequency bins. The binwidth is 0.0005.

Supplementary Table 1. Age and gender for participants who were exome sequenced as part of the ESP early-onset myocardial infarction study

Ethnicity	Sex	N	Mean age [min, max]
		Cases (n=1,027)	
European American (n=818)	Male	370	44 [19, 50]
	Female	445	53 [28, 60]
African American (n=209)	Male	66	43 [27, 50]
	Female	134	52 [26, 60]
		Controls (n=946)	
European American (n=613)	Male	317	73 [60, 97]
	Female	296	78 [70, 92]
African American (n=333)	Male	176	71 [60, 93]
	Female	157	77 [70, 93]

min: minimum age; max: maximum age.

Supplementary Table 2. Plasma lipids for participants who were exome sequenced as part of the ESP early-onset myocardial infarction study

Phenotype	Ethnicity	LDL-C (mean, std)	HDL-C (mean, std)	TG (mean, std)
Cases (n=1,027)	European American	113.3 (41.2)	42.3 (13.7)	215.6 (251.7)
	African American	122.0 (53.2)	44.6 (13.7)	139.3 (101.8)
Controls (n=946)	European American	140.8 (35.0)	44.6 (12.9)	158.4 (96.5)
	African American	144.8 (43.1)	47.2 (14.5)	143.7 (78.6)

std: standard deviation in mg/dl; LDL-C: low-density lipoprotein cholesterol in mg/dl; HDL-C: high-density lipoprotein cholesterol in mg/dl; TG: plasma triglycerides in mg/dl.

Supplementary Table 3. Source studies for cases and controls that were exome sequenced as part of the ESP early-onset myocardial infarction study

Source study	Cases	Controls
ARIC	83	316
CHS	0	104
CCGB	35	0
FHS	45	106
HARPS	406	0
JHS	0	61
MESA	1	54
MGH-PCAD	155	0
PennCath	35	0
TRIUMPH	122	0
WHI	145	305

ARIC: Atherosclerosis Risk in Communities; CHS: Cardiovascular Health Study; CCGB: Cleveland Clinic Genebank; FHS: Framingham Heart Study; HARPS: Heart Attack Risk in Puget Sound; JHS: Jackson Heart Study; MESA: Multi-Ethnic Study of Atherosclerosis; MGH-PCAD: Massachusetts General Hospital Premature Coronary Artery Disease Study; PennCath: PennCath study; TRIUMPH: Translational Research Underlying Disparities in Myocardial Infarction Patients' Health Status; WHI: Women's Health Initiative.

Supplementary Table 4. Genotyping platforms for samples used in follow-up imputation

Study	Genotyping Platform	Ref
MIGen	Affymetrix Genome-Wide Human SNP Array 6.0	1
WTCCC CAD	Affymetrix Mapping 500K Array Set	2
CCGB	Affymetrix Genome-Wide Human SNP array 6.0	3
DUKE	Axiom array	3
OHS A	Affymetrix Mapping 500K Array Set	3
OHS B	Affymetrix Genome-wide Human SNP Array 6.0	3
PennCath	Affymetrix Genome-Wide Human SNP Array 6.0	4
MedStar	Affymetrix Genome-Wide Human SNP Array 6.0	4
Luric HD	Affymetrix Genome-Wide Human SNP Array 6.0	5
ARIC EA	Affymetrix Genome-Wide Human SNP Array 6.0	6
ARIC AA	Affymetrix Genome-Wide Human SNP Array 6.0	6
PROMIS	Illumina HumanHap 670 Quad	7
PROCARDIS/ WTCCC controls	Illumina Infinium Human 1M, HumanHap 610 and Human 1.2M	7
GerMIFS1	Affymetrix Mapping 500K Array Set	5
GerMIFS2	Affymetrix Genome-Wide Human SNP Array 6.0	5
GerMIFS3	Affymetrix Genome-Wide Human SNP Array 5.0 / 6.0	5

Ref: Reference; MIGen: Myocardial Infarction Genetics Consortium; WTCCC CAD: Wellcome Trust Case Control Consortium Coronary Artery Disease; CCGB: Cleveland Clinic Genebank; DUKE: Duke CATHGEN study; OHS: Ottawa Heart Study; PennCath: PennCath study; MedStar: MedStar study; Luric HD: Luric study; ARIC: Atherosclerosis Risk in Communities; PROMIS: Pakistan Risk of Myocardial Infarction; PROCARDIS: Precocious coronary artery disease study; GerMIFS: German Myocardial Infarction Family Study.

Supplementary Table 5. Case and control definitions for studies used in follow-up imputation

Study	Cases	Controls	Case definition	Control definition	Ref.
MIGen	2,967	3,075	MI (men ≤ 50 yo / women ≤ 60 yo)	Hospital-based, no report of MI by history	[1]
WTCCC CAD	1,926	2,935	Validated MI, CABG, PTCA or angina with positive non-invasive testing at < 66 yo	Unselected	[2]
CCGB	1,628	368	Stable or unstable angina, MI, ≥ 50% stenosis in a single vessel at angiography, history of known CAD	≥ 50 yo with normal coronary arteries at cardiac catheterization	[3]
DUKE	1,216	653	MI; coronary stenosis ≥ 50%	Patients > 50 yo; no coronary stenosis greater than 30%; No history of ICC/PCI, CABG, MI or transplant	[3]
OHS A	947	1,008	Angiographic (>50% stenosis)	Asymptomatic	[3]
OHS B	1,294	1,529	Angiographic (>50% stenosis)	Asymptomatic	[3]
PennCath	921	459	Angiography (>1 coronary vessel with > 50% stenosis); < 55 yo for males and < 60 yo for females	Angiography normal, men > 40 yo / women > 45 yo	[4]
MedStar	873	445	Angiography (>1 coronary vessel with >50% stenosis); < 55 yo for males and < 60 yo for females	Angiography normal, > 45 yo	[4]
Luric HD	1,511	594	Symptoms of angina pectoris, NSTEMI, STEMI, or > 50% coronary	No coronary lesions or minor stenoses (<20%)	[8]

			stenosis		
ARIC EA	1,539	8,082	Incident definite or probable MI; silent MI by electrocardiogram; coronary revascularization	Population sample	[9]
ARIC AA	407	2,728	Incident definite or probable MI; silent MI by electrocardiogram; coronary revascularization	Population sample	[9]
PROMIS	4,667	4,478	Typical ECG characteristics; Positive troponin test; and MI symptoms	Age and sex-matched; No history of MI/CAD	[10]
PROCARDIS/ WTCCC controls	5,717	4,564	MI; CABG; ACS; coronary angioplasty	Procardis: No history of CAD; WTCCC: unselected	[11,12]
GerMIFS1	863	1,603	MI (< 65 yo) with >1 1st degree sibling with severe CAD (PTCA; MI; CABG)	Population sample	[5]
GerMIFS2	496	2,024	MI (< 60 yo); 59.4% with family history of CAD	Population sample	[5]
GerMIFS3	1,096	1,519	MI (< 60 yo); MONICA criteria	Population sample	[5]

MIGen: Myocardial Infarction Genetics Consortium; WTCCC CAD: Wellcome Trust Case Control Consortium Coronary Artery Disease; CCGB: Cleveland Clinic Genebank; DUKE: Duke CATHGEN study; OHS: Ottawa Heart Study; PennCath: PennCath study; MedStar: MedStar study; Luric HD: Luric study; ARIC: Atherosclerosis Risk in Communities; PROMIS: Pakistan Risk of Myocardial Infarction; PROCARDIS: Precocious coronary artery disease study; GerMIFS: German Myocardial Infarction Family Study; MI: myocardial infarction; CAD: coronary artery disease; CABG: coronary artery bypass; ACS: acute coronary syndrome; PTCA: Percutaneous transluminal coronary angioplasty; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; ECG: electrocardiogram; yo: years old.

Supplementary Table 6. Top association results from follow-up imputation

Chr	Position	SNV	A1	A2	Beta	SE	*P*	Gene/locus
9	22029445	rs10965215	A	G	-0.14	0.015	6.82×10^{-19}	9p21
6	160961137	rs3798220	T	C	0.50	0.053	1.83×10^{-18}	*LPA*
1	222802803	rs3748626	T	G	0.12	0.016	4.48×10^{-11}	*MIA3*
10	91007360	rs1051338	T	G	0.11	0.017	8.33×10^{-10}	*LIPA*
6	160557643	rs2282143	T	C	-0.26	0.046	1.19×10^{-9}	*SLC22A1*
2	203846817	rs72932557	A	T	0.14	0.022	1.56×10^{-9}	*ALS2CR8*
12	111884608	rs3184504	T	C	-0.10	0.016	3.46×10^{-9}	*SH2B3*
2	203765756	rs35212307	T	C	0.14	0.022	3.47×10^{-9}	*WDR12*
6	160493834	rs2230044	A	G	-0.22	0.043	1.21×10^{-8}	*IGF2R*
1	222919895	rs2378607	T	G	0.10	0.017	4.11×10^{-8}	*FAM177B*
2	85769711	rs1078004	C	G	0.074	0.014	5.84×10^{-8}	*MAT2A*

Chr: chromosome; SNV: single nucleotide variant; A1: allele 1; A2: allele 2; SE: standard error.

Supplementary Table 7. Case and control definitions for studies used in follow-up genotyping

Study	Cases	Controls	Case definition	Control definition	Ref.
ATVB	1,448	1,078	MI defined by chest pain; persistent electrocardiographic changes, and confirmed increase in total creatine phosphokinase-MB	No history of thromboembolic disease	13
OHS	1,019	2,255	Angiographic (> 50% stenosis) men < 55 yo; women < 65 yo	Asymptomatic men > 65 yo women > 70 yo	3
AMC-PAS	859	686	Symptomatic CAD before the age of 51yo, defined as MI, coronary revascularization, or evidence of at least 70% stenosis in a major epicardial artery	More than 95% of the controls are from the same region as the cases of the AMC-PAS cohort	14
PennCath	683	156	Angiography (≥ 1 coronary vessel with > 50% stenosis); ≤ 60 yo for males and ≤ 65 yo for females.	Angiography normal, men > 40 yo / women > 45 yo	4
PROCARDIS	2,485	2,218	MI; CABG; ACS; coronary angioplasty	No history of CAD	11,15
VHS	175	164	MI defined by medical history, ECG changes, and laboratory markers, before 45 yo in men and 50 yo in women.	No history of CAD or symptoms; Angiography normal, men > 60 yo, women > 65 yo	16
WHI	970	1,740	MI, coronary revascularization, hospitalized angina, or CAD death	Population-sample, free of CAD	17

ATVB: Atherosclerosis, Thrombosis and Vascular Biology Italian Study Group; OHS: Ottawa Heart Study; AMC-PAS: Academic Medical Center Amsterdam Premature Atherosclerosis Study; PennCath: PennCath study; MedStar: MedStar study; Luric HD: Luric study; ARIC: Atherosclerosis Risk in Communities; PROMIS: Pakistan Risk of

Myocardial Infarction; PROCARDIS: Precocious coronary artery disease study; VHS: Verona Heart Study; WHI: Women's Health Initiative; MI: myocardial infarction; CAD: coronary artery disease; CABG: coronary artery bypass; ACS: acute coronary syndrome; PTCA: Percutaneous transluminal coronary angioplasty; ECG: electrocardiogram; yo: years old

Supplementary Table 8. Association of myocardial infarction or coronary artery disease with single nucleotide variants genotyped using the 'Exome Chip' genotyping array

Locus	Chr	Position	SNV	Alleles[1]/MAF	Function[2]	OR	*P*
9p21	9	22098574	rs4977574	A/G/0.49	Intergenic	0.79	2×10^{-22}
LDLR	19	11202306	rs6511720	T/G/0.12	Intronic	0.76	8×10^{-13}
APOE	19	45410002	rs769449	A/G/0.11	Intronic	1.31	1×10^{-12}
PHACTR1	6	12903957	rs9349379	G/A/0.41	Intronic	1.19	3×10^{-12}
LPA	6	160961137	rs3798220	C/T/0.02	Missense [I4399M]	1.78	1×10^{-11}
ABO	9	136142203	rs514659	C/A/0.35	Intronic	1.18	1×10^{-10}
LIPA	10	91004886	rs2246942	G/A/0.34	Intronic	1.17	5×10^{-10}
APOB	2	227068080	rs2943634	T/C/0.35	Intergenic	0.87	3×10^{-8}
SORT1	1	109817590	rs12740374	T/G/0.20	3' UTR	0.85	4×10^{-8}

We present all association results exceeding genome-wide significance ($P<5 \times 10^{-8}$) after testing 44,291 variants from the Exome Chip genotyping array where the minor allele was observed at least 15 times. Chr: chromosome; SNV: single nucleotide variant; MAF: minor allele frequency; OR: odds ratio; UTR: untranslated region.
[1]Direction of effect (OR) and MAF are shown with regard to first allele.
[2]For missense variants, the protein change is also shown in brackets.

Supplementary Table 9. Case and control definitions in studies for follow-up targeted re-sequencing

Study	Cases	Controls	Case definition	Control definition	Ref.
ESP EOMI 1[a]	466	318	MI in men ≤ 50 yo or women ≤ 60 yo	MI in men ≥ 60 yo and women ≥ 70 yo	NA
VHS	977	350	Documented diagnosis of MI, coronary artery bypass grafting (CABG), CAD (by angiography).	Coronary angiography normal	16
OHS	552	586	MI, CABG, or angiographic (>50% stenosis) in men ≤ 50 yo or women ≤ 60 yo	Asymptomatic men & women>75 yo	3
ATVB	1,716	1,519	MI in men or women ≤ 45 yo	No history of thromboembolic disease	13
ESP EOMI 2[a]	571	663	MI in men ≤ 50 years old or women ≤ 60 yo	MI in men ≥ 60 years old and women ≥ 70 yo	NA
CCHS/CIHDS	1,054	1,776	MI defined by enzyme documentation, ischemic symptoms, ECG, coronary artery intervention; MI in men < 50 yo or women < 60 yo	Controls are free of MI or IHD but the same age (men < 50 yo and women < 60 yo)	18,19
PROCARDIS	1,385	1,499	Documented diagnoses of MI, symptomatic acute coronary syndrome, coronary revascularization, or chronic stable angina < 65 yo or less	Controls were self-reported free of coronary disease at age 65 yo	11

[a] Study is part of the NHLBI ESP EOMI study. ESP EOMI 1 represents the first 784 exomes sequenced in this study; ESP EOMI 2 represents the final portion of the exomes sequenced in this study; VHS: Verona Heart Study; OHS: Ottawa Heart Study; ATVB:

Atherosclerosis, Thrombosis and Vascular Biology Italian Study Group; CCHS/CIHDS: Copenhagen City Heart Study and Copenhagen Ischemic Heart Disease Study; PROCARDIS: Precocious Coronary Artery Disease study.

Supplementary Table 10. Case and control allele counts for all non-synonymous single nucleotide variants and insertions/deletions with frequency < 1% discovered from sequencing the apolipoprotein A-V (*APOA5*) gene

Chr	Pos	Type	Protein/ splice-site change	T1 alleles in cases	T1 alleles in controls	PolyPhen-2	[1]N deleterious predictions
11	116660857	Missense	L363R	0	1	Benign	0
11	116660857	Missense	L363Q	1	0	Benign	1
11	116660918	Missense	R343C	1	0	Probably damaging	5
11	116660944	Missense	G334V	2	0	Benign	1
11	116660983	Missense	H321L	6	3	Probably damaging	4
11	116660989	Missense	P319L	1	0	Probably damaging	3
11	116661001	Missense	A315V	20	11	Probably damaging	4
11	116661008	Nonsense	Q313*	1	0		5
11	116661062	Nonsense	Q295*	1	0		5
11	116661070	Missense	T292I	1	0	Probably damaging	4
11	116661080	Missense	R289C	0	1	Probably damaging	5
11	116661097	Missense	Q283R	0	1	Benign	0
11	116661101	Missense	R282C	3	0	Probably damaging	2
11	116661104	Missense	V281M	0	1	Probably damaging	3
11	116661108	Missense	E279D	1	0	Benign	0
11	116661115	Missense	L277P	1	0	Benign	2
11	116661130	Missense	P272Q	1	0	Benign	1
11	116661168	Missense	R259S	2	0	Benign	0
11	116661181	Missense	E255G	1	2	Benign	0
11	116661182	Missense	E255K	0	1	Benign	0
11	116661207	Missense	I246M	0	2	Probably damaging	3
11	116661212	Missense	R245C	1	0	Probably damaging	3

11	116661248	Missense	R233W	1	0	Probably damaging	3
11	116661280	Missense	A222V	2	0	Benign	0
11	116661301	Missense	P215L	1	1	Probably damaging	3
11	116661308	Missense	V213M	0	2	Probably damaging	4
11	116661356	Missense	S197G	1	0	Benign	0
11	116661392	Missense	G185C	8	2	Probably damaging	3
11	116661421	Missense	G175A	0	1	Benign	0
11	116661441	Missense	E168D	0	1	Possibly damaging	1
11	116661455	Missense	G164R	1	0	Probably damaging	3
11	116661511	Missense	Q145R	5	1	Benign	0
11	116661517	Indel frameshift	R143fs	1	0		5
11	116661518	Indel frameshift	R143fs	1	0		5
11	116661599	Nonsense	E116*	1	0		5
11	116661632	Missense	A105S	1	0	Benign	0
11	116661650	Missense	E99K	1	1	Probably damaging	4
11	116661651	Missense	E98D	1	1	Possibly damaging	2
11	116661656	Nonsense	Q97*	2	2		5
11	116661662	Nonsense	Q95*	1	0		5
11	116661665	Missense	R94W	8	3	Probably damaging	2
11	116661667	Missense	R93Q	1	0	Benign	0
11	116661671	Indel frameshift	M92fs	1	0		5
11	116661704	Missense	E81K	0	1	Benign	0
11	116662344	Missense	R40M	4	1	Benign	0
11	116662352	Missense	D37E	7	2	Benign	0

Chr: chromosome; Pos: position; Type: variant type; AA: amino acid change; T1: alleles from variants with minor allele frequency < 1%; PolyPhen-2: Prediction from PolyPhen-2 HumDiv software. [1]Number of deleterious predictions from five protein prediction algorithms of LRT score, MutationTaster, PolyPhen-2 HumDiv, PolyPhen-2 HumVar and Sorting Intolerant From Tolerant (SIFT). Disruptive variants (nonsense, indel frameshift and splice-site) were automatically assigned N=5 for deleterious predictions from five protein prediction algorithms.

Supplementary Table 11. Heritability explained by a burden of rare mutations in the apolipoprotein A-V (*APOA5*) gene

	Observed data		
	N	T1 alleles	Allele freq. (%)
Cases	6,721	93	0.69
Controls	6,711	42	0.31
	Allele freq. (%)	Population Effect Size (β, std.)	Variance Explained (h^2, %)
α=1, κ =0.03	0.32	-0.36	0.08
α=0.7, κ =0.03	0.32	-0.47	0.10
α=0.5, κ =0.03	0.32	-0.59	0.11
α=0.3, κ =0.03	0.32	-0.82	0.13
α=1, κ =0.05	0.33	-0.39	0.10
α=0.7, κ =0.05	0.33	-0.51	0.12
α=0.5, κ =0.05	0.33	-0.64	0.14
α=0.3, κ =0.05	0.33	-0.91	0.17

N: number of individuals; T1 alleles: number of T1 alleles; α: fraction of null; κ: prevalence of myocardial infarction; Allele freq.: allele frequency; std.: standard deviation.

Supplementary Table 12. Genetic variation in apolipoprotein A-V (*APOA5*) and plasma lipid levels among early-onset myocardial infarction cases and controls in the combined Copenhagen City Heart and Copenhagen Ischemic Heart Disease Studies

Trait	*APOA5* mutation carrier status[1]	N	Median lipid level (interquartile range)	*P*
TG	Non-carriers	2,810	103.6 (75.3-154.1)	-
	Carriers	20	166.5 (109.8-191.3)	0.007
HDL-C	Non-carriers	2,810	56.8 (44.9-69.2)	-
	Carriers	20	42.5 (34.8-54.1)	0.007
LDL-C	Non-carriers	2,810	108.3 (86.2-135.0)	-
	Carriers	20	110.2 (92.0-150.8)	0.66

[1]Carriers were defined as individuals who have an allele from a non-synonymous single nucleotide variant with < 1% frequency. TG: plasma triglyceride levels (mg/dl); LDL-C: plasma low-density lipoprotein cholesterol levels (mg/dl); HDL-C: plasma high-density lipoprotein cholesterol levels (mg/dl).

Supplementary Table 13. Case and control definitions for studies used in follow-up exome sequencing

Study	Cases	Controls	Case definition	Control definition	Ref.
ESP EOMI	977	1,422	MI (men ≤ 50 yo or women ≤ 60 yo)	Hospital-based, no report of MI by history	1
OHS	966	987	MI or CABG or angiographic disease (>50% stenosis) in men ≤ 50 yo or women ≤ 60 yo)	Asymptomatic	3
PROCARDIS	966	936	MI (men ≤ 50 yo or women ≤ 60 yo)	No history of CAD	11,12
ATVB	1,794	1,745	MI in men or women ≤ 45 yo	No history of thromboembolic disease	13

ESP EOMI: Exome Sequencing Project Early-onset Myocardial Infarction; OHS: Ottawa Heart Study; PROCARDIS: Precocious Coronary Artery Disease study; ATVB: Atherosclerosis, Thrombosis and Vascular Biology Italian Study Group; MI: myocardial infarction; CAD: coronary artery disease; CABG: coronary artery bypass; ACS: acute coronary syndrome; yo: years old.

Supplementary Table 14. Age and gender for participants from follow-up exome sequencing

Cohort	Sex	N	Mean age [min, max]
	Cases (n=3,726)		
ATVB (n=1,794)	Male	1,605	39.7 [16, 56]
	Female	189	39.2 [21, 48]
OHS (n=966)	Male	811	48.9 [21, 75]
	Female	155	51.9 [25, 75]
PROCARDIS (n=966)	Male	618	44.5 [23, 59]
	Female	348	51.3 [27, 60]
	Controls (n=3,668)		
ATVB (n=1,745)	Male	1,547	39.7 [16, 56]
	Female	198	39.2 [21, 52]
OHS (n=987)	Male	497	78.2 [72, 96]
	Female	490	79.8 [74, 96]
PROCARDIS (n=936)	Male	603	69.3 [62, 84]
	Female	333	71.1 [67, 88]

ATVB: Atherosclerosis, Thrombosis and Vascular Biology Italian Study Group; OHS: Ottawa Heart Study; PROCARDIS: Precocious Coronary Artery Disease study; min: minimum age; max: maximum age.

Supplementary Table 15. Top association results for T1 burden test of all non-synonymous variants from follow-up exome sequencing

Gene	*P*
PDK3	2.90×10^{-7}
LDLR	4.10×10^{-6}
TSPAN17	2.72×10^{-5}
GTF2E2	4.26×10^{-5}
SERPINH1	6.88×10^{-5}
ACTL6A	9.71×10^{-5}
TH	0.00013
TMEM69	0.00022
ARHGAP10	0.00025
ETNK1	0.00031

Supplementary Table 16. Top association results for T1 burden test of deleterious variants from follow-up exome sequencing

Gene	*P*
LDLR	1.46×10^{-11}
TH	2.08×10^{-5}
PCDHA2	2.36×10^{-5}
SERPINF2	4.50×10^{-5}
ATF5	7.50×10^{-5}
TAS2R40	0.00020
TCIRG1	0.00039
TOB1	0.00051
THTPA	0.0013
ACR	0.0023

Supplementary Table 17. Top association results for T1 burden test of disruptive variants from follow-up exome sequencing

Gene	*P*
CDX2	1.62×10^{-5}
PCDHA2	2.36×10^{-5}
LDLR	9.10×10^{-5}
BDP1	0.00033
PKHD1L1	0.00043
CCDC158	0.00069
EPS8L2	0.00078
OR6N2	0.00080
CCDC11	0.00087
SMAD5	0.0013

Supplementary Table 18. Case and control allele counts for non-synonymous single nucleotide variants and indels with frequency < 1% at the low-density lipoprotein receptor (*LDLR*) gene

Chr	Position	Ref	Alt	Type	Protein/ splice-site change	T1 alleles in cases	T1 alleles in controls	PolyPhen-2	[1]N deleterious predictions
19	11200266	G	C	Missense	L14F	1	0	Benign	0
19	11200282	G	A	Missense	G20R	15	15	Benign	0
19	11210922	G	A	Missense	E31K	0	1	Probably damaging	3
19	11210928	C	T	Nonsense	Q33*	2	0		5
19	11210974	G	A	Missense	G48D	0	1	Probably damaging	5
19	11210979	G	T	Missense	A50S	4	5	Benign	0
19	11211016	C	T	Missense	T62M	4	4	Probably damaging	4
19	11213359			Indel frameshift	S70fs	1	0		5
19	11213382	G	A	Missense	R78H	2	0	Probably damaging	3
19	11213390	C	T	Missense	R81C	1	0	Probably damaging	5
19	11213418	A	G	Missense	D90G	1	0	Probably damaging	5
19	11213445	C	G	Nonsense	S99*	1	0		5
19	11213450	G	A	Missense	E101K	1	0	Probably damaging	5
19	11213453	C	T	Nonsense	Q102*	1	0		5
19	11213463	G	A	Splice-site	c.313+ 1G>A	5	0		5
19	11215896	C	T	Missense	P105L	1	1	Benign	1
19	11215908	G	A	Missense	C109Y	1	0	Probably damaging	5
19	11215934	G	T	Missense	D118Y	2	0	Probably damaging	3
19	11215974	A	G	Missense	D131G	1	0	Possibly damaging	5
19	11215991	G	A	Missense	G137S	0	1	Probably damaging	5
19	11215992	G	T	Missense	G137V	1	0	Probably damaging	5
19	11216000	G	T	Nonsense	E140*	2	0		5
19	11216011	C	A	Nonsense	C143*	0	1		5
19	11216016	T	C	Missense	V145A	0	1	Benign	0
19	11216047	C	A	Nonsense	C155*	1	0		5

19	11216084	G	A	Missense	D168N	2	0	Probably damaging	5
19	11216090	G	A	Missense	D170N	0	1	Probably damaging	5
19	11216112	C	T	Missense	S177L	1	0	Probably damaging	5
19	11216124	C	G	Missense	P181R	3	1	Probably damaging	4
19	11216127	A	G	Missense	Q182R	1	0	Benign	1
19	11216147	G	C	Missense	V189L	0	1	Benign	0
19	11216171	T	C	Missense	C197R	1	0	Probably damaging	5
19	11216244	A	G	Missense	D221G	10	0	Probably damaging	5
19	11216247	G	A	Missense	C222Y	1	0	Probably damaging	5
19	11217256	G	A	Missense	R237H	0	3	Probably damaging	4
19	11217268	T	C	Missense	F241S	1	0	Probably damaging	5
19	11217303	C	T	Missense	R253W	2	2	Probably damaging	3
19	11217336	A	C	Missense	M264L	1	0	Benign	0
19	11217337	T	C	Missense	M264T	0	1	Benign	1
19	11217344	T	A	Missense	D266E	1	1	Probably damaging	5
19	11217352	G	A	Missense	G269D	1	1	Benign	2
19	11218068	T	G	Missense	V273G	0	0	Benign	4
19	11218077	G	C	Missense	C276S	1	0	Probably damaging	5
19	11218079	G	A	Missense	E277K	8	4	Benign	2
19	11218096	C	A	Missense	F282L	1	0	Benign	5
19	11218103	C	T	Missense	H285Y	0	1	Benign	3
19	11218109	G	A	Missense	G287S	0	1	Possibly damaging	5
19	11218142	A	G	Missense	M298V	0	3	Benign	0
19	11218148	A	G	Missense	R300G	1	1	Possibly damaging	4
19	11218157	C	T	Missense	R303W	1	3	Probably damaging	4
19	11218158	G	A	Missense	R303Q	1	0	Benign	0
19	11218160	G	A	Missense	D304N	1	0	Possibly damaging	5
19	11218182	A	C	Missense	K311T	1	0	Possibly damaging	5
19	11221334	A	G	Missense	N316S	2	1	Possibly damaging	5
19	11221354	G	A	Missense	G323S	0	1	Probably	5

								damaging	
								Probaby	
19	11221357	G	A	Missense	G324S	5	9	damaging	4
19	11221369	G	A	Missense	V328I	0	1	Benign	0
								Possibly	
19	11221375	A	C	Missense	N330H	1	1	damaging	2
								Probaby	
19	11221390	G	A	Missense	G335S	1	1	damaging	5
								Probaby	
19	11221391	G	A	Missense	G335D	0	1	damaging	5
19	11221411	G	A	Missense	D342N	4	10	Benign	0
								Probaby	
19	11221414	G	A	Missense	G343S	0	1	damaging	5
19	11221435	C	T	Nonsense	R350*	1	0		5
19	11221444	G	A	Missense	E353K	1	2	Benign	4
								Possibly	
19	11222214	A	C	Missense	D362A	5	3	damaging	4
								Probaby	
19	11222234	G	A	Missense	V369M	1	1	damaging	4
								Probaby	
19	11222258	T	C	Missense	C377R	1	0	damaging	5
19	11222262	A	C	Missense	Q378P	1	0	Benign	3
								Probaby	
19	11222295	C	T	Missense	T389M	1	0	damaging	5
								Probaby	
19	11223962	G	A	Missense	A399T	1	1	damaging	5
								Probaby	
19	11223989	G	A	Missense	E408K	1	0	damaging	5
								Probaby	
19	11224005	C	T	Missense	T413M	1	0	damaging	4
								Probaby	
19	11224013	C	T	Missense	R416W	1	0	damaging	5
19	11224024	C	G	Nonsense	Y419*	1	0		5
19	11224030	C	A	Missense	S421R	0	1	Benign	2
19	11224037	C	A	Missense	P424T	0	1	Benign	1
								Possibly	
19	11224061	C	G	Missense	L432V	2	0	damaging	5
								Possibly	
19	11224066	C	G	Missense	D433E	0	1	damaging	5
					c.1358				
19	11224126	G	A	Splice-site	+1G>A	1	0		5
19	11224228	C	G	Missense	A459G	0	1	Benign	1
19	11224233	G	T	Missense	G461C	1	0	Benign	3
19	11224245	T	A	Missense	Y465N	2	0	Benign	1
19	11224254	G	A	Missense	V468I	2	0	Benign	1
								Possibly	
19	11224266	G	T	Missense	D472Y	7	0	damaging	3
19	11224296	G	A	Missense	D482N	4	0	Probaby	5

19	11224319	C	G	Nonsense	Y489*	1	0	damaging	5
19	11224326	G	A	Missense	D492N	2	0	Probaby damaging	5
19	11224354	C	T	Missense	A501V	1	0	Possibly damaging	5
19	11224362	A	G	Missense	K504E	2	0	Benign	0
19	11224368	G	A	Missense	V506M	1	0	Possibly damaging	2
19	11224398	G	A	Missense	G516S	2	2	Possibly damaging	2
19	11224399	G	A	Missense	G516D	0	1	Benign	0
19	11224419	G	A	Missense	V523M	1	0	Probaby damaging	5
19	11224422	G	A	Missense	V524M	1	0	Probaby damaging	5
19	11224428	C	T	Missense	P526S	0	1	Probaby damaging	5
19	11224432	T	C	Missense	V527A	0	1	Benign	0
19	11224437	G	C	Missense	G529R	2	0	Probaby damaging	5
19	11224439	G	A	Splice-site	c.1586 +1G>A	1	0		5
19	11226781	G	A	Nonsense	W533*	1	0		5
19	11226829	G	A	Missense	G549D	5	0	Probaby damaging	4
19	11227549	C	T	Missense	R574C	1	0	Probaby damaging	5
19	11227576	C	G	Missense	H583D	1	0	Probaby damaging	5
19	11227594	G	C	Missense	D589H	1	0	Probaby damaging	4
19	11227604	G	A	Missense	G592E	2	1	Possibly damaging	5
19	11227613	G	A	Missense	R595Q	2	1	Probaby damaging	5
19	11227645	G	T	Missense	A606S	2	5	Benign	3
19	11227666	G	A	Missense	V613I	0	1	Benign	1
19	11227676	T	C	Splice-site	c.1845 +2T>C	1	0		5
19	11230798	G	A	Missense	E626K	4	3	Possibly damaging	3
19	11230858	C	A	Missense	L646I	1	0	Possibly damaging	5
19	11230873	G	A	Missense	D651N	1	0	Benign	5
19	11230876	A	G	Missense	M652V	0	1	Benign	0

19	11230880	T	C	Missense	V653A	0	1	Benign	1
19	11230888	C	A	Missense	H656N	0	1	Possibly damaging	5
19	11231057	T	C	Missense	C667R	1	2	Probaby damaging	5
19	11231075	A	C	Missense	S673R	1	0	Benign	0
19	11231081	G	A	Missense	G675S	0	1	Possibly damaging	5
19	11231087	T	C	Missense	C677R	1	0	Probaby damaging	5
19	11231101	C	A	Nonsense	C681*	1	0		5
19	11231112	C	T	Missense	P685L	4	0	Probaby damaging	5
19	11231118			Indel frameshift	I687fs	0	1		5
19	11231156	G	A	Missense	D700N	0	1	Probaby damaging	4
19	11231159	G	A	Missense	G701S	1	1	Probaby damaging	5
19	11231164	G	A	Missense	M702I	1	1	Benign	2
19	11231174	A	G	Missense	R706G	0	1	Benign	0
19	11231181	T	G	Missense	M708R	1	0	Benign	1
19	11231184	G	A	Missense	R709K	2	0	Probaby damaging	4
19	11233862	C	T	Missense	A718V	0	1	Benign	0
19	11233886	C	T	Missense	T726I	69	69	Benign	1
19	11233888	G	A	Missense	V727I	0	1	Benign	0
19	11233910	C	T	Missense	T734I	1	0	Benign	0
19	11233924	C	A	Missense	Q739K	1	0	Benign	0
19	11233939	C	T	Nonsense	R744*	0	0		5
19	11233940	G	A	Missense	R744Q	6	5	Benign	0
19	11233951	G	A	Missense	D748N	1	0	Benign	0
19	11233991	C	T	Missense	T761M	1	0	Probaby damaging	4
19	11234010	G	A	Missense	M767I	2	1	Benign	0
19	11234017	C	T	Nonsense	Q770*	1	0		5
19	11238684	C	T	Missense	A771V	0	0	Benign	0
19	11238692	G	A	Missense	D774N	0	0	Benign	0
19	11238695	G	A	Missense	V775I	1	0	Benign	0
19	11238719	A	C	Missense	K783Q	1	0	Benign	0
19	11238728	A	G	Missense	S786G	0	1	Benign	0
19	11240197	G	A	Missense	V800I	0	1	Benign	0
19	11240210			Indel frameshift	L804fs	2	0		5
19	11240239	C	T	Missense	R814W	1	1	Probaby damaging	5
19	11240240	G	A	Missense	R814Q	1	4	Probaby damaging	4

19	11240274	C	G	Missense	N825K	1	0	Probaby damaging	5
19	11240278	G	A	Missense	V827I	4	5	Probaby damaging	4
19	11240309	A	G	Missense	H837R	1	0	Probaby damaging	4
19	11240337	C	G	Missense	S846R	1	0	Possibly damaging	2
19	11240345	C	T	Missense	S849L	2	0	Probaby damaging	4
19	11241961	A	G	Missense	Q851R	1	0	Possibly damaging	5
19	11241965	G	T	Missense	M852I	0	1	Benign	2
19	11241984	G	A	Missense	V859M	1	0	Benign	1
19	11241988	C	T	Missense	A860V	1	0	Benign	3

Chr: chromosome; SNVs: single nucleotide variants; T1: alleles from variants with minor allele frequency < 1%; PolyPhen-2: Prediction from PolyPhen-2 HumDiv software. [1]Number of deleterious predictions from five protein prediction algorithms of LRT score, MutationTaster, PolyPhen-2 HumDiv, PolyPhen-2 HumVar and Sorting Intolerant From Tolerant (SIFT). Disruptive variants (nonsense, indel frameshift and splice-site) were automatically assigned N=5 for deleterious predictions from five protein prediction algorithms.

Supplementary Table 19. Heritability explained by a burden of rare mutations in the low-density lipoprotein receptor (*LDLR*) gene

	Observed data		
	N	T1 alleles	Allele freq. (%)
Cases	4,703	285	3.03
Controls	5,090	208	2.04
	Allele freq. (%)	Population Effect Size (β, std.)	Variance Explained (h^2, %)
α=1, κ =0.03	2.07	-0.18	0.13
α=0.7, κ =0.03	2.07	-0.24	0.16
α=0.5, κ =0.03	2.07	-0.31	0.20
α=0.3, κ =0.03	2.07	-0.46	0.26
α=1, κ =0.05	2.09	-0.19	0.15
α=0.7, κ =0.05	2.09	-0.26	0.19
α=0.5, κ =0.05	2.09	-0.34	0.24
α=0.3, κ =0.05	2.09	-0.50	0.32

N: number of individuals; T1 alleles: number of T1 alleles; α: fraction of null; κ: prevalence of myocardial infarction; Allele freq.: allele frequency; std.: standard deviation.

Supplementary Table 20. Low-density lipoprotein cholesterol levels and functional annotations in the low-density lipoprotein receptor (*LDLR*) gene

Variant type	Mean	Std
Non-carriers	134.8	42.1
Deleterious (PolyPhen)	210.4	94.5
Deleterious (Broad)	146.0	60.0
Deleterious (Strict)	219.9	93.5
Disruptive	278.5	91.1

Low-density lipoprotein cholesterol levels are shown for carriers of different types of variants with minor allele frequency < 1%. Std: standard deviation. Mean and Std are in mg/dl units. Non-Carriers: carriers without a missense or disruptive mutation; "Deleterious (PolyPhen)" as defined by nonsense, splice-site, indel frameshift, and missense annotated as "possibly damaging" or "probably damaging" by PolyPhen-2 HumDiv software; "Deleterious (Broad)" as defined by nonsense, splice-site, indel frameshift, and missense annotated as predicted deleterious by at least one of the five protein prediction algorithms of LRT score, MutationTaster, PolyPhen-2 HumDiv, PolyPhen-2 HumVar and Sorting Intolerant From Tolerant (SIFT); "Deleterious (Strict)" as defined by nonsense, splice-site, indel frameshift, and missense annotated as predicted deleterious by all five protein prediction algorithms; Disruptive: carriers of mutations that are nonsense, indel frameshift or splice-site.

Supplementary Table 21. Low-density lipoprotein receptor (*LDLR*) gene mutations in the *LDLR* Familial Hypercholesterolemia database

Chr	Position	Ref	Alt	Type	AA or splice change	*LDLR* FH database ID	FH allele name
19	11200266	G	C	Missense	L14F		
19	11200282	G	A	Missense	G20R	*LDLR*_00868	
19	11210922	G	A	Missense	E31K		
19	11210928	C	T	Nonsense	Q33*	*LDLR*_00005	FH Turkey/Milan-4
19	11210974	G	A	Missense	G48D		
19	11210979	G	T	Missense	A50S	*LDLR*_00330	
19	11211016	C	T	Missense	T62M	*LDLR*_01030	
19	11213359			Indel frameshift	S70fs		
19	11213382	G	A	Missense	R78H		
19	11213390	C	T	Missense	R81C	*LDLR*_00305	
19	11213418	A	G	Missense	D90G	*LDLR*_00012	FH London-4
19	11213445	C	G	Nonsense	S99*	*LDLR*_00162	FH Svartor
19	11213450	G	A	Missense	E101K	*LDLR*_00013	FH Lancashire
19	11213453	C	T	Nonsense	Q102*	*LDLR*_00014	FH Raponi
19	11213463	G	A	Splice-site	c.313+ 1G>A	*LDLR*_00163	FH-Elverum, FH Olbia
19	11215896	C	T	Missense	P105L		
19	11215908	G	A	Missense	C109Y	*LDLR*_00646	
19	11215934	G	T	Missense	D118Y	*LDLR*_00311	FH Naples-3
19	11215974	A	G	Missense	D131G		
19	11215991	G	A	Missense	G137S	*LDLR*_01145	
19	11215992	G	T	Missense	G137V		
19	11216000	G	T	Nonsense	E140*	*LDLR*_00019	FH Venezuela, FH Campobasso
19	11216011	C	A	Nonsense	C143*	*LDLR*_00154	
19	11216016	T	C	Missense	V145A	*LDLR*_01037	
19	11216047	C	A	Nonsense	C155*	*LDLR*_00416	
19	11216084	G	A	Missense	D168N	*LDLR*_00204	
19	11216090	G	A	Missense	D170N		

19	11216112	C	T	Missense	S177L	*LDLR*_00025	FH Puerto Rico
19	11216124	C	G	Missense	P181R	*LDLR*_00361	
19	11216127	A	G	Missense	Q182R		
19	11216147	G	C	Missense	V189L		
19	11216171	T	C	Missense	C197R	*LDLR*_00400	
19	11216244	A	G	Missense	D221G	*LDLR*_00031	FH Padova-1
19	11216247	G	A	Missense	C222Y	*LDLR*_00178	FH Finn-4, FH Genoa-2
19	11217256	G	A	Missense	R237H		
19	11217268	T	C	Missense	F241S	*LDLR*_00674	
19	11217303	C	T	Missense	R253W	*LDLR*_00375	
19	11217336	A	C	Missense	M264L		
19	11217337	T	C	Missense	M264T		
19	11217344	T	A	Missense	D266E	*LDLR*_00044	FH Cincinnati-1
19	11217352	G	A	Missense	G269D	*LDLR*_00504	FH Rome-3
19	11218068	T	G	Missense	V273G		
19	11218077	G	C	Missense	C276S		
19	11218079	G	A	Missense	E277K	*LDLR*_00195	FH Walloon, Genoa-3
19	11218096	C	A	Missense	F282L		
19	11218103	C	T	Missense	H285Y		
19	11218109	G	A	Missense	G287S		
19	11218142	A	G	Missense	M298V		
19	11218148	A	G	Missense	R300G		
19	11218157	C	T	Missense	R303W	*LDLR*_00512	
19	11218158	G	A	Missense	R303Q		
19	11218160	G	A	Missense	D304N	*LDLR*_00047	FH Denver-2
19	11218182	A	C	Missense	K311T	*LDLR*_01125	
19	11221334	A	G	Missense	N316S		
19	11221354	G	A	Missense	G323S	*LDLR*_00623	
19	11221357	G	A	Missense	G324S	*LDLR*_00640	
19	11221369	G	A	Missense	V328I		
19	11221375	A	C	Missense	N330H		
19	11221390	G	A	Missense	G335S	*LDLR*_00053	FH Paris-6
19	11221391	G	A	Missense	G335D		
19	11221411	G	A	Missense	D342N	*LDLR*_00212	

19	11221414	G	A	Missense	G343S	*LDLR*_00056	FH Picardie-3
19	11221435	C	T	Nonsense	R350*	*LDLR*_00215	FH Fossum
19	11221444	G	A	Missense	E353K		
19	11222214	A	C	Missense	D362A	*LDLR*_00792	
19	11222234	G	A	Missense	V369M		
19	11222258	T	C	Missense	C377R		
19	11222262	A	C	Missense	Q378P	*LDLR*_00530	
19	11222295	C	T	Missense	T389M	*LDLR*_00884	
19	11223962	G	A	Missense	A399T	*LDLR*_00534	FH Nuoro
19	11223989	G	A	Missense	E408K	*LDLR*_00065	FH Algeria-1, FH Osaka
19	11224005	C	T	Missense	T413M	*LDLR*_00967	
19	11224013	C	T	Missense	R416W	*LDLR*_00216	
19	11224024	C	G	Nonsense	Y419*	*LDLR*_00539	
19	11224030	C	A	Missense	S421R		
19	11224037	C	A	Missense	P424T		
19	11224061	C	G	Missense	L432V	*LDLR*_00541	
19	11224066	C	G	Missense	D433E		
19	11224126	G	A	Splice-site	c.1358 +1G>A	*LDLR*_00341	
19	11224228	C	G	Missense	A459G		
19	11224233	G	T	Missense	G461C		
19	11224245	T	A	Missense	Y465N		
19	11224254	G	A	Missense	V468I		
19	11224266	G	T	Missense	D472Y	*LDLR*_00886	
19	11224296	G	A	Missense	D482N	*LDLR*_00237	
19	11224319	C	G	Nonsense	Y489*	*LDLR*_00415	
19	11224326	G	A	Missense	D492N	*LDLR*_00548	
19	11224354	C	T	Missense	A501V	*LDLR*_00899	
19	11224362	A	G	Missense	K504E		
19	11224368	G	A	Missense	V506M		
19	11224398	G	A	Missense	G516S		
19	11224399	G	A	Missense	G516D		
19	11224419	G	A	Missense	V523M	*LDLR*_00075	FH Kuwait, FH Bari-2
19	11224422	G	A	Missense	V524M		
19	11224428	C	T	Missense	P526S	*LDLR*_00076	FH Cincinnati-3

19	11224432	T	C	Missense	V527A		
19	11224437	G	C	Missense	G529R		
19	11224439	G	A	Splice-site	c.1586 +1G>A	*LDLR*_00197	
19	11226781	G	A	Nonsense	W533*		
19	11226829	G	A	Missense	G549D	*LDLR*_00079	FH Genoa, FH Palermo-1
19	11227549	C	T	Missense	R574C	*LDLR*_00559	
19	11227576	C	G	Missense	H583D		
19	11227594	G	C	Missense	D589H		
19	11227604	G	A	Missense	G592E	*LDLR*_00084	FH Sicily, FH Foggia-1, FH Naples4
19	11227613	G	A	Missense	R595Q	*LDLR*_00563	
19	11227645	G	T	Missense	A606S	*LDLR*_00566	
19	11227666	G	A	Missense	V613I	*LDLR*_01070	
19	11227676	T	C	Splice-site	c.1845 +2T>C	*LDLR*_00087	FH Niigata
19	11230798	G	A	Missense	E626K	*LDLR*_01071	
19	11230858	C	A	Missense	L646I		
19	11230873	G	A	Missense	D651N	*LDLR*_00851	
19	11230876	A	G	Missense	M652V		
19	11230880	T	C	Missense	V653A		
19	11230888	C	A	Missense	H656N	*LDLR*_00852	
19	11231057	T	C	Missense	C667R	*LDLR*_00576	
19	11231075	A	C	Missense	S673R	*LDLR*_01005	
19	11231081	G	A	Missense	G675S	*LDLR*_00579	
19	11231087	T	C	Missense	C677R	*LDLR*_00090	FH New York-3
19	11231101	C	A	Nonsense	C681*	*LDLR*_00092	FH Lebanese
19	11231112	C	T	Missense	P685L	*LDLR*_00094	
19	11231118			Indel frameshift	I687fs		
19	11231156	G	A	Missense	D700N		
19	11231159	G	A	Missense	G701S	*LDLR*_01078	
19	11231164	G	A	Missense	M702I		
19	11231174	A	G	Missense	R706G		
19	11231181	T	G	Missense	M708R		
19	11231184	G	A	Missense	R709K		

19	11233862	C	T	Missense	A718V		
19	11233886	C	T	Missense	T726I	*LDLR*_00096[a]	FH Paris-9
19	11233888	G	A	Missense	V727I		
19	11233910	C	T	Missense	T734I		
19	11233924	C	A	Missense	Q739K		
19	11233939	C	T	Nonsense	R744*		
19	11233940	G	A	Missense	R744Q	*LDLR*_00588[a]	
19	11233951	G	A	Missense	D748N		
19	11233991	C	T	Missense	T761M	*LDLR*_00907	
19	11234010	G	A	Missense	M767I		
19	11234017	C	T	Nonsense	Q770*	*LDLR*_00589	FH Mondovi
19	11238684	C	T	Missense	A771V		
19	11238692	G	A	Missense	D774N		
19	11238695	G	A	Missense	V775I		
19	11238719	A	C	Missense	K783Q		
19	11238728	A	G	Missense	S786G		
19	11240197	G	A	Missense	V800I		
19	11240210			Indel frameshift	L804fs		
19	11240239	C	T	Missense	R814W		
19	11240240	G	A	Missense	R814Q		
19	11240274	C	G	Missense	N825K		
19	11240278	G	A	Missense	V827I	*LDLR*_00101	FH New York-5
19	11240309	A	G	Missense	H837R		
19	11240337	C	G	Missense	S846R		
19	11240345	C	T	Missense	S849L		
19	11241961	A	G	Missense	Q851R		
19	11241965	G	T	Missense	M852I		
19	11241984	G	A	Missense	V859M		
19	11241988	C	T	Missense	A860V		

AA change: Amino-acid change. *LDLR* mutations in the *LDLR* Familial Hypercholesterolemia (FH) database are shown . *LDLR*: Low-Density Lipoprotein Receptor; FH: Familial Hypercholesterolemia. [a]Listed in *LDLR* FH database[20] as "benign polymorphism."

Supplementary Table 22. Genomic inflation factor by study for follow-up imputation

Study	Genomic inflation factor
MIGen	1.07
WTCCC CAD	1.06
CCGB	1.03
DUKE	0.98
OHS A	1.12
OHS B	1.14
PennCath	1.00
MedStar	1.01
Luric HD	1.03
ARIC EA	1.02
ARIC AA	1.00
PROMIS	1.07
PROCARDIS/WTCCC	1.09
GerMIFS1	1.29
GerMIFS2	0.96
GerMIFS3	0.77

MIGen: Myocardial Infarction Genetics Consortium; WTCCC CAD: Wellcome Trust Case Control Consortium Coronary Artery Disease; CCGB: Cleveland Clinic Genebank; DUKE: Duke CATHGEN study; OHS: Ottawa Heart Study; PennCath: PennCath study; MedStar: MedStar study; Luric HD: Luric study; ARIC: Atherosclerosis Risk in Communities; PROMIS: Pakistan Risk of Myocardial Infarction; PROCARDIS: Precocious coronary artery disease study; GerMIFS: German Myocardial Infarction Family Study.

Supplementary Table 23. Genomic inflation factor by study for follow-up genotyping

Study	Genomic inflation factor
ATVB	0.98
OHS	0.99
AMC-PAS	0.97
PennCath	0.97
PROCARDIS	1.0
VHS	0.97
WHI	0.98

ATVB: Atherosclerosis, Thrombosis and Vascular Biology Italian Study Group; OHS: Ottawa Heart Study; AMC-PAS: Academic Medical Center Amsterdam Premature Atherosclerosis Study; PennCath: PennCath study; MedStar: MedStar study; Luric HD: Luric study; PROCARDIS: Precocious coronary artery disease study; VHS: Verona Heart Study; WHI: Women's Health Initiative.

Supplementary Table 24. Follow-up sequencing of six genes in the Italian Atherosclerosis, Thrombosis, and Vascular Biology study

Study	Reason selected for follow-up	Class of variants analyzed	T1 cases[1]	T1 controls	T1 freq cases (%)[2]	T1 freq controls (%)	*P*
APOA5	statistical/ biologic	nonsyn	24	11	1.4	0.72	0.031
CHRM5	statistical	nonsyn	32	22	1.9	1.4	0.18
SMG7	statistical	nonsyn	72	59	4.2	3.9	0.33
LYRM1	statistical	nonsyn	4	2	0.23	0.13	0.27
APOC3	biologic	nonsyn	8	12	0.47	0.79	0.87
NBEAL1	statistical	nonsyn	98	101	5.7	6.6	0.86

[1]Number of alleles in cases with non-synonymous single nucleotide variant that has frequency < 1%; [2]Frequency of cases with non-synonymous single nucleotide variants with frequency < 1%; nonsyn: non-synonymous; freq: frequency.

Supplementary Table 25. Follow-up sequencing of six genes in the Ottawa Heart Study

Study	T1 cases[1]	T1 controls	T1 frequency cases (%)[2]	T1 frequency controls (%)	*P*
APOA5	5	1	0.91	0.17	0.053
CHRM5	14	5	2.54	0.85	0.023
NBEAL1	25	23	4.53	3.92	0.74
LYRM1	7	8	1.27	1.37	0.54
APOC3	3	5	0.54	0.85	0.40
SMG7	20	15	3.62	2.56	0.57

[1]Number of cases with non-synonymous single nucleotide variant that has frequency < 1%; [2]Frequency of cases with non-synonymous single nucleotide variants with frequency < 1%.

Supplementary Table 26. Association of a burden of rare mutations in the apolipoprotein A-V (*APOA5*) gene with risk for early-onset myocardial infarction/coronary artery disease

Variants analyzed	Study	N cases/controls	T1 cases	T1 controls	% freq cases	% freq controls	OR	*P*
Nonsyn	ESP EOMI	1037/981	25	10	2.4	1.0	2.4	0.002
	VHS	977/350	12	2	1.2	0.57	2.2	0.18
	OHS	552/586	5	1	0.91	0.17	5.3	0.05
	ATVB	1716/1519	24	11	1.4	0.72	1.9	0.03
	CCHS/CIHDS	1054/1776	11	9	1.0	0.51	2.1	0.06
	PROCARDIS	1385/1499	16	9	1.2	0.60	1.9	0.06
	Meta-analysis	**6721/6711**	**93**	**42**	**1.4**	**0.63**	**2.2**	**5 x 10^{-7}**
Deleterious (PolyPhen)	ESP EOMI	1037/981	15	9	1.4	0.92	1.6	0.08
	VHS	977/350	9	2	0.92	0.57	1.6	0.29
	OHS	552/586	1	1	0.18	0.17	1.1	0.49
	ATVB	1716/1519	18	7	1.0	0.46	2.3	0.03
	CCHS/CIHDS	1054/1776	9	7	0.85	0.39	2.2	0.06
	PROCARDIS	1385/1499	11	5	0.79	0.33	2.4	0.05
	Meta-analysis	**6721/6711**	**63**	**31**	**0.94**	**0.46**	**2.0**	**6 x 10^{-5}**
Deleterious (Broad)	ESP EOMI	1037/981	18	9	1.7	0.92	1.9	0.03
	VHS	977/350	9	2	0.92	0.57	1.6	0.29
	OHS	552/586	1	1	0.18	0.17	1.1	0.49
	ATVB	1716/1519	19	7	1.1	0.46	2.4	0.02
	CCHS/CIHDS	1054/1776	10	7	0.95	0.39	2.4	0.08
	PROCARDIS	1385/1499	11	5	0.79	0.33	2.4	0.05
	Meta-analysis	**6721/6711**	**68**	**31**	**1.0**	**0.46**	**2.2**	**2 x 10^{-5}**
Deleterious (Strict)	ESP EOMI	1037/981	1	0	0.10	0	-	0.35
	VHS	977/350	0	0	0	0	-	-
	OHS	552/586	0	0	0	0	-	-
	ATVB	1716/1519	3	2	0.17	0.13	1.3	0.39
	CCHS/CIHDS	1054/1776	3	0	0.28	0	-	0.04
	PROCARDIS	1385/1499	3	1	0.22	0.07	3.3	0.17
	Meta-analysis	**6721/6711**	**10**	**3**	**0.15**	**0.045**	**3.3**	**0.008**
Disruptive	ESP EOMI	1037/981	1	0	0.10	0	-	0.35
	VHS	977/350	0	0	0	0	-	-
	OHS	552/586	0	0	0	0	-	-
	ATVB	1716/1519	2	1	0.12	0.07	1.8	0.34
	CCHS/CIHDS	1054/1776	3	0	0.28	0	-	0.04
	PROCARDIS	1385/1499	3	1	0.22	0.07	3.3	0.17
	Meta-analysis	**6721/6711**	**9**	**2**	**0.13**	**0.03**	**4.5**	**0.007**

Summary allele counts and carrier frequencies are shown for cases and controls in each study. The majority of samples in the 1,973 exomes sequenced for the exome-wide discovery scan overlap with the 2,018 exomes used for the "ESP EOMI" study sample for the *APOA5* meta-analysis. A small number of exomes (N<100) were included in only one of the aforementioned study samples. Only SNVs and indels with minor allele frequency less than 1% were considered in burden analysis. Meta-analysis combines evidence across all studies. Nonsyn: non-

synonymous; “Deleterious (PolyPhen)” as defined by nonsense, splice-site, indel frameshift, and missense annotated as “possibly damaging” or “probably damaging” by PolyPhen-2 HumDiv software; “Deleterious (Broad)” as defined by nonsense, splice-site, indel frameshift, and missense annotated as predicted deleterious by at least one of the five protein prediction algorithms of LRT score, MutationTaster, PolyPhen-2 HumDiv, PolyPhen-2 HumVar and Sorting Intolerant From Tolerant (SIFT); “Deleterious (Strict)” as defined by nonsense, splice-site, indel frameshift, and missense annotated as predicted deleterious by all five protein prediction algorithms; Disruptive defined as nonsense, splice-site or indel frameshift; T1: alleles with variants with minor allele frequency less than 1%; % freq: percentage of cases or controls carrying a T1 allele; OR: odds ratio; ESP EOMI: Exome Sequencing Project Early-onset MI Study; VHS: Verona Heart Study; OHS: Ottawa Heart Study; ATVB: Italian Atherosclerosis, Thrombosis, and Vascular Biology study; CCHS/CIHDS: Copenhagen City Heart Study and Copenhagen Ischemic Heart Disease Study; PROCARDIS: Precocious Coronary Artery Disease study.

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