SUPPLEMENTAL MATERIAL

A Genome Wide Association Study for Coronary Artery Disease Identifies a Novel Susceptibility Locus in the Major Histocompatibility Complex

Index

Supplementary Methods

Cohort descriptions

OHGS_A and OHGS_CCGB_B: Details on study criteria for the Ottawa Heart Genomics Study (OHGS), in collaboration with the Cleveland Clinic GeneBank (CCGB), have been published previously. [1] For the purposes of this study, subjects were divided into two cohorts; those genotyped on the Affymetrix 500K (OHGS_A) and those on the Affymetrix 6.0 (OHGS_CCGB_B). Note that these are different front previously published studies, such as CARDIoGRAM[2], which featured OHGS1 and OHGS2; the re-branding into OHGS_A and OHGS_B was primarily done to ensure uniformity of array type in OHGS_A and OHGS_B, as OHGS1 was a mix of Affymetrix 500K and 6.0 arrays.

Cases and controls were recruited from each of the lipid clinic at the University of Ottawa Heart Institute (UOHI), the catherization laboratory at the UOHI, or at the catherization laboratory of the Cleveland Clinic (CC). All cases in OHGS_A and OHGS_CCGB_B were required to have at least one of: a stenosis in a major epicardial vessel of at least 50%; have had a percuteneous intervention (PCI); have had coronary artery bypass surgery (CABG); or have had a myocardial infarction (MI). Cases with diabetes mellitus were excluded. Age of onset of CAD was required to be ≤ 55y for men and ≤ 65y for women. Controls were either healthy asymptomatic elderly individuals (UOHI) or were recruited through the catherization laboratory at either the UOHI or the CC with no stenosis ≥50% in any major epicardial vessel and were required to be ≥at least 65y for men and ≥70y for women. The study protocol was approved by the Human Research Ethics Board of the University of Ottawa Heart Institute and all participants provided informed consent.

DUKE: Details on the study criteria for the Duke Cathgen study (DUKE) as used in this study have not been published previously. Subjects were recruited from the catherization laboratory at Duke. Cases had at least one epicardial coronary vessel with ≥50% stenosis. Cases were required to be ≤ 55y for men and ≤ 65y for women. Controls were required to be at ≥50 y. Any subject with diabetes mellitus, severe pulmonary hypertension or congenital heart disease was excluded. Controls were required to have no epicardial coronary vessel with ≥30% stenosis. Controls with a history of ICC/PCI, CABG, MI or transplant were excluded. The study protocol was approved by the ethics committee and all participants provided informed consent.

ITH: Details of the INTERHEART cohort have been published previously.[3] Briefly, INTERHEART is a standardized case-control study of acute MI from 262 centers in 52 countries. Women and men were recruited in Asia, Europe, the Middle East, Africa, Australia, North America, and South America. Only self-described Caucasian participants were considered for the present analysis. Briefly, cases of incident acute MI, presenting to a hospital within 24 hours of symptom onset, were age-(± 5 y) and sex-matched with controls who were hospital- or community-based individuals with no previous diagnosis of heart disease or history of

exertional chest pain. A subset of the INTERHEART cohort (<1000) of self-described European ancestry was available for analysis in the present study. The study protocol was approved by the ethics committees in all participating centers and all participants provided informed consent. A full list of ITH investigators is found at http://www.phri.ca/interheart/index2.html.

WTCCC: Details of the Wellcome Trust Case Control Consortium (WTCCC) CAD cohort have been published previously. [4] Briefly, cases had a history of MI, CABG or PCI. Cases were required to be ≤65y. Controls subjects were recruited from the National Blood Services and the 1958 Birth Cohort with no specific age or phenotype exclusions.

Description of Stage 2 Studies

GerMIFS and GerMIFS2: Details of the German Myocardial Infarction Family Study (GerMIFS1 and GerMIFS2) have been published previously. [5, 6] Cases in GerMIFS1 had a history of MI and were required to have at least one first degree relative with premature coronary artery disease. Cases in GerMIFS2 also had a history of MI and most had a family history of disease (59.4%). Cases were required to be ≤60y. Controls for both GerMIFS1 and GerMIFS2 were population controls. The study protocol was approved by the ethics committees in all participating centers and all participants provided informed consent.

PennCath/MedStar: Details of the PennCath and MedStar cohorts have been published previously.[7] Briefly, cases and controls were recruited from the catherization laboratory at the University of Pennsylvania Medical Center (PennCath) and the catherization laboratory at the Washington Hospital Center by the MedStar Health Research Institute (MedStar). Cases were required to have at least one stenosis of ≥50% in at least one major epicardial vessel; controls were required to have no stenoses exceeding 10% in any vessel. Cases were required to be ≤ 55y for men and ≤ 65y for women; controls were required to be aged at least 45 (40 for men in PennCath). The study protocol was approved by the ethics committees in all participating centers and all participants provided informed consent.

OHGS_CCGB_S: The Ottawa Heart Genomics Consortium in collaboration with the Cleveland Clinic GeneBank Supplementary (OHGS_CCGB_S) cohort has not been published previously. OHGS_CCGB_S is a supplementary cohort assembled for the purposes of this study. Cases are derived both the UOHI and CC and were genotyped following the primary meta-analysis. Cases were required to be ≤ 65y for men and ≤ 70y for women. Cases with diabetes mellitus were removed. Controls for OHGS_CCGB_S came from the WTCCC2; specifically, we used more recently recruited controls distinct from those used in the original WTCCC publication. [6]

Supplemental Table 1. Stage 1 Studies SNP Details

Type	Model	Value	OHGS_A	OHGS_ CCGB_B	DUKE	WTCCC	ITH	Meta-analysis
G	add	N	367,036	640,404	499,931	399,471	648,636	N/A
G	add	**λ**	1.112	1.126	1.024	1.070	1.018	N/A
G	dom	N	359,551	631,530	476,439	388,193	620,261	N/A
G	dom	**λ**	1.060	1.095	0.961	1.029	0.958	N/A
G	rec	N	358,525	631,163	480,726	387,575	618,582	N/A
G	rec	**λ**	1.051	1.094	0.970	1.032	0.956	N/A
I	add	N	4,389,233	5,501,436	4,102,281	4,582,413	5,441,076	4,916,498
I	add	**λ**	1.094	1.107	1.014	1.059	1.007	1.032
I	dom	N	4,340,557	5,463,566	4,034,131	4,543,802	5,354,571	4,889,746
I	dom	**λ**	1.073	1.088	1.001	1.032	0.991	1.036
I	rec	N	3,930,417	5,163,210	3,543,352	4,268,249	4,606,865	4,637,828
I	rec	**λ**	0.927	0.977	0.850	0.933	0.832	0.918

G = Genotyped, I = Imputed, add=Additive, dom=Dominant, rec=Recessive

Note that the number of dominant or recessive SNPs may be lower than additive due to instances where the relevant homozygote is not present. Also note the difference between recessive and dominant lambdas post-imputation; this is largely driven by fact that the major allele distribution is highly non-symmetric in the haplotypc imputation panel as opposed to the original genotyped data.

Supplemental Table 2. Loci Which Met Discovery Threshold

rsid	Rank	Gene or band	Ref[1]	p add	p dom	p rec	best	MOI	MOI p-value
rs1333049	1	9p21.3	[4, 6, 8, 9]	2.91E-32	2.07E-24	2.93E-21	2.91E-32	add	2.91E-32
rs11556924	2	ZC3HC1	[10]	2.81E-08	4.33E-06	2.07E-06	2.81E-08	add	2.81E-08
rs629301	3	SORT1	[6]	1.19E-07	0.000915	4.82E-07	1.19E-07	add	1.19E-07
rs12006148	4	4p15.3		1.97E-05	1.81E-07	0.236911	1.81E-07	dom	1.81E-07
rs3740107	5	ALOX5		7.92E-06	0.506477	1.85E-07	1.85E-07	rec	1.85E-07
rs2133189	6	MIA3	[11]	2.73E-07	1.96E-05	1.36E-05	2.73E-07	add	2.73E-07
rs9295125	7	LPA	[12, 13]	4.64E-07	3.19E-07	0.002957	3.19E-07	dom	3.19E-07
rs3869109	8	HCG27/HLA-C		3.30E-07	1.23E-05	3.45E-05	3.30E-07	add	3.3E-07
rs7278845	9	MRPS6/KCNE2	[11]	3.76E-07	3.61E-07	0.036935	3.61E-07	dom	3.61E-07
rs73196173	10	DIAPH3		4.22E-07	4.79E-07	0.111914	4.22E-07	dom	4.79E-07
rs2301241	11	TXN		1.30E-05	5.19E-07	0.016414	5.19E-07	dom	5.19E-07
rs6982502	12	TRIB1	[14]	5.35E-07	5.14E-05	1.77E-05	5.35E-07	add	5.35E-07
rs73013202	13	LDLR	[11]	8.73E-07	7.15E-07	0.014376	7.15E-07	dom	7.15E-07
rs12503914	14	GALNT7		2.49E-05	8.86E-07	0.268191	8.86E-07	dom	8.86E-07
rs2247374	15	FAM129B		0.496035	1.10E-06	0.289277	1.10E-06	dom	1.1E-06
rs12651275	16	4q31.3		0.112958	0.974024	1.14E-06	1.14E-06	rec	1.14E-06
rs2229238	17	ILR6		0.003164	1.25E-06	0.123347	1.25E-06	dom	1.25E-06
rs952227	18	2q26 / rs952227[2]		1.05E-06	0.003116	1.57E-06	1.05E-06	rec	1.57E-06
rs35008336	19	PKDIL2		4.08E-06	1.80E-06	0.027632	1.80E-06	dom	1.8E-06
rs4675310	20	WDR12	[11]	4.60E-06	0.142034	1.85E-06	1.85E-06	rec	1.85E-06
8-9862032	21	8p23.1		7.73E-06	2.40E-06	0.871994	2.40E-06	dom	2.4E-06
rs9625066	22	MIAT		0.000208	0.023167	2.56E-06	2.56E-06	rec	2.56E-06
rs1919484	23	LPL	[14]	2.68E-06	0.000175	1.31E-05	2.68E-06	add	2.68E-06
rs1537340	24	PHACTR1	[11]	4.73E-05	2.77E-06	0.288574	2.77E-06	dom	2.77E-06
rs10779058	25	12q21.3		9.39E-05	3.22E-06	0.084287	3.22E-06	dom	3.22E-06
rs501120	26	CXCL12	[6, 11]	9.58E-07	3.70E-06	0.004097	9.58E-07	dom	3.7E-06
4-130146736	27	SCLT1		0.00796	0.280579	3.73E-06	3.73E-06	rec	3.73E-06
rs6905288	28	VEGFA		0.000314	3.98E-06	0.091886	3.98E-06	dom	3.98E-06
rs17114046	29	PPAP2B	[10]	8.73E-06	4.04E-06	0.250999	4.04E-06	dom	4.04E-06
rs12200560	30	FHL5		4.09E-06	0.000173	9.14E-05	4.09E-06	add	4.09E-06
rs9894220	31	UBE2Z	[10]	2.77E-05	4.10E-06	0.034446	4.10E-06	dom	4.1E-06
rs6001811	32	TNRC6B		5.59E-05	4.15E-06	0.10883	4.15E-06	dom	4.15E-06
9-135134129	33	ABO	[7, 10]	1.91E-05	4.20E-06	0.097983	4.20E-06	dom	4.2E-06
rs6958243	34	CASD1		0.000382	0.243518	4.39E-06	4.39E-06	rec	4.39E-06
rs73241008	35	13q31.1		0.167896	0.845427	4.42E-06	4.42E-06	rec	4.42E-06
rs10182781	36	2p25.1		0.000226	0.825524	4.66E-06	4.66E-06	rec	4.66E-06
rs17458018	37	FN		1.17E-05	4.92E-06	0.514205	4.92E-06	dom	4.92E-06

MOI = Method of Inheritance, add=Additive, dom=Dominant, rec=Recessive, ref=Reference

[1] Reference refers to the original publication (values correspond to main text reference list)

2 rs952227 was suggested to be associated with CAD based on the original WTCCC publication, but this association has not been convincingly replicated, and in this analysis the association was largely driven by the WTCCC cohort.

Supplemental Table 3. Replication and Global Meta-Analysis of Putative Loci

						Discovery				Replication				Global			
rsID	Locus	MOI	AL	AF[1]	CAF[2]	OR	p	N	I^2	OR	P	N	I^2	OR	P	N	I^2
rs12006148	4p15.3	dom	G	35.8	58.1	1.24	1.81E-07	4	0.0	1.01	8.80E-01	5	0.0	1.13	8.56E-05	9	50.2
rs3740107	ALOX5	rec	G	72.1	50.0	1.23	1.85E-07	4	17.8	0.94	1.90E-01	3	0.0	1.11	1.09E-03	7	73.4
rs3869109	HCG27/HLA-C	add	G	54.5	54.5	1.16	3.3E-07	4	0.0	1.11	5.28E-04	5	0.0	1.14	1.12E-09	9	0.0
rs2301241	TXN	dom	A	59.4	84.5	0.67	5.19E-07	2	0.0	1.04	6.36E-01	2	0.0	0.83	9.59E-04	4	80.9
rs73196173	DIAPH3	dom	C	6.2	11.9	0.74	5.94E-07	5	11.8	1.08	2.87E-01	5	21.1	0.87	2.05E-03	10	65.6
rs12503914	GALNT7	dom	T	32.1	55.7	0.82	8.86E-07	4	0.0	0.98	7.13E-01	3	0.0	0.88	5.16E-05	7	47.0
rs2247374	FAM129B	dom	T	82.4	97.6	0.57	1.1E-06	4	0.0	1.12	3.79E-01	5	0.0	0.76	1.86E-03	9	58.3
rs12651275	4q31.3	rec	T	15.4	4.2	0.39	1.14E-06	2	0.0	0.89	5.26E-01	4	49.2	0.60	1.23E-04	6	67.6
rs2229238	ILR6	dom	C	82.1	97.0	0.61	1.25E-06	5	12.0	0.79	4.34E-02	4	65.0	0.69	6.91E-07	9	50.2
rs35008336	PKDIL2	dom	T	29.7	50.6	0.81	1.8E-06	3	0.0	1.00	9.91E-01	5	43.1	0.90	8.14E-04	8	65.1
8-9862032	8p23.1	dom	C	1.3	2.6	1.63	2.4E-06	5	0.0	0.94	7.11E-01	3	42.3	1.40	1.42E-04	8	43.6
rs9625066	MIAT	rec	A	30.0	10.1	0.57	2.56E-06	2	0.0	1.02	8.53E-01	3	0.0	0.77	1.82E-03	5	72.3
rs10779058	12q21.3	dom	A	46.4	69.6	1.21	3.22E-06	5	39.4	1.04	5.20E-01	3	0.0	1.15	3.57E-05	8	42.2
4-130146736	SCLT1	rec	G	22.5	3.7	1.98	3.73E-06	2	0.0	0.79	8.17E-02	2	71.7	1.20	6.33E-02	4	87.8
rs6905288	VEGFA	dom	T	55.9	79.4	1.28	3.98E-06	3	0.0	1.18	2.97E-03	5	77.2	1.23	6.97E-08	8	62.7
rs12200560	FHL5	add	A	50.8	50.8	0.88	4.1E-06	5	0.0	0.92	2.94E-02	3	0.0	0.90	5.99E-07	8	0.0
rs6001811	TNRC6B	dom	G	34.5	55.6	1.34	4.15E-06	2	0.0	1.08	1.52E-01	3	0.0	1.18	5.23E-05	5	46.3
rs6958243	CASD1	rec	C	56.2	32.4	0.80	4.39E-06	3	26.9	1.02	6.96E-01	3	0.0	0.89	1.41E-03	6	65.2
rs73241008	13q31.1	rec	C	19.2	2.6	1.60	4.42E-06	5	0.0	1.11	3.15E-01	5	0.0	1.34	7.39E-05	10	20.0
rs10182781	2p25.1	rec	C	69.9	46.7	1.33	4.66E-06	2	0.0	0.92	1.03E-01	3	80.6	1.07	1.02E-01	5	87.2
rs17458018	FN	dom	C	6.5	12.7	0.77	4.92E-06	5	0.0	0.90	1.16E-01	5	0.0	0.82	6.90E-06	10	0.0

MOI = Method of Inheritance, AL = Allele, AF = Allele Frequency, CAF = Current Allele Frequency

[1] Allele Frequency refers to the traditional (minor) allele frequency

[2] Current allele Frequency refers to the frequency of the risk variant. For an additive SNP, this is the traditional minor allele frequency. For a dominant SNP, having two copies of the allele represents the risk variant, so CAF is the frequency of people who are heterozygote and homozygote AL/AL. For a recessive SNP, CAF is the frequency of being homozygote for AL/AL.

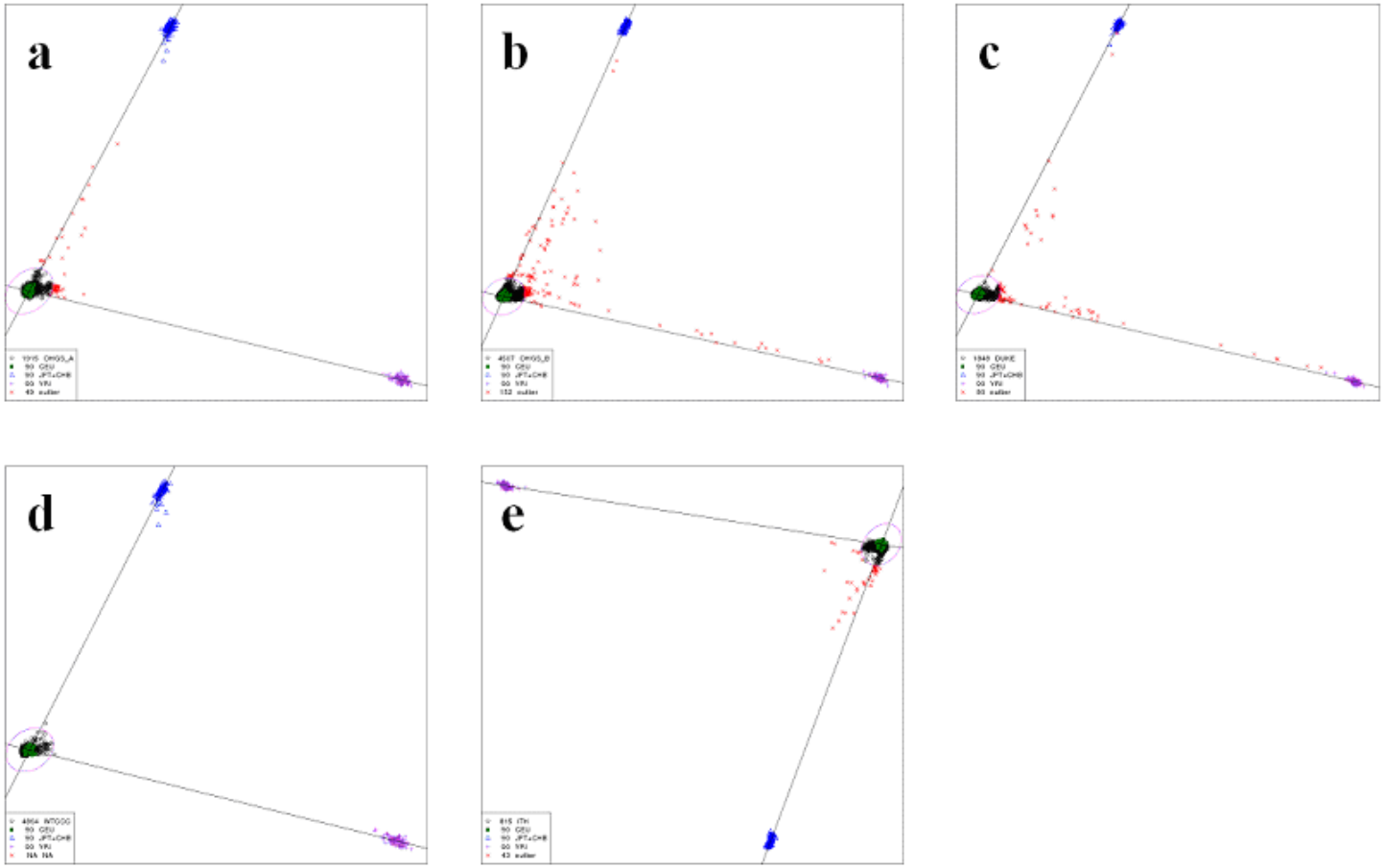
Supplemental Table 4. HLA Imputation Accuracy Measures

HLA allele	Proportion below threshold[1]	Allele freq[2]	Median posterior probability
HLA-A*0101	0.019953	0.171444	0.992701
HLA-A*0201	0.018948	0.274935	0.989347
HLA-A*0301	0.004907	0.143075	0.993223
HLA-A*1101	0.006861	0.064501	1
HLA-A*2402	0.039837	0.07876	0.98082
HLA-A*2902	0.011324	0.042146	1
HLA-A*3101	0.016645	0.028518	1
HLA-A*3201	0.040309	0.041552	0.999988
HLA-A*6801	0.064228	0.038953	0.996485
HLA-B*0702	0.01136	0.132797	0.993318
HLA-B*0801	0.01194	0.123195	0.99991
HLA-B*1302	0.01129	0.022815	0.998027
HLA-B*1402	0.018692	0.027356	0.999304
HLA-B*1501	0.021612	0.062342	0.999544
HLA-B*1801	0.024535	0.042914	0.999996
HLA-B*2705	0.01141	0.045147	0.99765
HLA-B*3501	0.052774	0.052107	0.989926
HLA-B*4001	0.00848	0.056573	0.999988
HLA-B*4402	0.015466	0.10425	0.996899
HLA-B*5101	0.031898	0.045184	0.999937
HLA-B*5701	0.036087	0.037777	0.997935
HLA-C*0102	0.035614	0.037763	0.999974
HLA-C*0202	0.017974	0.044112	0.999934
HLA-C*0303	0.038579	0.057617	0.986484
HLA-C*0304	0.029218	0.075599	0.985524
HLA-C*0401	0.005484	0.09982	0.99811
HLA-C*0501	0.010443	0.100848	0.985129
HLA-C*0602	0.015093	0.093398	0.999982
HLA-C*0701	0.027226	0.159969	0.973167
HLA-C*0702	0.006208	0.140996	0.987051
HLA-C*0802	0.067708	0.039414	0.990639
HLA-C*1203	0.023296	0.041543	0.999498
HLA-C*1601	0.011255	0.04191	0.996597

[1] For a specific allele, gives proportion of observed probabilities below threshold of 0.7

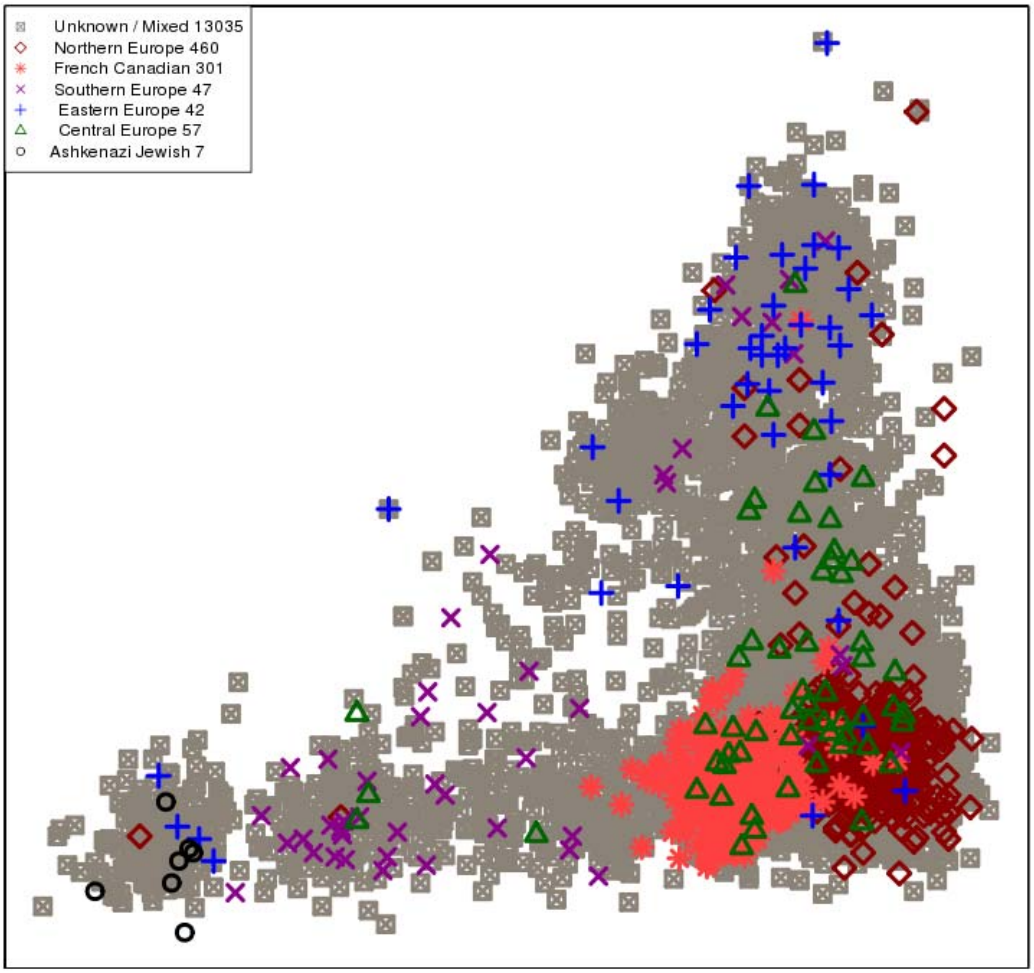
[2] Estimated allele frequency. Does not sum to 1 as low frequency alleles not considered here

Supplemental Figure 1. First two principal components from discovery cohorts



Included HapMap phase 2 samples are shown in green (CEU), blue (JPT+CHB) and purple (YRI). Note that the two subjects which would have been removed from this analysis for the WTCCC were retained to facilitate comparisons with the original publication.

Supplemental Figure 2. First two principal components from merged discovery cohorts



Plot of the first two main principal components in the combined discovery dataset (n=13,949). Superimposed are ethnicities available from a subset of the cohort. Only SNPs common to the Affymetrix 500k, 6.0 and Axiom were considered, which, following QC, 55,032 SNPs (no LD filter was applied). Note that no SNPs from the MHC were included in this analysis (chromosome 6 26-34MBp, build 36).

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