The American Journal of Human Genetics, Volume *89*

Supplemental Data

Abdominal Aortic Aneurysm Is Associated with a Variant in Low-Density Lipoprotein Receptor-Related Protein 1

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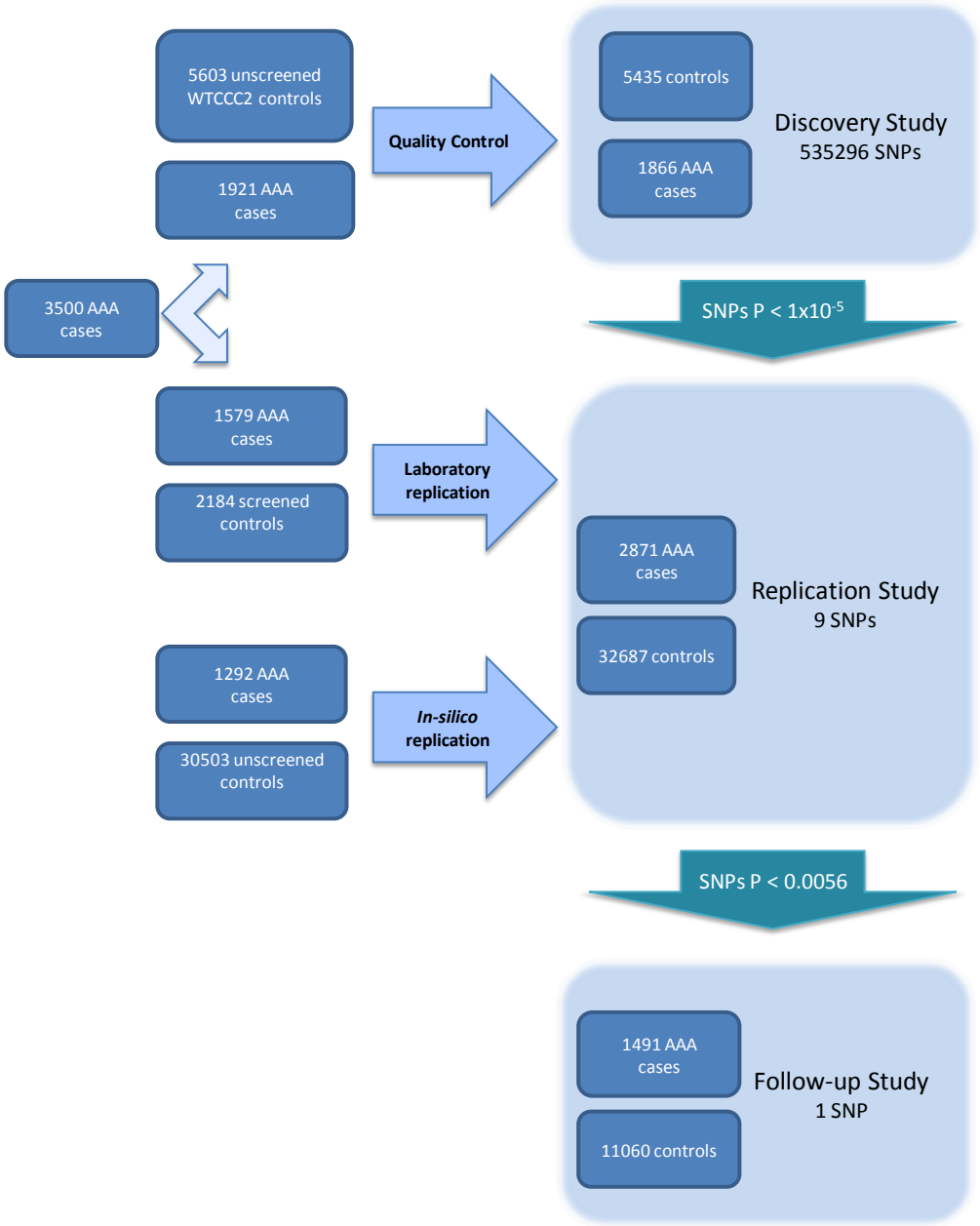
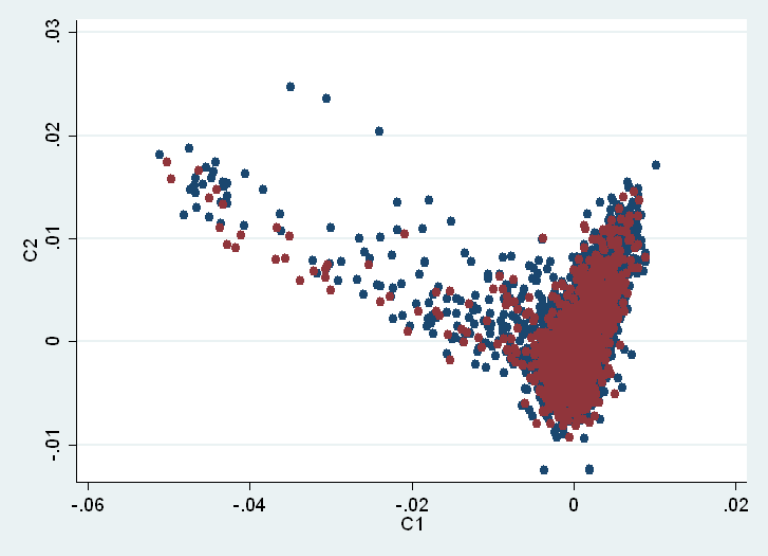
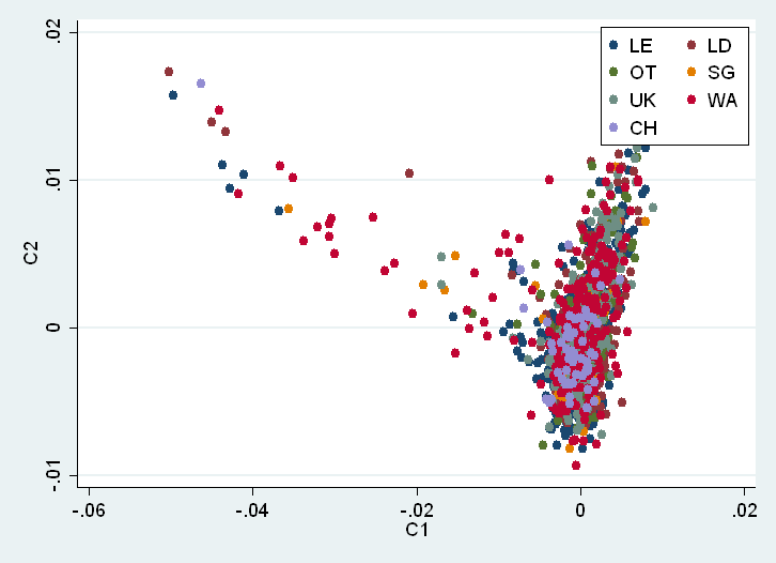


Figure S1. Study flow diagram.



a)



b)

Figure S2. Multi-dimensional scaling plot showing the first two dimensions for a) cases (dark red) and controls (dark blue) used in the discovery study and b) the cases used in the discovery study subdivided by contributing centre (LE=Leicester, LD=Leeds, OT=Otago, SG=StGeorges', UK=UK Small Aneurysm Trial, WA=Western Australia, CH=Chichester).

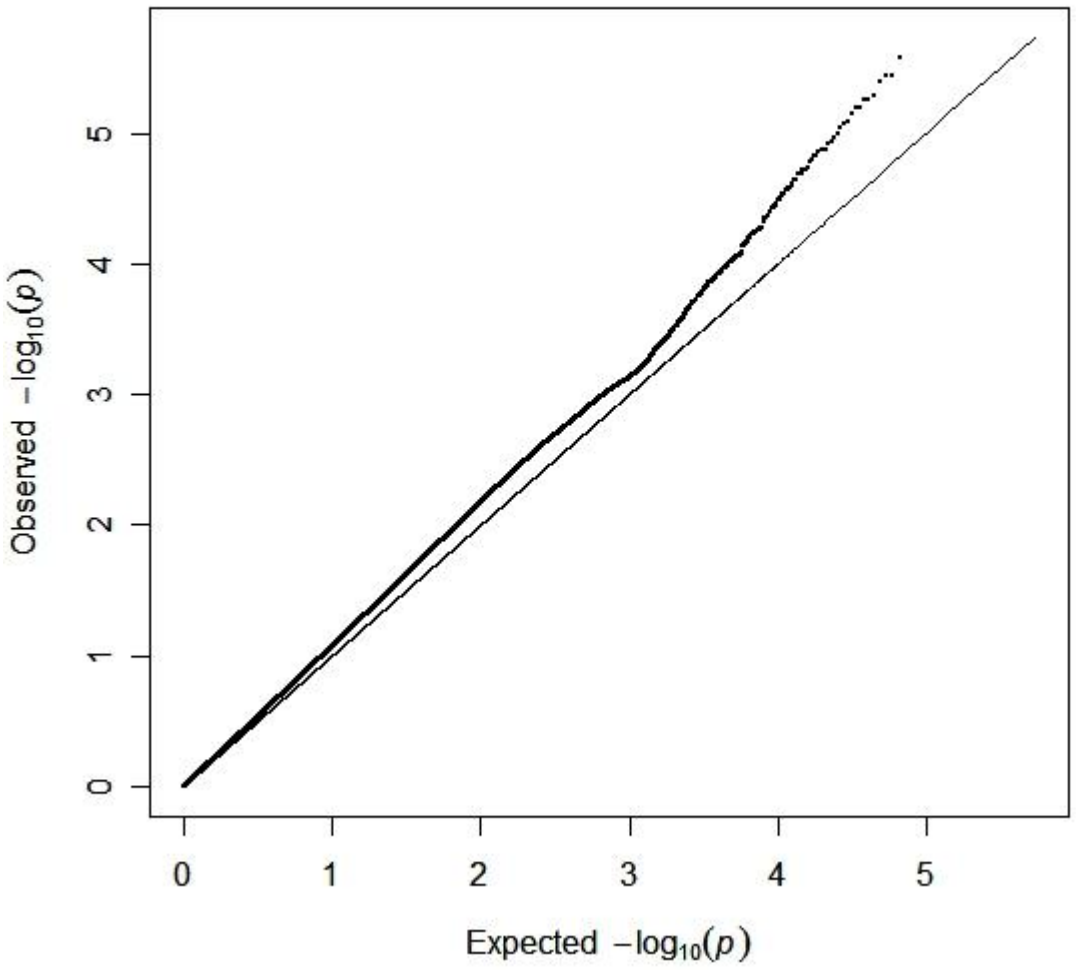


Figure S3. Quantile-quantile plot of the P-values obtained from the discovery study after adjustment for multi-dimensional scaling dimensions. The solid black line shows a slope of 1.0.

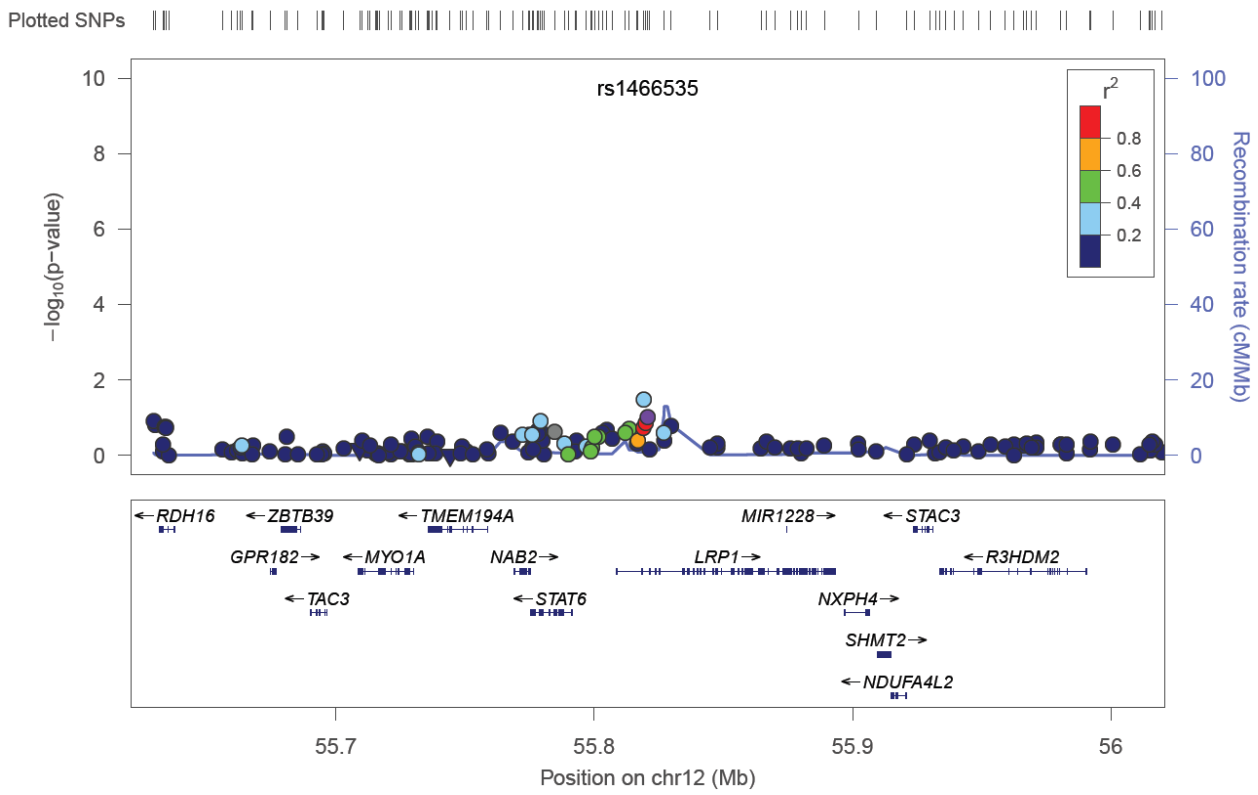


Figure S4. Regional association plot of data from the CARDIoGRAM study (22233 individuals with coronary artery disease and 64762 controls) showing data from that study for the region (±200 kb) around rs1466535 demonstrating no association of this locus with coronary heart disease. rs1466535 is indicated by the purple circle, the other SNPs typed in the study are shown as filled circles with the colour corresponding to their linkage with rs1466535. The solid blue line shows the regional recombination rate (right axis).

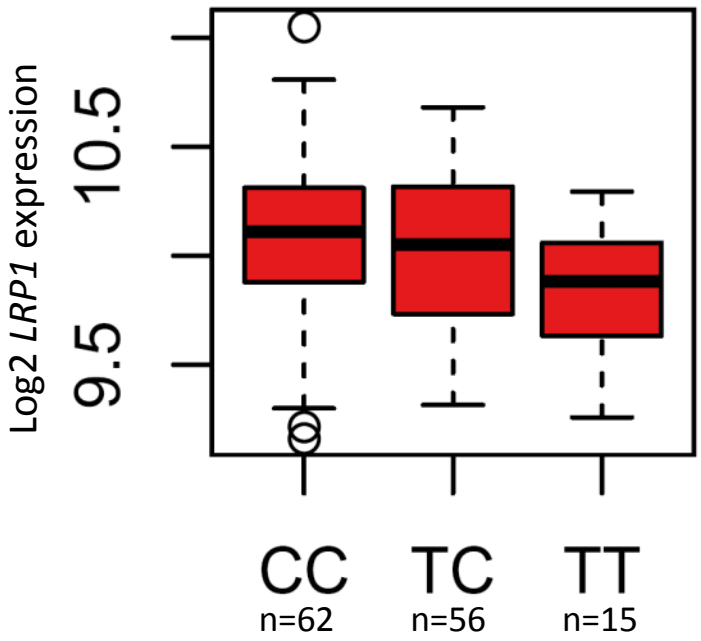


Figure S5. log2 expression levels of *LRP1* (P=0.029 using an additive linear model) in adventitial samples from the ascending aorta according to rs1466535 genotype (see Table 2 in the main text for details of expression in other tissues). The C allele is the risk allele for AAA. Numbers in each genotype group are: CC – 62, TC – 56, TT – 15.

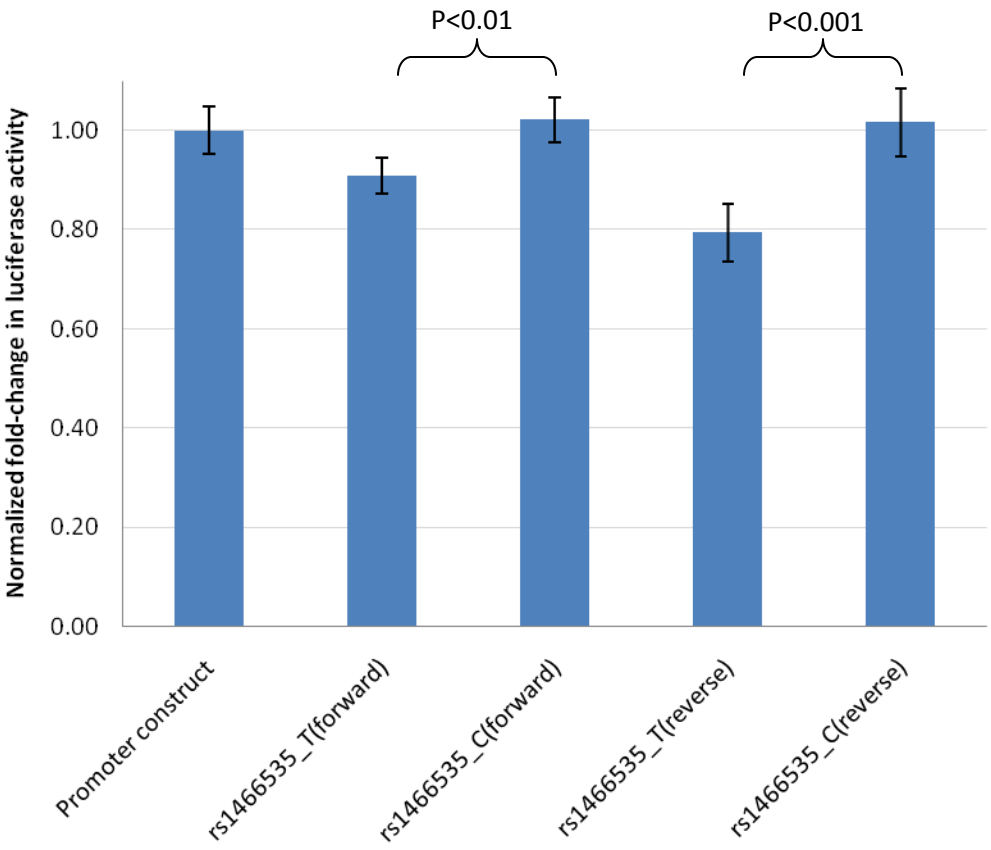


Figure S6. Results of the luciferase reporter assay showing relative expression of the LRP1-luciferase-enhancer constructs relative to the LRP1-luciferase construct (promoter only without intron 2 inserted). In both the forward and reverse direction there is reduced luciferase expression for the non-risk allele (T) compared to the risk allele (C).

Table S1. **Sample cohorts contributing to study**

		AAA		Controls	
	Centre	N	n male (%)	n	n male (%)
Discovery Study	Chichester, UK	58	58 (100.0)		
	Leeds, UK	319	319 (100.0)		
	Leicester, UK	778	777 (99.9)		
	Otago, NZ	129	98 (76.0)		
	St Georges, London, UK	70	61 (87.1)		
	UKSAT	262	262 (100.0)		
	Western Australia	250	250 (100.0)		
	WTCCC2: 1958 Birth Cohort			4157*	2088 (50.2)
	WTCCC2: National Blood Service			1278*	648 (50.7)
Replication study	Belfast, UK	228	210 (92.1)	244	234 (95.9)
	Chichester, UK	190	185 (97.4)		
	Kings College, London, UK	210	182 (86.7)		
	Leeds, UK	27	21 (77.8)		
	Leicester, UK	152	131 (86.2)	761	744 (97.8)
	Otago, NZ	623	486 (78.0)	515	378 (73.4)
	St Georges, London, UK	24	24 (100.0)		
	UKSAT	90	72 (80.0)		
	Western Australia	35	35 (100.0)	664	664 (100.0)

Numbers stated are those following sample and genotyping quality control. UKSAT = United Kingdom Small Aneurysm Trial, WTCCC2 = Wellcome Trust Case Control Consortium. Numbers for the samples used in the follow-up studies are detailed in **Table 3**. *Controls from the WTCCC2 study were not screened for AAA. Additional in-silico data was available[8]. The study design is shown in Supplementary Figure 1.

Table S2. Electrophoretic mobility shift assay primers *Primers used in the competitor assay with a SREBP-1 consensus binding site

Primer name	*Primer sequence*
rs1466535 C allele: forward	5’-GGTCCATGGCAGAGAAACTCCAATGATAAAGAAA-3’
rs1466535 C allele: reverse	5’–TTTCTTTATCATTGGAGTTTCTCTGCCATGGACC-3’
rs1466535 T allele: forward	5’–GGTCCATGGCAGAGAAATTCCAATGATAAAGAAA-3’
rs1466535 T allele: reverse	5’ – TTTCTTTATCATTGGAATTTCTCTGCCATGGACC-3’
competitor assay*: forward	5’- TTTGAAAATCACCCCATGCAAACTC-3’
competitor assay*: reverse	5’-GAGTTTGCATGGGGTGATTTTCAAA-3’

Table S3. Luciferase assay: Primers used to amplify LRP1 fragment. Tails are denoted by italicised text, restriction enzymes are shown in bold.

Primer name	*Tail/enzyme primer sequence*
LRP1FF	*5′CGC/***GGATCC** GGCTACGTATTGGGCAGTGAA*3′*
LRP1RF	*5′ACGC/***GTCGAC** TGAGCTGAGATTGCACCACTG*3′*
LRP1FR	*5′ACGC/***GTCGAC** GGCTACGTATTGGGCAGTGAA*3′*
LRP1RR	*5′CGC/***GGATCC** TGAGCTGAGATTGCACCACTG*3′*

Table S4. Luciferase assay: Primers for the site-directed mutagenesis.

Primer name	*Primer sequence*
SDM For G	*5′GAGTTTTTCTTTATCATTGGA**G**TTTCTCTGCCATGGACCCTG3′*
SDM Rev G	*5′CAGGGTCCATGGCAGAGAAA**C**TCCAATGATAAAGAAAAACTC3′*

Table S5. Replication study data.

Chr	Gene	SNP (alleles)	Risk allele	Discovery Study (1866 AAA, 5435 controls)			Laboratory replication (1579 AAA, 2184 controls)			Netherlands in-silico replication dataset (840 AAA, 2791 controls)			Iceland in-silico replication dataset (452 AAA, 27712 controls)			Combined Replication P value	Combined Discovery and replication P value
				FA/FC	OR (95% CI)	P	FA/FC	OR (95% CI)	P	FA/FC	OR (95% CI)	P	FA/FC	OR (95% CI)	P		
1	*TDRD10*	rs6674171 (A/G)	G	0.214/0.181	1.23 (1.12-1.35)	$9.32x10^{-6}$	0.200/0.194	1.04 (0.93-1.16)	0.55	0.230/0.201	1.12 (1.03-1.22)	0.0082	0.192/0.177	1.20 (0.90-1.61)	0.22	0.037	$1.15x10^{-5}$
2	*AC016912.2 (processed transcript)*	rs7565770 (A/C)	A	0.585/0.539	1.21 (1.12-1.31)	$1.78x10^{-6}$	0.548/0.529	1.08 (0.98-1.19)	0.13	0.470/0.454	1.07 (0.96-1.20)	0.24	0.486/0.473	1.05 (0.93-1.19)	0.44	0.20	$2.61x10^{-5}$
2	*MYT1L*	rs4853946 (A/G)	A	0.555/0.539	1.19 (1.10-1.28)	$6.41x10^{-6}$	0.524/0.519	1.02 (0.92-1.12)	0.71	0.536/0.547	0.96 (1.06-0.87)	0.42	0.552/0.555	0.99 (1.01-0.97)	0.22	0.84	$2.73x10^{-4}$
8	*SLC30A8*	rs3019885 (G/T)	T	0.510/0.449	1.27 (1.18-1.37)	$1.24x10^{-10}$	0.462/0.422	1.08 (0.99-1.19)	0.09	0.577/0.553	1.1 (0.99-1.23)	0.086	0.539/0.572	0.87 (0.76-1.00)	0.045	0.010	$2.32x10^{-10}$
9	*C9orf92*	rs7044238 (C/T)	C	0.375/0.335	1.19 (1.11-1.29)	$9.60x10^{-6}$	0.345/0.351	0.98 (0.88-1.08)	0.64	0.669/0.656	1.06 (0.94-1.19)	0.32	0.644/0.629	1.07 (0.92-1.24)	0.37	0.52	$4.26x10^{-4}$
12	*LRP1*	rs1466535 (C/T)	C	0.679/0.634	1.22 (1.13-1.32)	$9.99x10^{-7}$	0.679/0.653	1.12 (1.02-1.23)	0.02	0.677/0.648	1.14 (1.02-1.28)	0.026	0.610/0.583	1.12 (0.98-1.28)	0.10	0.0042	$2.86x10^{-9}$
13	*GPC6*	rs2892667 (A/G)	G	0.327/0.287	1.21 (1.12-1.31)	$2.32x10^{-6}$	0.292/0.308	0.93 (0.84-1.03)	0.17	0.301/0.299	1.01 (0.92-1.11)	0.84	0.329/0.334	0.98 (1.09-0.88)	0.72	0.60	$1.73x10^{-4}$
14	*BMP4*	rs2071047 (C/T)	C	0.628/0.587	1.19 (1.10-1.28)	$6.05x10^{-6}$	0.591/0.593	0.99 (0.90-1.09)	0.65	0.618/0.633	0.93 (1.05-0.83)	0.23	0.642/0.632	1.06 (0.90-1.25)	0.48	0.57	$3.51x10^{-4}$
19	*ZNF665*	rs11666426 (C/T)	C	0.442/0.400	1.19 (1.11-1.29)	$5.73x10^{-6}$	0.404/0.413	0.96 (0.88-1.06)	0.41	0.615/0.610	1.03 (0.91-1.17)	0.64	0.655/0.644	1.09 (0.96-1.23)	0.36	0.47	$3.36x10^{-4}$

Results of wet-lab and in-silico replication studies for SNPs with P<1x10-5 in the discovery study. Replication study data were combined using Fishers method. Bonferroni adjusted P-value threshold for significance 0.0056 (9 SNPs). Results listed in chromosome order. The risk allele is that observed in the discovery study. P-values are for two-tailed Cochran-Armitage trend tests. FA = allele frequency in affected (AAA), FC = allele frequency in controls.

Table S6. rs1466535 C (risk) allele frequencies for contributing cohorts.

		AAA		Controls	
	Centre	n	rs1466535[C]	n	rs1466535[C]
Discovery Study	Belfast				
	Chichester	58	0.707		
	Kings College, London				
	Leeds	319	0.646		
	Leicester	778	0.683		
	Otago	129	0.625		
	St Georges, London	70	0.707		
	UKSAT	262	0.700		
	Western Australia	250	0.696		
	WTCC2*:			5435	0.634
Replication study	Belfast	228	0.638	244	0.631
	Chichester	190	0.668		
	Kings College, London	210	0.698		
	Leeds	27	0.714		
	Leicester	152	0.711	761	0.658
	Otago	623	0.679	515	0.636
	St Georges, London	24	0.646		
	UKSAT	90	0.661		
	Western Australia	35	0.706	664	0.661

rs1466535 C (risk) allele frequencies in the individual sample cohorts contributing to the discovery and replication studies. Numbers stated are those following sample and genotyping quality control. UKSAT = United Kingdom Small Aneurysm Trial, WTCCC2 = Wellcome Trust Case Control Consortium. *Controls from the WTCCC2 study were not screened for AAA. The frequencies for the in-silico replication data and the follow-up studies are shown in Table 3.

Table S7. Association of rs1466535 with AAA adjusted for cardiovascular risk factors.

Risk factor	n AAA/n controls	OR (95% CI)	P
CAD	969/177	1.13 (1.04-1.24)	0.0050
Smoking history	2444/1122	1.12 (1.02-1.22)	0.018
Hyperlipidaemia	1184/579	1.15 (1.06-1.26)	0.0013
Diabetes Mellitus	307/181	1.12 (1.03-1.22)	0.0061

Adjustment for cardiovascular risk factors in combined data from both the discovery and replication studies (where available) for rs1466535. Coronary Artery Disease (CAD) was defined as a history of previous myocardial infarction or previous/current history of angina pectoris. Smoking history was defined as current or previous tobacco use. Hyperlipidaemia was defined as treatment for, or, self reported hyperlipidaemia. Diabetes Mellitus includes both type 1 and type 2. The adjusted analyses were performed using logistic regression analyses based upon genotypic effect with each risk factor added as a covariate to separate analyses.

Table S8: Association of rs1466535 in GWAS of Diabetes, hyperlipidaemia and hypertension.

Type 2 Diabetes Mellitus	n cases/n controls	rs1466535 [C] frequency	OR (95% CI)	P
Type 2 Diabetes Mellitus	7862/35277	0.581-0.701	0.98 (0.94-1.03)	0.45
Hyperlipidaemia	**n**		**z-score**	**P**
Total cholesterol	100184		0.371	0.71
High-density lipoprotein cholesterol	99900		0.296	0.77
Low-density lipoprotein cholesterol	94454		-0.132	0.90
Triglycerides	96598		-0.565	0.57
Blood Pressure and Hypertension	**n**	**rs1466535 [C] frequency**	**beta (SE)**	**P**
Systolic blood pressure	34210	0.681	0.22 (0.14)	0.11
Diastolic blood pressure	34206	0.681	0.19 (0.09)	0.04
Hypertension	19883 cases/10105 controls	0.665	0.041 (0.026)	0.12

Association of rs1466535 with type 2 Diabetes Mellitus, hyperlipidaemia, and hypertension in GWAS for these traits. Full details of the methods used in these analyses have previously been reported.[15-17] All lipid traits, systolic blood pressure and diastolic blood pressure were analysed as continuous traits. For the lipid traits effect size estimate is given as a z-score. Allele frequencies were not available for the lipid traits and the allele frequency for Type 2 Diabetes Mellitus is the range of frequencies observed in the 7 studies contributing to this analysis.

Acknowledgments

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