

Supplemental text

Characteristics of study cohorts

A total of 24,320 individuals recruited from 11 populations of white European ancestry were included in this project (1). All the studies included biologically unrelated individuals. Further details for each cohort used are given below.

Wellcome Trust Case-Control Consortium Study (WTCCC)

WTCCC cases: This British population includes 1,988 individuals with a validated history of either myocardial infarction (MI) or coronary revascularization (coronary artery bypass surgery - CABG or percutaneous coronary angioplasty - PCA) before the age of 66 years. Recruitment was carried out on a national basis and lasted 5 years (April 1998 – November 2003). A major proportion of biologically unrelated individuals with coronary artery disease (CAD) in this study come from families with two or more affected siblings conducted in UK - British Heart Foundation Family Heart Study (BHF-FHS) (2). Some individuals in this resource come from GRACE Study (3) that recruited individuals with CAD and familial history of premature CAD (in parents or sibling) but in whom an affected sibling was not available for recruitment.

In the WTCCC study, subjects from both BHF-FHS and GRACE cohorts were used together totalling 2,000 unrelated cases affected by premature CAD. 1,518 of those subjects were derived from BHF-FHS (2) and 470 subjects were from families included in GRACE study (3).

WTCCC controls: A population of 3,004 control subjects was derived from two independent publicly accessible sources: the British 1958 Birth Cohort (58BC) and a sample of blood donors from UK Blood Services (UKBS).

The 58BC, also known as the National Child Development Study (4), includes all births in England, Wales and Scotland during one week in 1958. From an original sample of over 17,000 births, survivors were followed up at ages 7, 11, 16, 23, 33 and 42 years. In a biomedical examination at 44-45 years, 9,377 cohort members were visited at home providing 7,692 blood samples. DNA was extracted from 1,500 cell lines (5) of subjects with self-reported white ethnicity and representative of gender and each geographical region were selected for use as controls.

The UKBS provided 1,500 controls from a sample of healthy blood donors recruited as a part of the WTCCC project (6). WTCCC in collaboration with UKBS set up a UK national repository of anonymised samples of DNA and viable mononuclear cells from 3,622 consenting blood donors (age range: 18-69 years, majority of them between 40-59 years). DNA used in this project was extracted from the leukocyte fraction retrieved from the standard blood sample. A set of 1,564 samples was selected from the total number of samples based on sex and geographical region to reproduce the distribution of the samples of the 1958 Birth Cohort for use as common controls in the WTCCC study. The subjects were about equally divided into males and females and both control groups were geographically widely distributed across the UK. Except from gender information and 10 year age-band, additional phenotypic information was not available on the control cohorts (5-6).

German Myocardial Infarction Family Study I (GerMIFSI)

GerMIFSI cases: This population consists of 875 biologically unrelated individuals with a validated history of MI before the age of 60 years. The recruitment was carried out after screening >200,000 clinical charts in 17 cardiac in-hospital rehabilitation centres. The majority (>70%) of individuals were recruited in the surrounding area of Augsburg and the Southern part of Germany between 1997 and 2002. All individuals were of white German origin. If at least one additional first-degree family member (preferentially a sibling) had suffered from MI or had severe CAD (history of PCA or CABG), the family (index patient, available parents and all siblings) was approached and asked to join the study (7-8). All events in index cases and family members were validated through inspection of hospital charts.

GerMIFSI controls: All 1,644 CAD-free controls had German descent and were collected for the MONICA/KORA Augsburg population study in the years 1994/1995 and a follow up of this project in the years 2004/2005 that was undertaken as part of the German National Genome

Research Network (NGFN) (9). This population represents a gender- and age- stratified random sample of all German residents of the Augsburg area and consists of individuals 25 to 74 years of age, with about 300 subjects for each 10-year age band. These individuals were studied by physical examination, blood testing, and a standardized interview including medical history, physical activity, medication and personal habits.

German Myocardial Infarction Family Study II (GerMIFSII)

GerMIFSII cases: This population consists of 1,222 individuals with a validated history of MI before the age of 60 years for both men and women (10). A positive family history for CAD was documented in 726 (59.4%) of individuals. Individuals were identified following their admission for acute treatment of MI or in cardiac rehabilitation clinics.

GerMIFSII controls: A total of 820 CAD-free controls were derived from the MONICA/KORA Augsburg survey S4 (11). A sample of 478 controls was taken from PopGen blood donor sample 2 (PopGen-DSP) (12).

German Myocardial Infarction Family Study III (GerMIFSI - KORA)

GerMIFSI cases: A total of 1,157 subjects with available DNA were derived from individuals with non-fatal MI in the KORA registry (13). Hospitalised survivors of MI aged 26-74 years are routinely entered into this registry (14). The diagnosis of MI was made with the use of algorithm of the World Health Organization's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project (15).

GerMIFSI controls: A total of 996 and 752 CAD-free controls were derived from the population-based Augsburg KORA S4/F4 study (16) and PopGen respectively (12).

Ottawa Heart Genomics Study (OHGS)

The OHGS is a hospital-based study of CAD conducted at the Ottawa Heart Institute in Ottawa, Canada. Individuals who underwent CABG, coronary artery angiography, or receive treatment for MI were invited to participate in the study (17-18). Three independent samples (OHGS-A, OHGS-B and OHGS-C) were ascertained consecutively for this study.

OHGS cases: Individuals with documented CAD (stenosis in a major epicardial vessel of at least 50%; PCA; CABG or MI before the age of 55 years in men and 65 years in women) were recruited for OHGS as cases. Individuals with history of diabetes mellitus of severe dyslipidemia were excluded.

OHGS controls: Healthy elderly controls (men aged >65 years and women aged >70 years) were recruited via an extensive newspaper and television advertising campaign in the Ottawa community. Controls were carefully interviewed by a physician or nurse to ascertain that they were free of symptoms of possible ischemic arterial disease and had no past history of cardiovascular symptoms, a positive stress test, coronary angiography demonstrating stenosis (>50%) in any artery or clinical cardiovascular events. Individuals with the same ethnic background as the cases were included in this study. Controls for all three studies were collected consecutively as described for cases.

Cleveland Clinic Gene Bank (CCGB)

All cases in CCGB study were recruited using the same criteria as in OHGS (18). Individuals were included if they had at least one of the following before the age of 55 years (men) or 65 years (women): angiographically documented stenosis in a major epicardial artery of at least 50%; history of MI, PCA or CABG. Diabetes was an exclusion criterion.

The Duke Cathgen Study (DUKE)

Subjects were recruited from the cardiac centre at Duke, Canada. Cases had at least one epicardial coronary vessel with $\geq 50\%$ stenosis documented before age of 55 years (men) or 65 years (women). Controls (≥ 50 years of age) were recruited from amongst individuals who underwent coronary angiography and had no more than 30% stenosis in maximally one epicardial coronary artery. Any subject with diabetes mellitus, severe pulmonary hypertension or congenital heart disease was excluded from DUKE Study.

PennCATH

PennCATH is a university of Pennsylvania Medical Center based coronary angiographic study. Briefly, between July 1998 and March 2003, PennCATH recruited a consecutive cohort of individuals undergoing cardiac catheterization and coronary angiography (19-20). Cases were required to have at least one stenosis of $\geq 50\%$ in at least one of major epicardial arteries before the age of 60 for males and 65 for women. In contrast, CAD-free controls (aged >40 years /men/ and >45 years /women/) had no stenosis exceeding 10% in any major epicardial artery.

INTERHEART study

The INTERHEART study used worldwide cases and controls of European ethnicity (21). Study participants were recruited from 262 centres from 52 countries in Asia, Europe, the Middle East, Africa, Australia, North America, and South America. In this project only a small subset of Canadian individuals (848) of European ancestry was used. Briefly, all individuals (irrespective of age) admitted to the coronary care unit presenting within 24 hours of symptom onset, were screened. Cases were eligible if they had characteristic symptoms plus electrocardiogram changes indicative of a new MI. At least one age-matched (up to 5 years older or younger) and sex-matched control (no previous diagnosis of heart disease or history of exertional chest pain) was recruited per case, using specific criteria.

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Supplemental Figures

Figure S1: Measures of homozygosity in each cohort. A - average run number, B - average run length, C - average total run length in the autosomal genome. The boxes are median values, the upper edge of the box - the 75th percentile, the lower edge - the 25th percentile of runs of homozygosity distribution.

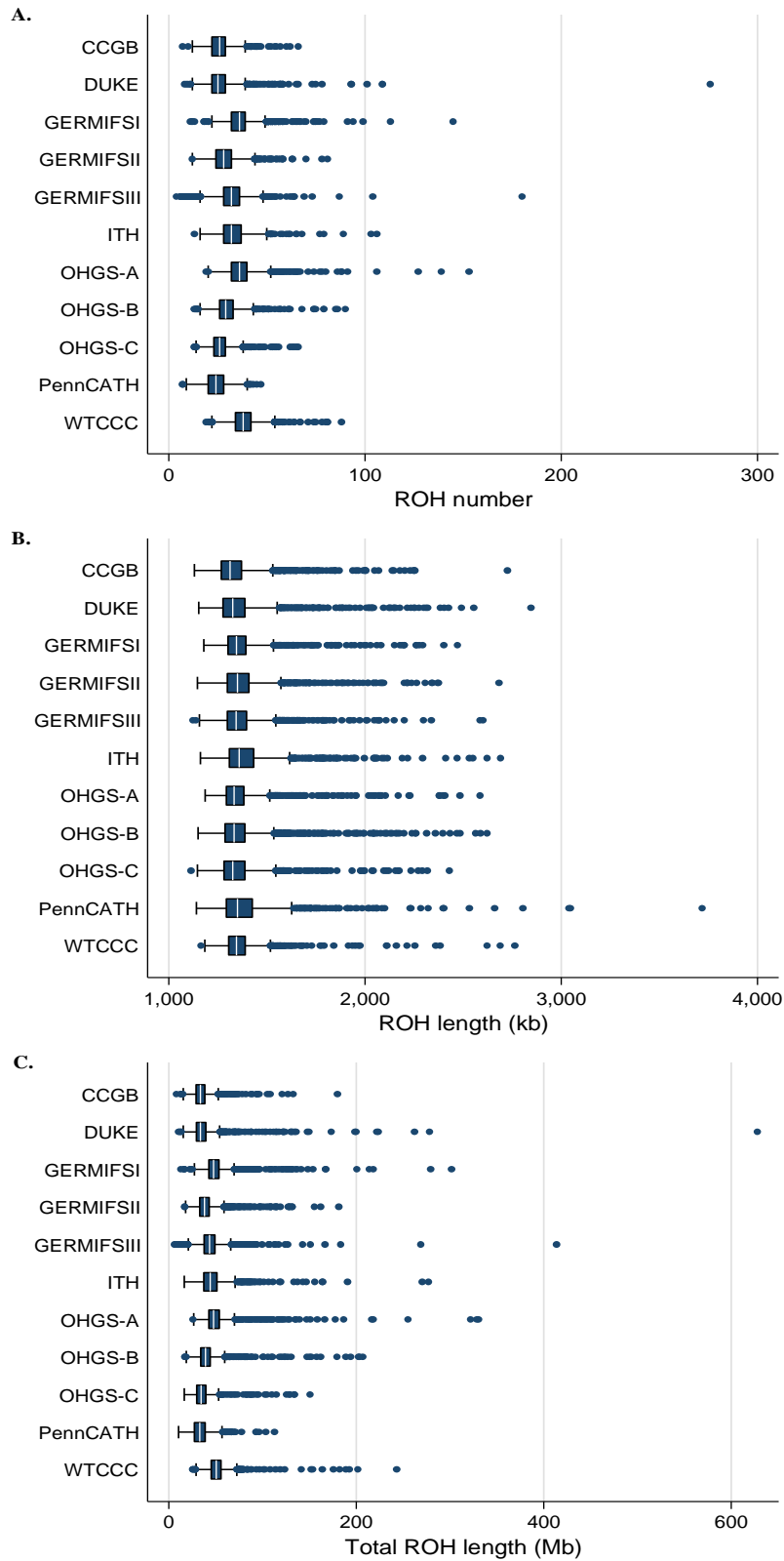


Figure S2: Measures of homozygosity in each cohort split by case control status. A - average run number, B - average run length, C - average total run length in the autosomal genome. The boxes are median values, the upper edge of the box - the 75th percentile, the lower edge - the 25th percentile of runs of homozygosity distribution.

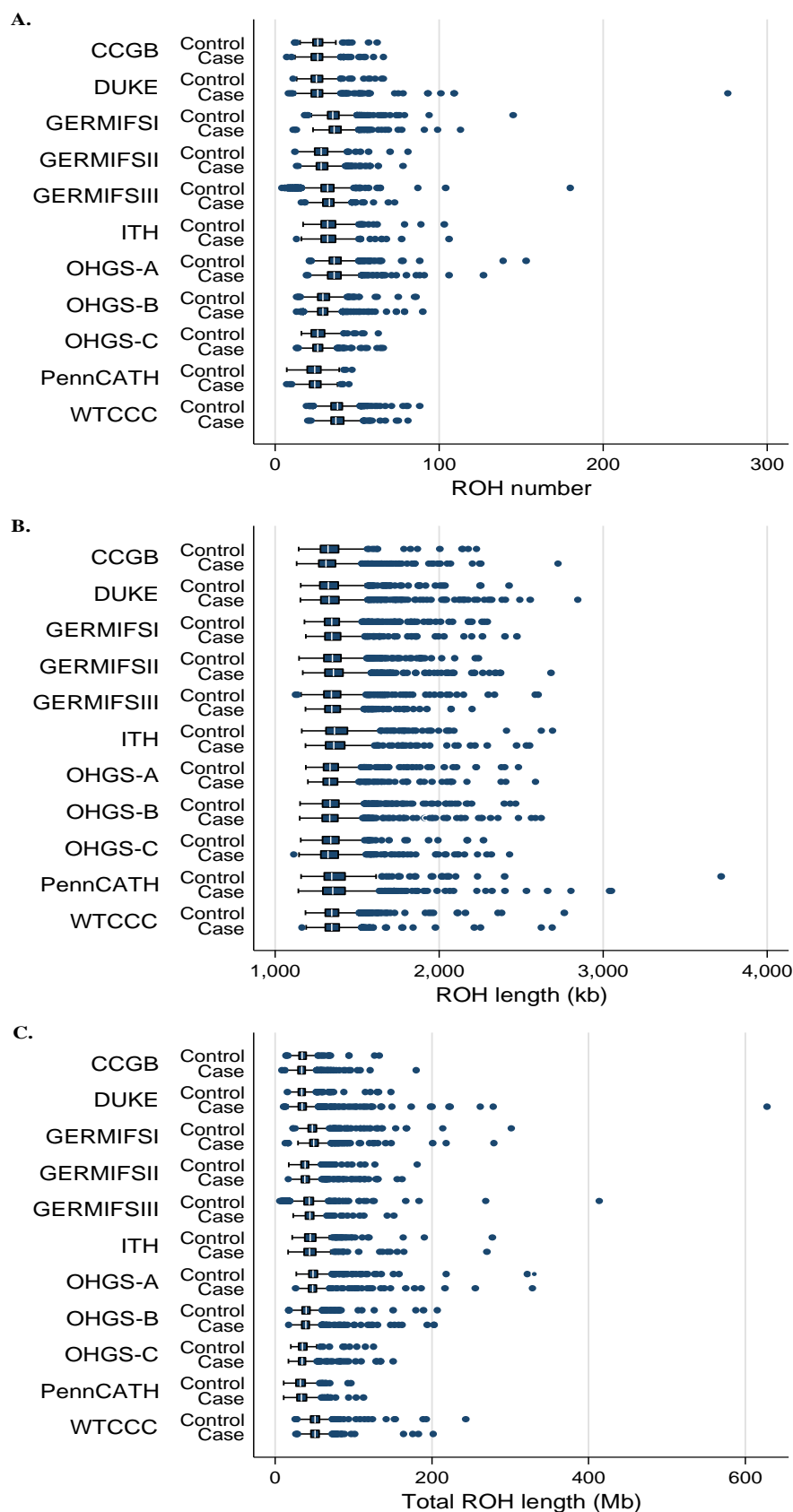
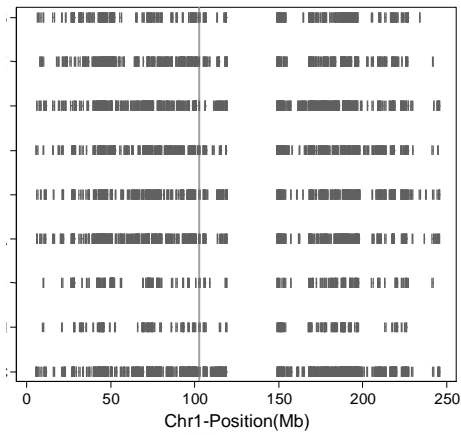
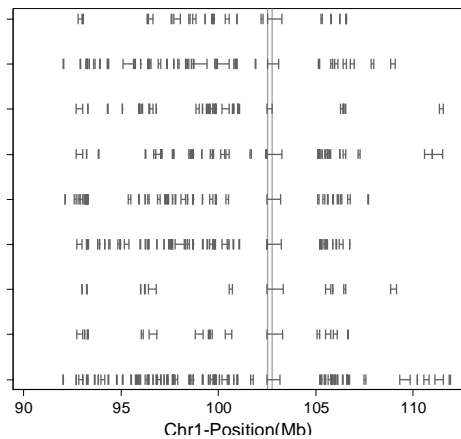


Figure S3: An example of overlapping consensus ROH on chromosome 1 shared by 9 populations. X axis - physical distance of the chromosome, Y axis - individual populations

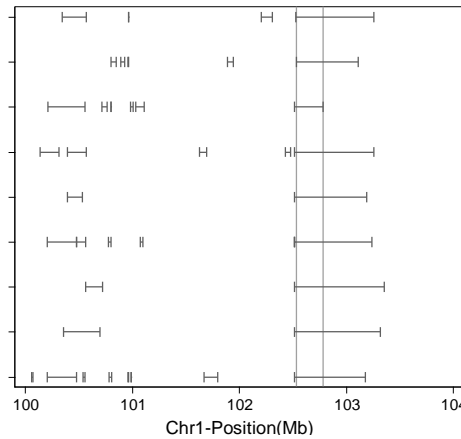
A.



B.



C.



Supplemental Tables

Table S1: Characteristics of cohorts used in the analysis.

Study	Origin	Number of subjects	Cases/Controls	%MI	%female (cases/controls)	Cases age (years)	Controls age (years)	CAD definition
CCGB	Canadian	1971	1607/364	60.3	24.2/46.7	48.5 (7.3)	73.9 (5.2)	Angiographic (>50% stenosis)
DUKE	Canadian	1820	1180/640	48.1	30.7/57.8	56.6 (9.8)	63.3 (8.7)	Angiographic (>50% stenosis)
GERMIFSI	German	2486	882/1604	100	32.8/50.8	50.2 (7.9)	62.6 (10.0)	MI (<65 yrs) with >1 1 st degree sibling with severe CAD (PTCA; MI; CABG)
GERMIFSII	German	2506	1222/1284	100	20.9/48.1	51.4 (7.5)	51.1 (12.0)	MI (<60 yrs); 59.4% with family history of CAD
GERMIFSIII	German	2900	1152/1748	100	20.2/48.9	58.6 (8.7)	55.9 (10.7)	MI (<60 yrs); MONICA criteria
ITH	Canadian	848	402/446	64.0	29.1/33.0	63.1 (10.6)	64.2 (10.3)	Angiographic (>50% stenosis)
OHGS-A	Canadian	1911	913/998	64.3	22.0/45.5	48.2 (6.9)	74.9 (4.9)	Angiographic (>50% stenosis)
OHGS-B	Canadian	2778	1272/1506	55.6	26.8/52.8	49.3 (7.4)	75.0 (5.3)	Angiographic (>50% stenosis)

OHGS-C	Canadian	1152	835/317	44.3	6.2/64.7	56.1 (6.9)	76.0 (6.3)	Angiographic (>50% stenosis)
								Angiography (≥ 1 coronary vessel
								with >50% stenosis); ≤ 60 for
PennCATH	USA	1084	732/352	50.3	22.1/48.9	52.6 (7.6)	61.3 (9.5)	males and
								≤ 65 for females.
								Validated MI, CABG, PTCA or
WTCCC	British	4864	1926/2938	71.5	20.7/50.8	49.8 (7.7)	43.7 (8.7)	angina with positive non-invasive
								testing <66 yrs

Data are counts and percentages or means and standard deviations, CAD – coronary artery disease, MI – myocardial infarction, CABG – coronary artery bypass grafting, PTCA – percutaneous transluminal coronary angioplasty, CCGB – Cleveland Clinic Gene Bank, DUKE – Duke Cathgen Study, GERMIFSI, II, III – German Myocardial Infarction Family Studies, ITH – InterHeart Study, OHGS-A,B,C – Ottawa Heart Genomics Studies, WTCCC – Wellcome Trust Case Control Consortium, yrs – years

Table S2: Genotyping information for each study.

Study acronym	CCGB	DUKE	GerMIFSI	GerMIFSII	GerMIFSI	ITH	OHGS-A	OHGS-B	OHGS-C	PennCATH	WTCCC
Platform	Affymetrix 6.0	Affymetrix Axiom	Affymetrix NSP and STY	Affymetrix 6.0	Affymetrix Genome-Wide Human SNP Array 6.0	Affymetrix Human SNP Array 6.0	Affymetrix Mapping 500K	Affymetrix Human SNP Array 6.0	Affymetrix Axiom	Affymetrix 6.0	Affymetrix Mapping 500K Array Set
Calling algorithm	Birdseed	AxiomGT1	Birdseed	BRLMM	Birdseed	Birdseed	BRLMM	Birdseed	AxiomGT1	Birdseed	CHIAMO
Genotyped SNPs	447,580	360,462	262,338(NSP)/ 238,378(STY)	909,622	503,590	492,837	349,183	420,531	366,254	869,223	477,459
Total SNPs	1,779,828	1,999,530	2,543,887	2,543,887	2,536,369	2,004,234	1,688,980	1,756,731	1,990,154	2,749,197	2,614,446

SNP – single nucleotide polymorphism, CCGB – Cleveland Clinic Gene Bank, DUKE – Duke Cathgen Study, GERMIFSI, II, III – German Myocardial Infarction Family Studies, ITH – InterHeart Study, OHGS-A, B, C – Ottawa Heart Genomics Studies, WTCCC – Wellcome Trust Case Control Consortium.

Table S3: Summary of homozygosity measures for each examined study.

Study	Number of subjects	Average ROH number	ROH number range	Average total ROH length (kb)	Average ROH length (kb)	FROH
CCGB	1971	25.92 (5.60)	7-66	34885.64 (10257.83)	1336.86 (122.87)	1.26 (0.37)
DUKE	1820	26.59 (9.54)	8-276	36948.16 (22189.18)	1359.07 (157.21)	1.33 (0.80)
GERMIFSI	2486	36.35 (7.40)	11-145	49924.54 (15203.16)	1362.30 (112.46)	1.80 (0.55)
GERMIFSII	2506	28.48 (6.09)	12-81	39399.01 (11876.63)	1372.28 (129.59)	1.42 (0.43)
GERMIFSIIII	2900	31.79 (8.12)	4-180	43538.19 (14700.81)	1359.09 (106.40)	1.57 (0.53)
ITH	848	33.22 (8.37)	13-106	47501.14 (19879.07)	1404.99 (181.33)	1.71 (0.72)
OHGS-A	1911	36.70 (8.31)	19-153	50399.93 (18662.56)	1357.36 (126.61)	1.82 (0.67)
OHGS-B	2778	29.57 (6.31)	13-90	40508.82 (13225.52)	1357.49 (134.19)	1.46 (0.48)
OHGS-C	1152	26.43 (6.11)	13-66	36155.99 (12257.42)	1354.30 (137.87)	1.30 (0.44)
PennCATH	1084	24.32 (5.74)	7-47	34093.18 (10505.12)	1393.30 (198.39)	1.23 (0.38)
WTCCC	4864	37.78 (6.09)	19-88	51250.29 (10376.44)	1354.20 (84.65)	1.85 (0.37)

Data are means and standard deviations or absolute values and percentages, ROH – run of homozygosity, FROH – proportion of autosomal genome in ROHs, CCGB – Cleveland Clinic Gene Bank, DUKE – Duke Cathgen Study, GERMIFSI, II, III – German Myocardial Infarction Family Studies, ITH – InterHeart Study, OHGS-A, B, C – Ottawa Heart Genomics Studies, WTCCC – Wellcome Trust Case Control Consortium.

Table S4: Differences in homozygosity measures between individuals with coronary artery disease and controls – random effects model-based sensitivity analysis.

Measure	Un-adjusted analysis			Age-adjusted analysis			Age- and sex-adjusted analysis		
	β -coefficient/ OR	95% CI	P-value	β -coefficient/ OR	95% CI	P-value	β -coefficient/ OR	95% CI	P-value
Average ROH number	0.38	0.20, 0.57	5.21×10^{-5}	0.66	0.46, 0.86	6.25×10^{-11}	0.62	0.42, 0.83	2.08×10^{-9}
Average ROH length (kb)	2.47	-0.84, 5.77	0.144	5.16	1.61, 8.71	0.004	4.46	0.81, 8.11	0.017
Average total length of ROHs (kb)	668.01	294.31, 1041.70	4.59×10^{-4}	1124.83	723.67, 1525.99	3.89×10^{-8}	1028.30	615.78, 1440.83	1.03×10^{-6}
FROH	1.06	1.03, 1.10	1.46×10^{-4}	1.13	1.10, 1.17	4.67×10^{-13}	1.13	1.09, 1.17	3.24×10^{-11}

Data for number, average length and total length of ROHs are β -coefficients [with respective confidence intervals and level of statistical significance (P-value)] from regressing homozygosity measures on case-control status with adjustment for cohort as a random effect, age and sex (where appropriate)]; data on FROH are expressed as odds ratios (OR) of coronary artery disease risk (with confidence intervals and level of statistical significance) with adjustment for cohort as a random effect, age and sex (where appropriate); 95% CI – 95% confidence intervals, ROH – run of homozygosity, FROH – proportion of autosomal genome in ROHs.

Table S5. Differences in homozygosity measures between individuals with coronary artery disease and disease free controls after exclusion of WTCCC controls from the British 1958 Birth Cohort – sensitivity analysis.

Measure	Fixed			Random		
	β /OR	95% CI	P-value	β /OR	95% CI	P-value
Average ROH number	0.73	0.52, 0.94	2.28×10^{-11}	0.73	0.51, 0.94	2.76×10^{-11}
Average ROH length (kb)	4.83	0.95, 8.71	0.015	4.78	0.90, 8.65	0.016
Average total length of ROHs (kb)	1199.71	763.39, 1636.04	7.14×10^{-8}	1188.71	752.43, 1624.99	9.28×10^{-8}
FROH	1.15	1.11, 1.19	1.84×10^{-13}	1.14	1.10, 1.19	4.27×10^{-13}

Data for average number of homozygosity runs (ROH number), average ROH length and average total length of ROHs are β -coefficients [with respective confidence intervals and level of statistical significance (P-value) from regressing this homozygosity measure on case-control status with adjustment for cohort, age and sex (where appropriate)]; data on FROH (proportion of autosomal genome in ROHs) are expressed as odds ratios (OR) of coronary artery disease risk (with confidence intervals and corresponding level of statistical significance) with adjustment for cohort, age and sex (where appropriate); 95% CI – 95% confidence intervals, fixed – models with cohort as fixed effect, random – models with cohort as random effect

Table S6: Differences in average ROH number and FROH between individuals with coronary artery disease and controls after exclusion of cohorts with statistically significant CADxcohort or FROHxcohort interaction terms – sensitivity analysis

Measure	Fixed		Random	
	β /OR (95% CI)	P-value	β /OR (95% CI)	P-value
Average ROH Number	1.06 (0.81, 1.31)	1.04×10^{-16}	1.05 (0.80, 1.30)	1.48×10^{-16}
FROH	1.14 (1.10, 1.18)	2.01×10^{-12}	1.14 (1.10, 1.18)	4.52×10^{-12}

Data for average number of homozygosity runs (ROH number) are β -coefficients [with respective confidence intervals and level of statistical significance (P-value) from regressing this homozygosity measure on case-control status with adjustment for cohort, age and sex (where appropriate)]; data on FROH (proportion of autosomal genome in ROHs) are expressed as odds ratios (OR) of coronary artery disease risk (with confidence intervals and level of statistical significance) with adjustment for cohort, age and sex (where appropriate); 95% CI – 95% confidence intervals, sensitivity analysis – analysis of association conducted after exclusion of studies with significant CADxcohort or FROHxcohort interaction terms (WTCCC for average ROH number, and CCGB, GERMIFSIII, OHGS-A and OHGS-B for FROH), fixed – models with cohort as fixed effect, random – models with cohort as random effect

Table S7: Single nucleotide polymorphism enrichment of identified overlapping consensus ROHs.

Number of SNPs in overlapping consensus ROH	Values
2-9	1852 (10.90)
10-49	6018 (35.42)
50-99	3408 (20.06)
100+	5711 (33.62)
Total	16,989

Data are counts and percentages, ROH – runs of homozygosity, SNP – single nucleotide polymorphism

Table S8: Top 10 overlapping consensus ROHs from analysis of association with coronary artery disease – age- and sex-adjusted analysis.

Reg	Chr	BP1	BP2	Studies	SNPs	Cases	Controls	OR (95% CI)	P-value
1	3	34,972,502	34,973,514	7 (B, C, D, E, H, I, J)	102	74	64	0.85 (0.40, 1.30)	1.99x10 ⁻⁴
2	7	123,048,204	123,057,055	4 (C, D, I, J)	55	42	80	0.83 (0.38, 1.28)	2.74x10 ⁻⁴
3	5	151,895,125	152,036,927	3 (C, D, J)	199	46	25	1.01 (0.46, 1.55)	3.06x10 ⁻⁴
4	12	109,552,479	109,586,957	4 (A, E, G, I)	98	499	513	0.34 (0.15, 0.53)	4.22x10 ⁻⁴
5	2	197,612,440	197,618,211	2 (C, I)	5	87	113	0.76 (0.34, 1.19)	4.75x10 ⁻⁴
6	4	103,891,412	103,894,628	2 (E, J)	29	148	114	0.48 (0.21, 0.75)	4.93x10 ⁻⁴
7	2	197,110,028	197,111,431	2 (C, E)	22	117	135	0.47 (0.21, 0.74)	5.11x10 ⁻⁴
8	18	30,443,158	30,445,323	6 (A, B, D, E, I, K)	192	137	132	0.48 (0.21, 0.76)	5.96x10 ⁻⁴
9	5	32,901,811	32,998,002	6 (C, D, E, G, H, K)	208	24	17	1.28 (0.54, 2.01)	6.74x10 ⁻⁴
10	3	35,241,188	35,249,754	4 (D, E, G, J)	43	46	21	0.99 (0.41, 1.57)	8.18x10 ⁻⁴

ROH – run of homozygosity, Reg – region, Chr – chromosome, BP1 – starting base pair position of the overlapping consensus ROH, BP2 – ending base pair position of the overlapping consensus ROH, OR – odds ratio of coronary artery disease after adjustment for age, sex, and study, P-value – level of statistical significance for case-control difference, A:CCGB, B:DUKE, C:GERMIFSI, D:GERMIFSII, E:GERMIFSI, F:ITH, G:OHGS-A, H:OHGS-B, I:OHGS-C, J:PennCATH, K:WTCCC, SNPs – average number of SNPs that each study contributed in the overlapping consensus ROH.

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