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Supplement to: Charchar FJ, Bloomer LDS, Barnes TA, et al. Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome. *Lancet* 2012; published online Feb 9. DOI:10.1016/S0140-6736(11)61453-0.

Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome

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Supplementary material

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Acknowledgments

This study was funded by the British Heart Foundation Project grant (PG/06/097/21331) to MT. NJS holds a personal Chair supported by the British Heart Foundation and is a UK NIHR Senior Investigator. FJC is supported by research grants from the L.E.W. Carty and National Health and Medical Research Council of Australia. The Cardiogenics project was supported by the European Union 6th Framework Programme (LSHM-CT-2006-037593). AFD held a personal Chair supported by the British Heart Foundation between 1006 and 2010. MAJ is a Wellcome Trust Senior Fellow in Biomedical Science (087576). Collection of the healthy subjects for this study was supported by the Cambridge NIHR Biomedical Research Centre and by an NIHR Programme Grant to WHO (RP-PG-0310-1002) and a project grant from the Wellcome Trust to WHO (WT-0841383/2/07/2). Work described in this paper is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease. Funders played no role by in the design, analysis or interpretation of this study and MT had full access to data and final responsibility to submit.

Supplementary Table 1. Single nucleotide polymorphisms that define major Y chromosome haplogroups in Europe.

Polymorphism symbol	db SNP "rs" number	Alleles	Haplogroup
M201	rs2032636	G->T	G
M304	rs13447352	A->C	J
M269	rs9786153	C->T	R1b1b2
M207	rs2032658	A->G	R
M45	rs2032631	G->A	P
SRY_{10831}	rs2534636	A->G; G->A	B-R; R1a
M173	rs2032624	A->C	R1
M35	N/A	G->C	E1b1b1
M89	rs2032652	C->T	F-R
M9	rs3900	C->G	K-R
M170	rs2032597	A->C	I

SRY_{10831} is a recurrent mutation.

Supplementary Table 2. Association between haplogroup I and coronary artery disease in the West of Scotland Coronary Prevention Study (WOSCOPS) – logistic regression analysis.

Independent variable	Odds ratio	95% CI	P-value
Haplogroup I	1.60	1.16-2.19	0.004
Age (years)	1.00	0.98-1.03	0.750
Body mass index (kg/m^2)	1.01	0.97-1.05	0.532
Systolic blood pressure (mmHg)	1.01	1.00-1.02	0.030
Diastolic blood pressure (mmHg)	1.01	0.99-1.03	0.198
HDL-cholesterol (mmol/L)	0.22	0.12-0.40	<0.0001
LDL-cholesterol (mmol/L)	1.39	1.08-1.80	0.012
Triglycerides (mmol/L)	0.86	0.62-1.21	0.393
Pravastatin-based treatment	0.61	0.48-0.77	<0.0001
Glucose (mmol/L)	1.08	0.90-1.30	0.405
Diabetes	0.98	0.34-2.81	0.975
CRP (mg/L)	1.17	1.03-1.32	0.013
Smoking	0.90	0.70-1.16	0.428
Alcohol consumption ≥ 20 units/week	1.11	0.80-1.55	0.522
Carstairs deprivation index	0.98	0.95-1.02	0.330
Highest educational attainment	1.04	0.91-1.20	0.547
Employment status - employed	1.00	0.76-1.31	0.986

CI - confidence intervals; the odds ratios refer to the change of coronary artery disease risk in relation to a reference category (binary phenotypes) or per unit change in quantitative traits

Supplementary Table 3. Dimensions from multidimensional scaling (MDS) analysis in the British Heart Foundation Family Heart Study (BHF-FHS) and Cardiogenics Study - men with haplogroup I versus carriers of the other haplogroups.

Dimension	BHF-FHS	Cardiogenics
C1	0.874	0.181
C2	0.6613	0.8831
C3	0.4828	0.5397
C4	0.2332	0.0624

C1-C4 – the first four dimensions extracted from the matrix of genome-wide identity-by-state pair-wise distances in the MDS analysis; data are P-values from statistical comparisons of each of the four dimensions between carriers of haplogroup I and men with other haplogroups

Supplementary Table 4. Genotype distribution of autosomal SNPs associated with coronary artery disease in previous genome-wide association studies – stratification on Y chromosome haplogroup status in British Heart Foundation Family Heart Study.

No	Locus	Genes	SNP	A	Haplo I – genotype 0	Haplo I – genotype 1	Haplo I – genotype 2	Others – genotype 0	Others – genotype 1	Others – genotype 2	P-value
1	1p13.3	CELSR2-PSRC1-SORT1	rs646776	G	150 (63.6)	78 (33.0)	8 (3.4)	726 (63.2)	373 (33.5)	50 (4.4)	0.7955
2	1p32.2	PPAP2B	rs17114036	G	192 (85.7)	29 (13.0)	3 (1.3)	944 (83.2)	178 (15.7)	12 (1.1)	0.5493
3	1p32.3	PCSK9	rs11206510	C	168 (68.6)	68 (27.8)	9 (3.7)	805 (67.2)	352 (29.4)	41 (3.4)	0.8698
4	1q41	MIA3	rs17465637	T	143 (58.1)	86 (35)	17 (6.9)	621 (51.9)	466 (38.9)	110 (9.2)	0.1694
5	2p21	ABCG8	rs4299376	G	122 (49.6)	107 (43.5)	17 (6.9)	507 (42.3)	539 (45)	152 (12.7)	0.0150
6	2q33.1	WDR12	rs6725887	C	165 (67.1)	76 (30.9)	5 (2.0)	873 (72.9)	288 (24.1)	36 (3.0)	0.0660
7	3q22.3	MRAS	rs2306374	C	174 (70.7)	62 (25.2)	10 (4.1)	840 (70.1)	328 (27.4)	30 (2.5)	0.3390
8	5q31.1	IL5	rs2706399	A	65 (27.0)	127 (52.7)	49 (20.3)	330 (28.1)	571 (48.5)	275 (23.4)	0.4500
9	6p21.31	ANKS1A	rs17609940	C	150 (61)	85 (34.6)	11 (4.5)	756 (63.1)	391 (32.6)	51 (4.3)	0.8202
10	6p24.1	PHACTR1	rs12526453	G	108 (43.9)	111 (45.1)	27 (11.0)	564 (47.1)	526 (44.0)	106 (8.9)	0.4697
11	6q23.2	TCF21	rs12190287	G	80 (39.6)	93 (46.0)	29 (14.4)	411 (41.7)	445 (45.2)	129 (13.1)	0.8147
12	6q25.1	MTHFD1L	rs6922269	A	132 (53.7)	93 (37.8)	21 (8.5)	645 (53.8)	456 (38.1)	97 (8.1)	0.9738
13	6q25.3	LPA	rs3798220	C	226 (95.8)	10 (4.2)	0 (0)	1075 (93.5)	74 (6.4)	1 (0.1)	0.3917
14	7q22-q31	BCAP29	rs10953541	T	131 (53.3)	95 (38.6)	20 (8.1)	659 (55.1)	454 (38.0)	83 (6.9)	0.7576
15	7q32.2	ZC3HC1	rs11556924	T	99 (41.3)	104 (43.3)	37 (15.4)	445 (38.3)	521 (44.9)	195 (16.8)	0.6800
16	8q24.13	TRIB1	rs17321515	G	69 (28.0)	118 (48.0)	59 (24.0)	355 (29.7)	575 (48.0)	267 (22.3)	0.8048
17	9p21.3	CDKN2A/B, ANRIL	rs4977574	A	83 (33.9)	107 (43.7)	55 (22.4)	302 (25.3)	613 (51.3)	280 (23.4)	0.0176
18	9q34.2	ABO	rs579459	C	125 (60.7)	71 (34.5)	10 (4.8)	653 (63.0)	351 (33.9)	32 (3.1)	0.4162
19	10p11.23	KIAA1462	rs2505083	C	65 (31.9)	101 (49.5)	38 (18.6)	340 (34.8)	459 (47.0)	178 (18.2)	0.7161
20	10q11.21	CXCL12	rs1746048	T	186 (75.6)	58 (23.6)	2 (0.8)	899 (75.1)	278 (23.2)	20 (1.7)	0.6060
21	10q23.31	LIPA	rs2246942	G	116 (48.7)	101 (42.5)	21 (8.8)	493 (42.9)	530 (46.1)	126 (11.0)	0.2263
22	10q24.32	CYP17A1, CNNM2, NT5C2	rs12413409	A	211 (86.8)	32 (13.2)	0 (0.0)	1058 (88.8)	133 (11.1)	1 (0.1)	0.6070
23	11q22.3	PDGFD	rs974819	T	128 (52.7)	100 (41.1)	15 (6.2)	594 (50.1)	481 (40.6)	110 (9.3)	0.2861
24	11q23.3	ZNF259, APOA5-A4-C3-A1	rs964184	G	186 (77.5)	50 (20.8)	4 (1.7)	855 (72.3)	303 (25.6)	25 (2.1)	0.2494
25	13q34	COL4A1, COL4A2	rs4773144	G	79 (32.5)	116 (47.7)	48 (19.8)	388 (32.6)	560 (47.1)	241 (20.3)	0.9778
26	15q25.1	ADAMTS7	rs3825807	G	77 (32.6)	125 (53.0)	34 (14.4)	390 (34.4)	555 (49.0)	188 (16.6)	0.5007
27	17p13.3	SMG6, SRR	rs216172	C	91 (37.8)	111 (46.1)	39 (16.2)	487 (41.4)	533 (45.3)	13.3 (196)	0.3988
28	17q21.32	UBE2Z, GIP, ATP5G1	rs46522	C	75 (30.5)	122 (49.6)	49 (19.9)	344 (28.8)	589 (49.3)	261 (21.9)	0.7570
29	19p13.2	LDLR (SMARCA4)	rs1122608	T	141 (57.3)	93 (37.8)	12 (4.9)	680 (56.8)	442 (36.9)	75 (6.3)	0.7034
30	19p13.2	LDLR	rs2228671	T	191 (79.3)	48 (19.9)	2 (0.8)	929 (78.3)	244 (20.6)	13 (1.1)	0.9053
31	21q22.11	MRPS6	rs9982601	T	164 (73.5)	57 (25.6)	2 (0.9)	774 (70.5)	300 (27.3)	24 (2.2)	0.3641

A – coded allele; Haplo I – carriers of haplogroup I, Others – carriers of the other Y chromosome haplogroups; genotype 0 – no coded alleles (homozygous for non-coded allele), genotype 1 – one coded allele (heterozygote), genotype 2 – two coded alleles (homozygous for coded allele); P-value – nominal statistical significance from the χ^2 test; 3 SNPs (rs3184504, rs2895811, rs12936587) were excluded from further analyses because of low (<80%) informative genotypes

Supplementary Table 5. Association between haplogroup I and coronary artery disease after accounting for autosomal SNPs associated with coronary artery disease in previous genome-wide association studies – multiple regression analysis in men from British Heart Foundation Family Heart Study.

No	Locus	Genes	SNP	A	% informative genotypes	Odds ratios	95% CI	P-value
1	1p13.3	CELSR2-PSRC1-SORT1	rs646776	G	0.9591	1.69	1.15-2.47	0.0075
2	1p32.2	PPAP2B	rs17114036	G	0.9404	1.70	1.15-2.52	0.0081
3	1p32.3	PCSK9	rs11206510	C	0.9993	1.76	1.21-2.57	0.0033
4	1q41	MIA3	rs17465637	T	0.9993	1.74	1.19-2.53	0.0040
5	2p21	ABCG8	rs4299376	G	1	1.74	1.19-2.53	0.0040
6	2q33.1	WDR12	rs6725887	C	0.9993	1.73	1.19-2.52	0.0042
7	3q22.3	MRAS	rs2306374	C	1	1.75	1.20-2.55	0.0035
8	5q31.1	IL5	rs2706399	A	0.9813	1.69	1.16-2.47	0.0066
9	6p21.31	ANKS1A	rs17609940	C	1	1.76	1.21-2.56	0.0033
10	6p24.1	PHACTR1	rs12526453	G	0.9986	1.75	1.20-2.55	0.0035
11	6q23.2	TCF21	rs12190287	G	0.822	1.70	1.13-2.56	0.0110
12	6q25.1	MTHFD1L	rs6922269	A	1	1.76	1.20-2.56	0.0034
13	6q25.3	LPA	rs3798220	C	0.9598	1.70	1.16-2.49	0.0063
14	7q22-q31	BCAP29	rs10953541	T	0.9986	1.78	1.22-2.60	0.0027
15	7q32.2	ZC3HC1	rs11556924	T	0.9702	1.68	1.15-2.46	0.0079
16	8q24.13	TRIB1	rs17321515	G	0.9993	1.77	1.22-2.58	0.0029
17	9p21.3	CDKN2A/B, ANRIL	rs4977574	A	0.9972	1.69	1.16-2.47	0.0068
18	9q34.2	ABO	rs579459	C	0.8601	1.54	1.02-2.32	0.0387
19	10p11.23	KIAA1462	rs2505083	C	0.8179	1.79	1.19-2.71	0.0054
20	10q11.21	CXCL12	rs1746048	T	0.9993	1.76	1.21-2.57	0.0034
21	10q23.31	LIPA	rs2246942	G	0.9605	1.74	1.19-2.55	0.0044
22	10q24.32	CYP17A1, CNNM2, NT5C2	rs12413409	A	0.9938	1.77	1.21-2.59	0.0032
23	11q22.3	PDGFD	rs974819	T	0.9889	1.75	1.20-2.55	0.0039
24	11q23.3	ZNF259, APOA5-A4-C3-A1	rs964184	G	0.9855	1.76	1.21-2.58	0.0034
25	13q34	COL4A1, COL4A2	rs4773144	G	0.9917	1.71	1.17-2.49	0.0054
26	15q25.1	ADAMTS7	rs3825807	G	0.9481	1.73	1.18-2.54	0.0047
27	17p13.3	SMG6, SRR	rs216172	C	0.982	1.79	1.22-2.62	0.0029
28	17q21.32	UBE2Z, GIP, ATP5G1	rs46522	C	0.9972	1.75	1.20-2.55	0.0036
29	19p13.2	LDLR (SMARCA4)	rs1122608	T	0.9993	1.73	1.19-2.53	0.0045
30	19p13.2	LDLR	rs2228671	T	0.9882	1.72	1.18-2.51	0.0050
31	21q22.11	MRPS6	rs9982601	T	0.9148	1.57	1.07-2.32	0.0224

A – coded allele; CI – confidence intervals; P-values, odds ratios and respective 95% confidence intervals refer to associations between haplogroup I and coronary artery disease in multiple regression models accounting for age and genotypes of autosomal SNP

Supplementary Table 6. Characteristics of men from Cardiogenics Study used in transcriptomic analysis - stratification based on case-control status.

Phenotype	Cases	Controls	P-value
n	121	134	
Age (years)	54.8 (7.1)	53.9 (7.1)	0.305
Body mass index (kg/m^2)	29.2 (4.8)	25.8 (3.2_	<0.0001

Data are means and standard deviations

Supplementary Table 7. Characteristics of men from Cardiogenics Study used in transcriptomic analysis - stratification based on the Y chromosome haplogroup status.

Phenotype	Haplogroup I	Other haplogroups	P-value
n	54	201	
Age (years)	54.2 (7.5)	54.3 (7.1)	0.890
Body mass index (kg/m^2)	27.4 (3.9)	27.5 (4.5)	0.910

Data are means and standard deviations

Supplementary Table 8. Pathways that are significantly up- or down-regulated in macrophages from men with haplogroup I compared to other haplogroups – Gene Set Enrichment Analysis (GSEA) in the Cardiogenics Study.

KEGG Pathway	FDR	Genes in KEGG pathway (n)	Up/ Down regulated	Leading edge subset of genes	Lead cells	Comments
Allograft rejection	0.0001	25	↓	HLA-F, HLA-DPB1, HLA-DMB, HLA-A, HLA-DRA, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	T cell, Antigen presenting cells	The consequence of the recipient's allo-immune response to non-self antigens expressed by donor tissues.
Antigen processing and presentation	0.0001	52	↓	CTSS, HSPA5, HLA-G, LGMN, HSP90AB1, IFI30, HLA-F, HLA-DPB1, HLA-DMB, HLA-A, HLA-DRA, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	Antigen presenting cells, T cell, NK cell	Capturing, processing and presentation of antigens to enable their recognition by T cells is a basis of adaptive immunity.
Asthma	0.0001	19	↓	HLA-DPB1, HLA-DMB, HLA-DRA, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	Antigen presenting cells, mast cell, T cell, B cell, eosinophil	Chronic inflammation of airways initiated by T cells and propagated by B cells, mast cells and eosinophils.
Autoimmune thyroid disease	0.0001	26	↓	HLA-F, HLA-DPB1, HLA-DMB, HLA-A, HLA-DRA, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	Antigen presenting cells, T cell, B cell	Activation of immune effector mechanisms against self antigens leads to the damage of thyroid epithelial cells.
Graft versus host disease	0.0001	26	↓	HLA-F, HLA-DPB1, HLA-DMB, HLA-A, HLA-DRA, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	Antigen presenting cells, T cell	Complication of allogenic transplantation driven by immunocompetent donor T cells that attack the genetically disparate host cells.
Systemic lupus erythematosus	0.0001	63	↓	HLA-DPB1, TRIM21, HLA-DMB, C1QB, HLA-DRA, H2AFY2, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	Antigen presenting cells, macrophage, B cell, neutrophil	Autoimmune disease associated with production of autoantibodies against self-antigens (DNA, nuclear proteins and cytoplasmic components) leading to inflammation, vasculitis, immune complex deposition and activation of complement system as well as macrophage- and neutrophil-mediated tissue injury.
Type 1 diabetes mellitus	0.0001	28	↓	HLA-F, HLA-DPB1, HLA-DMB, HLA-A, HLA-DRA, HLA-DPA1, HLA-DRB3, HLA-	Antigen presenting cells, macrophage, T cell	Autoimmune destruction of the insulin-producing β-cell of the pancreatic islets by macrophages and cytotoxic T cells as well

				DQA1, HLA-DRB1, HLA-DRB5		as non-specific inflammatory mediators.
Viral myocarditis	0.0001	46	↓	HLA-F, HLA-DPB1, HLA-DMB, HLA-A, HLA-DRA, ITGAL, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	T cell, B cell, Antigen presenting cells	Cardiac disease (in which Coxsackievirus B3 is the dominant etiological factor) associated with inflammation and injury of myocardium.
Intestinal immune network for IGA production	0.001	28	↓	HLA-DPB1, HLA-DMB, HLA-DRA, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	B cell	Secreted IgA promotes immune exclusion by entrapping dietary antigens and microorganisms in the mucus and neutralization of toxins.
Leishmaniasis	0.01	57	↓	PTPN6, IFNGR1, JUN, MYD88, HLA-DPB1, HLA-DMB, HLA-DRA, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	Macrophage, T cell	A disease with visceral and cutaneous manifestations caused by an intracellular protozoan parasite of macrophages. Silenced T cell activation leads to abnormal immune response. This pathway contains 13 genes showing prior evidence for association with coronary artery disease.[4]
Cell adhesion molecules	0.011	69	↓	CD6, NCAM1, MPZL1, HLA-F, HLA-DPB1, ICAM2, CD99, HLA-DMB, HLA-A, HLA-DRA, ITGAL, HLA-DPA1, HLA-DRB3, HLA-DQA1, HLA-DRB1, HLA-DRB5	Antigen presenting cells, T cell, B cell, endothelial cell, platelet, monocyte, neurons	Integrin family, the immunoglobulin superfamily, selectins, and cadherins are glycoproteins expressed on the cell surface and playing a critical role in hemostasis, the immune response, inflammation, embryogenesis, and development of neuronal tissue.
Glutathione metabolism	0.048	36	↓	MGST1, GPX3, MGST2, GSTK1, IDH1, GPX4, GGCT, GSTP1, MGST3, ANPEP, PGD, SMS, GGT1, GSTT1	-	Glutathione is a major endogenous anti-oxidant with an important role in defence against reactive oxygen species. It contributes to regulation of several fundamental biological processes including DNA and protein synthesis as well as cytokine production and immune response.
Haematopoietic cell lineage	0.06	55	↓	CD37, ANPEP, HLA-DRA, HLA-DRB3, HLA-DRB1, HLA-DRB5	Hematopoietic stem cell	Blood cells originate from hematopoietic stem cell that differentiates into multilineage committed progenitor cells. Hematopeietic cell lineage pathway is enriched in genes with prior evidence of association with CAD.[4]
Metabolism of	0.062	21	↓	CYP2S1, MGST1, MGST2,	-	One of the major pathways of xenobiotic

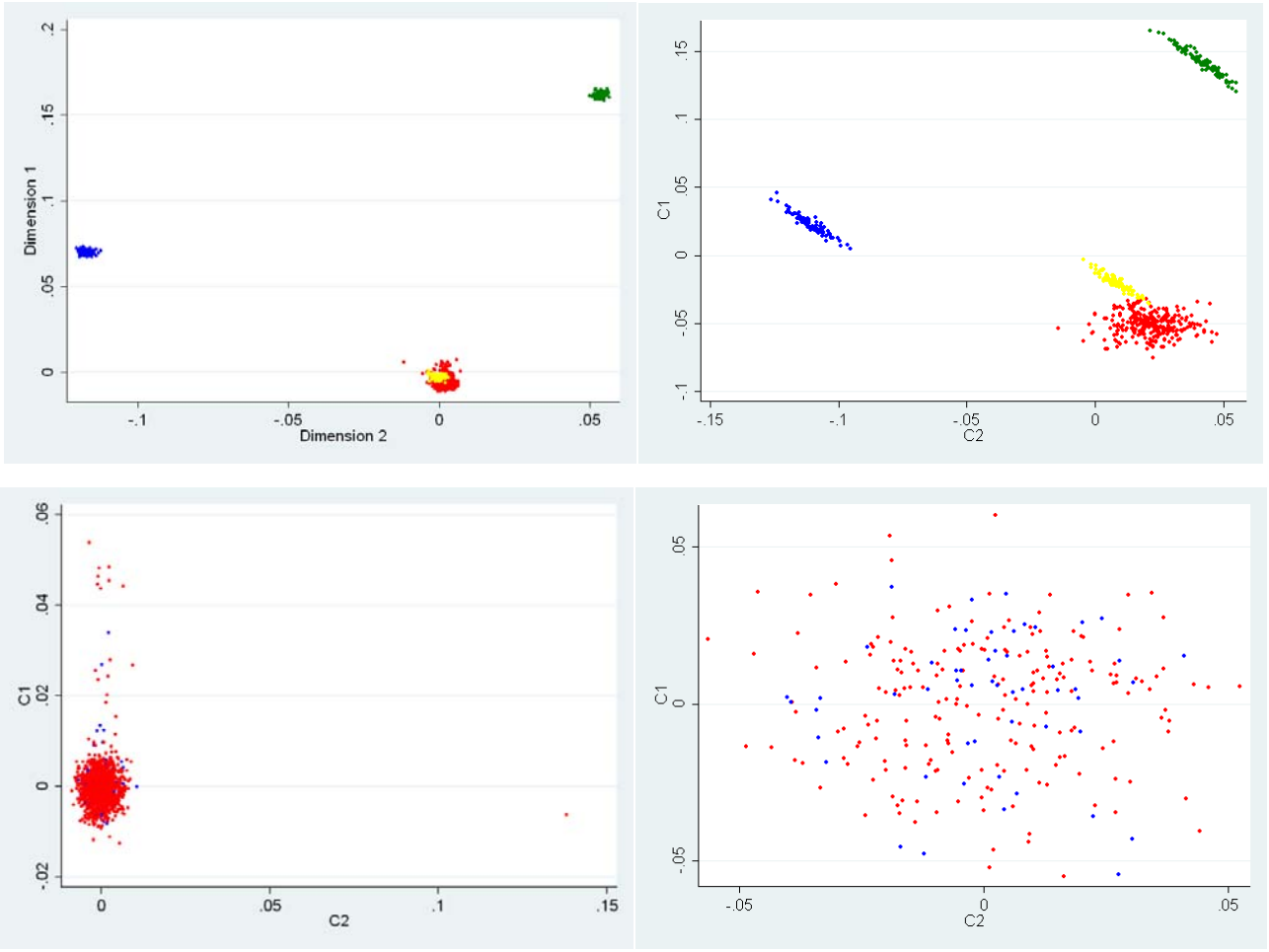
xenobiotics by cytochrome P450				GSTK1, GSTP1, MGST3, EPHX1, AKR1C3, AKR1C2, GSTT1		biodegradation.
Glycosaminoglycan degradation	0.197	15	↓	NAGLU, HEXA, HYAL2, SGSH, HYAL3, IDUA	-	Major components of the extracellular matrix and cell surface of most cell types are degraded in lysosome by the concerted action of exohydrolase activities following partial catabolism by endoenzymes.[8]
Arrhythmogenic right ventricular cardiomyopathy	0.078	28	↑	ITGB3, CTNNA1, ATP2A2, CACNB3, CACNA2D4, SGCB, ITGA5, ITGB1, DSC2, ITGAV, ITGB7, ITGB5, JUP, CTNNB1, ITGA6	Cardiomyocyte	Inherited heart muscle disease caused by genetically mediated disruption of desmosomal function and myocardial injury accompanied by inflammation.
Glycolysis gluconeogenesis	0.093	41	↑	PGAM1, ALDOA, ALDH3A2, ALDH3B1, HK3, HK1, DLAT, PFKM, ALDOC, PGM2, GAPDH, LDHA, PDHA1, DLD, PGK1, LDHB, PKM2, HK2	-	Glycolysis is the process of converting glucose into pyruvate and generating small amounts of ATP and NADH. Gluconeogenesis is a synthesis of glucose from non-carbohydrate precursors and essentially a reversal of glycolysis.
Extracellular matrix (ECM) receptor interaction	0.098	32	↑	ITGB1, CD47, COL6A1, SPP1, SDC2, ITGAV, LAMC1, ITGB7, ITGB5, CD36, ITGA6	-	Extracellular matrix is a mixture of structural and functional macromolecules that play an important role in tissue and organ morphogenesis and in the maintenance of cell and tissue structure and function. ECM receptor interaction pathway is strongly enriched in genes associated with CAD.[4]
Hypertrophic cardiomyopathy	0.109	33	↑	ITGB3, TPM3, ATP2A2, CACNB3, CACNA2D4, SGCB, ITGA5, ITGB1, TPM2, ITGAV, PRKAA1, TPM4, ITGB7, ITGB5, ITGA6	Cardiomyocyte	One of the most common inherited cardiac disorders with cardiomyocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis. Hypertrophic cardiomyopathy pathway is enriched in genes showing association with coronary artery disease.[4]
Starch and sucrose metabolism	0.109	20	↑	AGL, HK3, PYGL, AMY2B, HK1, PGM2L1, UGDH, PGM2, GBE1, AMY1A, UGP2, HK2	-	2 major dietary carbohydrates that influence postprandial glucose levels.
Leukocyte transendothelial	0.11	68	↑	PTK2, MYL9, PIK3R1, ITGB1, CLDN23, ROCK1, VASP,	Leukocyte	The rolling, adhesion and transmigration of leukocytes across the endothelial barrier

migration				PTPN11, ITGAM, VCL, RHOA, PRKCA, RAP1B, CLDN14, ROCK2, VAV3, PIK3CG, NCF1, F11R, CTNNB1		into the intima is a major part of atherosclerosis development.[1]
Dilated cardiomyopathy	0.111	36	↑	ADCY3, ITGB3, TPM3, ATP2A2, CACNB3, CACNA2D4, SGCB, PRKACB, ITGA5, ITGB1, TPM2, ITGAV, TPM4, ITGB7, ITGB5, ITGA6	Cardiomyocyte, T cell	Progressive heart muscle disease with a significant immune and autoimmune component (increased serum levels of autoantibodies, cytokines, viral genomes); may develop as a consequence of viral myocarditis.[6]
Focal adhesion	0.115	108	↑	ITGA5, PPP1R12A, PDPK1, PDGFC, ILK, PTK2, BIRC2, MYL9, PIK3R1, ITGB1, COL6A1, RAPGEF1, PAK2, ROCK1, VASP, BIRC3, TLN1, VCL, SPP1, RHOA, PRKCA, PPP1CB, ITGAV, RAP1B, ROCK2, VAV3, PIK3CG, LAMC1, CCND2, ITGB7, ITGB5, CCND1, CTNNB1, ITGA6	-	Focal adhesion regulates cytoskeletal/adhesion dynamics and in consequence cellular shape and motility. Molecules signalling within this pathway are targets for drugs used in treatment of acute coronary syndromes.[2-5] There is a very strong enrichment of this pathway in genes with prior evidence of association with CAD.[4]
TGFβ signalling pathway	0.115	43	↑	TGFBR2, ID3, PPP2CA, BMPR2, ACVR1, RBX1, SMAD5, SMAD7, ZFYVE16, ROCK1, ACVR2A, MYC, RHOA, ROCK2, PPP2CB, ID2	-	Activation of TGFβ pathway in the vascular wall may have both pro-atherogenic and anti-atherogenic effects.[7]
Primary immunodeficiency	0.119	20	↑	PTPRC, IL7R, ADA, DCLRE1C, BTK, AIRE	T cell, B cell, NK cells	A heterogeneous group of disorders, which affect cellular and humoral immunity or non-specific host defence mechanisms mediated by complement proteins, and cells such as natural killer (NK) cells. These disorders of the immune system cause increased susceptibility to infection, autoimmune disease, and malignancy.
Cytokine cytokine receptor interaction	0.125	114	↑	TGFBR2, TNFRSF12A, IFNA10, IL28RA, TSLP, PPBP, TNFRSF9, BMPR2, IL7R, IL6R, CSF2RA, TNFRSF4, PDGFC,	-	Cytokines and their receptors are expressed in human atherosclerotic plaques and modulate plaque development and stability.[9] The pathway is enrichment for

				CCR5, CSF3R, ACVR1, CXCL10, ACVR2A, IL13RA1, TNFSF15, TNFRSF1B, IL18, CXCL5, CSF1R, IL10RB, TNFSF14, LEP, IL10, LEPR, CCL2, CCR6, CCL8, CCL5, IL1B, CCL7, CCL22, CCL4L1, TNFRSF21		genes with prior evidence of association with CAD.[4]
PPAR signalling pathway	0.125	44	↑	ACSL3, PDPK1, DBI, ILK, OLR1, ACOX2, FABP3, PLTP, PPARG, ACADM, NR1H3, ME1, CD36, ACSL1, ACSL4, LPL, FABP4	-	PPAR have effects on both metabolic risk factors and vascular inflammation and are expressed in atherosclerotic lesions.[10]
Pathogenic Escherichia coli infection	0.126	42	↑	TUBB2A, TUBB6, ITGB1, ROCK1, YWHAQ, ARPC4, RHOA, PRKCA, ROCK2, TLR4, TUBA4A, ARPC5, CTNNB1	Enterocyte	Enteropathogenic E. coli and enterohaemorrhagic E. coli mediated colonisation and damage of intestinal epithelial cells.
Arginine and proline metabolism	0.158	31	↑	GAMT, LAP3, ABP1, GLS, AMD1, P4HA1, MAOA	-	Co-metabolism of several amino-acids: arginine, ornithine, proline, citrulline and glutamate.
Citrate cycle	0.159	27	↑	DLAT, SUCLA2, SUCLG2, ACO1, PDHA1, DLD, SDHD, FH	-	Important aerobic pathway for the final steps of the oxidation of carbohydrates and fatty acids

FDR – false discovery rate; leading edge subset of genes - genes which make the major contribution to up-regulation or down-regulation of a given pathway as measured by the Enrichment Score (ES) in GSEA

Supplementary Figure 1. Analysis of population stratification in British Heart Foundation Family Heart Study (BHF-FHS) and Cardiogenics based on autosomal SNPs from previous genome-wide association scan. The X and Y axes represent the first two dimensions from multidimensional scaling (MDS) analysis on the matrix of genome-wide identity-by-state pair-wise distances. The upper panels show an overlap between men from the BHF-FHS (left - yellow) and Cardiogenics (right - yellow) and HapMap CEU population (red). HapMap YRI and JPT+CHB populations are shown in green and blue, respectively (upper panels). The bottom panels show individuals with haplogroup I (blue) versus carriers of all other haplogroups in BHF-FHS (left) and Cardiogenics (right).



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