Supplemental Data

A Sequence Variant Associated with Sortilin-1 (*SORT1*) on 1p13.3 is Independently Associated with Abdominal Aortic Aneurysm

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Study Cohort Descriptions

NZ AAA Genetics Study: The Vascular Research Consortium of New Zealand (www.vrcnz.org), recruited New Zealand men and women with a proven history of AAA (infra-renal aortic diameter ≥ 3cm proven on ultrasound or CT scan). Approximately 80% had undergone surgical AAA repair (typically AAA's > 50 mm in diameter). The vast majority of cases (>97%) were of Anglo-European ancestry as reported previously (1, 2). The control group underwent an abdominal ultrasound scan to exclude (>25mm) concurrent abdominal aortic aneurysm and Anglo-European ancestry was required for inclusion. Controls were also screened for peripheral artery disease (ankle brachial index), carotid artery disease (ultrasound) and other cardiovascular risk factors (Supplementary Table S1).

WTCCC Aneurysm Consortium: The Aneurysm Consortium recruited cases of AAA from centres across the United Kingdom, New Zealand and Western Australia. Only the UK cases were used in this study to prevent overlap with the NZ and Australian case groups. Cases were defined as an infra-renal aortic diameter ≥ 3cm proven on ultrasound or CT scan. Controls were taken from the WTCCC2 common control group (1, 3) and were therefore unscreened for AAA.

Iceland: Icelandic individuals with AAA (defined as infra-renal aortic diameter ≥ 30 mm) were recruited from a registry of individuals who were admitted at Landspitali University Hospital, in Reykjavik, Iceland, 1980 – 2006. AAA patients were either followed up or treated by intervention for emergency repair of symptomatic or ruptured AAA or for an elective repair by surgery or endovascular intervention. Subjects with AAA were enrolled as part of the CVD genetics program at deCODE. The Icelandic controls used were selected from among individuals who have participated in various GWA studies and who were recruited as part of genetic programs at deCODE. Individuals with known cardiovascular disease were excluded as controls (2) but controls were unscreened for AAA.

The Netherlands: The AAA sample set from Utrecht was recruited in 2007-2009 from eight centres in The Netherland (2), mainly when individuals visited their vascular surgeon in the polyclinic or, in rare cases, during hospital admission for elective or emergency AAA surgery. An AAA was defined as an infrarenal aorta ≥ 30 mm. The sample set comprised 89.9% males, with a mean AAA diameter of 58.4 mm, 61.7% had received surgery, of which 8.1 % was after rupture. The Dutch controls used in the AAA GWAS were recruited as part of the Nijmegen Biomedical Study and the Nijmegen Bladder Cancer Study (seehttp://dceg.cancer.gov/icbc/membership.html).

Western Australia, The Health in Men Study (HIMS): is a population-based randomized trial of screening for abdominal aortic aneurysms (AAAs) conducted in Perth, Western Australia in 1996–99. Men over 65 years of age were identified from the electoral roll and a randomized sample of 12,203 underwent baseline aortic ultrasound screening. The greatest transverse and antero-posterior diameter of the infra-renal aorta was measured using a Toshiba Capasee ultrasound machine with a 3.75 MHz probe (Toshiba Australia, North Ryde, NSW). The baseline and follow-up epidemiological and clinical measurements have been described previously (4). The 750 individuals examined in this study were a sub-set of the HIMS sample, with the 377 cases having a mean infra-renal aortic diameter of 36mm and the 373 controls of 21mm (5).

LEeds Aneurysm Development Study (LEADS), Leeds, United Kingdom: The Leads Aneurysm Development Study recruited both men and women, of Caucasian ethnic origin, aged ≥ 55 years. Other uses of this study have been described elsewhere (6, 7). AAA cases were recruited from patients undergoing routine ultrasound surveillance for small AAA (3.0 to 5.4 cm) and patients attending for elective surgical repair of AAA within the Leeds Teaching Hospitals NHS Trust; AAA was defined using ultrasonography as an AAA ≥ 3 cm in the maximum anterior-posterior diameter.
Age-matched controls were recruited from a variety of sources comparable with the initial source of referral of the AAA case, including Vascular Surgery and other medical and surgical specialty out-patients departments. Additional controls were recruited through community discussion groups and others self-referred through 'word-of-mouth' from study participants. Controls underwent the same investigation protocol as cases, including abdominal ultrasound to exclude the presence of AAA – those with a normal aortic diameter after age 65 years were assumed to be aneurysm free for life. Exclusion criteria included participants of non-Caucasian ethnic origin, aged < 65 years with uncured malignancy, recent (< 3 months) operation and active inflammatory conditions**.**

Danville, Pennsylvania, USA: AAA patients were enrolled through the Geisinger Clinic Department of Vascular Surgery at Geisinger Medical Center, Danville, PA. Details of this case-control set have been reported previously (8), and the samples have been used in previous association studies (2, 8). AAA cases were defined as infrarenal aortic diameter ≥ 30 mm as revealed by abdominal imaging. Approximately 20% of individuals with AAA had a family history of AAA. An unselected control group was obtained through the Geisinger MyCode® Project, a cohort of Geisinger Clinic primary care patients recruited for genomic studies. The MyCode® controls were matched for age distribution and sex to the Geisinger Vascular Clinic AAA cases. Based on electronic medical records, controls had no ICD-9 codes for AAA in their records, but they were not screened by ultrasonography for AAA. Both cases and controls from the Geisinger Clinic were of European descent.

Belgium and Canada: These sample-sets, in which all individuals were of European descent, include individuals with AAA who were admitted either for emergency repair of ruptured AAA or for an elective surgery to the University Hospital of Liege (Liege, Belgium) and to Dalhousie University Hospital (Halifax, Canada). AAA was defined as an infrarenal aortic diameter ≥ 30 mm. Details of these case-control sets have been reported previously (9, 10). Thirty-five individuals were diagnosed with AAA using ultrasonography and did not undergo surgery either because of old age or because the aneurysm was relatively small. Approximately 40% of individuals with AAA had a family history of AAA. Control samples (51% males) were obtained from spouses of individuals with AAA or from individuals admitted to the same hospitals for reasons other than AAA. Controls had no known AAA, but they were not screened by ultrasonography for AAA.

The Mayo eMERGE phase II cohort, consists of 6916 unique patients, the majority (>95%) of whom are of European ancestry. The participants included peripheral arterial disease cases and controls, venous thromboembolism cases and controls, resistant hypertension cases and controls and pancreatic cancer controls. Cases of abdominal aortic aneurysm (AAA) were ascertained as follows. Patients with billing codes for AAA or any procedure codes for open or endovascular AAA repair were first identified. AAA case status was confirmed by presence of distal, infrarenal or juxtarenal abdominal aortic anteroposterior diameter ≥3 cm, measured with

ultrasound, conventional or angiography of computed tomography or magnetic resonance, or the presence of postoperative change of abdominal aortic aneurysm repair on imaging. AAA controls were defined based on absence of billing or procedure codes for AAA.

1 Bown, M.J., Jones, G.T., Harrison, S.C., Wright, B.J., Bumpstead, S., Baas, A.F., Gretarsdottir, S., Badger, S.A., Bradley, D.T., Burnand, K. et al. (2011) Abdominal aortic aneurysm is associated with a variant in low-density lipoprotein receptor-related protein 1. Am. J. Hum. Genet., 89, 619-627.

2 Gretarsdottir, S., Baas, A.F., Thorleifsson, G., Holm, H., den Heijer, M., de Vries, J.P., Kranendonk, S.E., Zeebregts, C.J., van Sterkenburg, S.M., Geelkerken, R.H. et al. (2010) Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. Nat. Genet., 42, 692-697.

3 Harrison, S.C., Smith, A.J., Jones, G.T., Swerdlow, D.I., Rampuri, R., Bown, M.J., Folkersen, L., Baas, A.F., de Borst, G.J., Blankensteijn, J.D. et al. (2012) Interleukin-6 receptor pathways in abdominal aortic aneurysm. Eur. Heart. J. DOI:10.1093/eurheartj/ehs354

4 Norman, P.E., Flicker, L., Almeida, O.P., Hankey, G.J., Hyde, Z. and Jamrozik, K. (2009) Cohort Profile: The Health In Men Study (HIMS). Int. J. Epidemiol., 38, 48-52.

5 Jones, G.T., Thompson, A.R., van Bockxmeer, F.M., Hafez, H., Cooper, J.A., Golledge, J., Humphries, S.E., Norman, P.E. and van Rij, A.M. (2008) Angiotensin II type 1 receptor 1166C polymorphism is associated with abdominal aortic aneurysm in three independent cohorts. Arterioscler. Thromb. Vasc. Biol., 28, 764-770.

6 Scott, D.J., Prasad, P., Philippou, H., Rashid, S.T., Sohrabi, S., Whalley, D., Kordowicz, A., Tang, Q., West, R.M., Johnson, A. et al. (2011) Clot architecture is altered in abdominal aortic aneurysms and correlates with aneurysm size. Arterioscler. Thromb. Vasc. Biol., 31, 3004-3010.

7 Parry, D.J., Al-Barjas, H.S., Chappell, L., Rashid, S.T., Ariens, R.A. and Scott, D.J. (2010) Markers of inflammation in men with small abdominal aortic aneurysm. J. Vasc. Surg., 52, 145-151.

8 Elmore, J.R., Obmann, M.A., Kuivaniemi, H., Tromp, G., Gerhard, G.S., Franklin, D.P., Boddy, A.M. and Carey, D.J. (2009) Identification of a genetic variant associated with abdominal aortic aneurysms on chromosome 3p12.3 by genome wide association. J. Vasc. Surg., 49, 1525-1531.

9 Helgadottir, A., Thorleifsson, G., Magnusson, K.P., Gretarsdottir, S., Steinthorsdottir, V., Manolescu, A., Jones, G.T., Rinkel, G.J., Blankensteijn, J.D., Ronkainen, A. et al. (2008) The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat. Genet., 40, 217-224.

10 Ogata, T., Shibamura, H., Tromp, G., Sinha, M., Goddard, K.A., Sakalihasan, N., Limet, R., MacKean, G.L., Arthur, C., Sueda, T. et al. (2005) Genetic analysis of polymorphisms in biologically relevant candidate genes in patients with abdominal aortic aneurysms. J. Vasc. Surg., 41, 1036-1042.

Supplementary Table S1. Demographic and clinical features of the New Zealand AAA cases control populations.

	GWAS Discovery Cohort		NZ Validation Cohort		Discovery P-value	Validation P-value	Combined P-value
	Controls n=608	AAA n=612	Controls n=1812	AAA n=713			
Age (years)	67.6 ± 6.6	74.1 ± 7.7	68.0 ± 10.0	74.1 ± 8.2	<0.0001	<0.0001	<0.0001
Sex (% male)	74.1	77.4	62.2	81.2	0.18	<0.0001	<0.0001
Infrarenal aortic diameter (mm)	19.8 ± 2.2	58.4 ± 16.1	19.2 ± 3.5	54.8 ± 17.4	<0.0001	<0.0001	<0.0001
Body Mass Index	26.0 ± 3.6	25.4 ± 6.8	27.5 ± 4.8	26.6 ± 5.7	0.12	0.0004	0.0001
Hypertension (%)	27.4	56.9	50.8	58.6	<0.0001	0.0002	<0.0001
Dyslipidemia (%)	27.9	48.9	47.1	51.9	<0.0001	0.02	<0.0001
HDL-cholesterol (mmol/L)	1.41 ± 0.48	1.15 ± 0.38	1.28 ± 0.53	1.15 ± 0.38	<0.0001	<0.0001	<0.0001
hs-CRP, (mg/L), median (IQR)	1.4 (0.7-2.7)	4.3 (1.9-10.3)	2.9 (1.3-6.3)	3.7 (1.8-7.5)	<0.0001	<0.0001	<0.0001
Diabetes (%)	3.6	11.5	16.2	9.9	<0.0001	<0.0001	0.04
Smoking (% mild, moderate, heavy)	19, 15, 13	12, 22, 49	14, 19, 33	12, 23, 48	<0.0001	<0.0001	<0.0001
Coronary artery disease (%)*	0	37.3	39.4	42.6	<0.0001	0.12	<0.0001
Peripheral vascular disease (%)	0	17.8	39.1	18.7		<0.0001	<0.0001
Any arterial disease	0	48.4	69.7	52.4	<0.0001	<0.0001	0.68
Venous disease (%)	30.7	26.8	28.6	31.7	0.13	0.10	0.48

*While both control groups were free of AAA, the discovery cohort controls were also free of a history of arterial disease in contrast to the validation controls for whom over two thirds had a history of symptomatic arterial disease.

Supplementary Table S2. Genotyping of dyslipidemia and CAD genetic markers in the NZ AAA GWAS discovery population

Chr	Gene locus	Lead SNP	Trait (Secondary trait)	Position (build 37.3)	Allele	Control MAF	Case MAF	AAA OR	AAA 95% CI	AAA p-values
1	*PCSK9*	rs11206510	CAD	55496039	C	0.19	0.20	1.08	0.88 - 1.33	0.47
		rs2479409	LDL (TC)	55504650	G	0.38	0.36	0.95	0.81 – 1.12	0.56
		rs2479394	AAA	55486064	C	0.32	0.25	0.70	0.59 - 0.84	8.4×10^{-5}
	PPAB2B	rs17114036	CAD	56962821	G	0.10	0.08	0.79	0.59 – 1.07	0.13
		rs1261411	AAA	57017739	T	0.43	0.38	0.80	0.68 - 0.95	8.2×10^{-3}
	ANGPTL3	rs2131925	TG (TC, LDL)	63025942	G	0.34	0.35	1.04	0.88 - 1.23	0.63
	SORT1	rs599839	CAD AAA	109822166	G	0.25	0.17	0.66	0.54 - 0.80	2.5×10^{-5}
		rs629301	LDL (TC, HDL)	109818306	G	0.24	0.19	0.73	0.60 - 0.89	1.8×10^{-3}
		rs12740374	*	109817590	T	0.24	0.18	0.70	0.58 – 0.86	4.3×10^{-4}
	MOSC1	rs2642442	TC (LDL)	220973563	C	0.32	0.31	0.96	0.81 - 1.15	0.68
		rs17649913	AAA	220983402	G	0.23	0.17	0.72	0.59 - 0.88	1.2×10^{-3}
	MIA3	rs17465637	CAD	222823529	A	0.30	0.27	0.85	0.71 - 1.03	0.08
	GALNT2	rs4846914	HDL (TG)	230295691	G	0.38	0.40	1.07	0.91 - 1.26	0.41
2	*APOB*	rs1367117	LDL (TC)	21263900	A	0.34	0.34	1.01	0.84 - 1.23	0.89
		rs1042034	TG (HDL)	21225281	C	0.21	0.22	1.03	0.85 - 1.25	0.76
	GCKR	rs1260326	TG (TC)	27730940	T	0.38	0.36	0.91	0.77 - 1.08	0.28
	ABCG5/8	rs4299376	LDL (TC)	44072576	G	0.30	0.34	1.22	1.02 - 1.45	0.03
	WDR12	rs6725887	CAD	203454130	C	0.13	0.14	0.93	0.73 - 1.17	0.52
	IRS1	rs2972146	HDL (TG)	227100698	G	0.33	0.31	0.92	0.78 - 1.10	0.39
		rs10933136	AAA	227184088	C	0.19	0.26	1.44	1.19 - 1.74	1.9×10^{-4}
3	*MRAS*	rs2306374	CAD	138119952	C	0.15	0.16	1.07	0.86 - 1.34	0.53
5	*HMGCR*	rs12916	TC (LDL)	74656539	A	0.39	0.41	1.09	0.93 - 1.28	0.31
	TIMD4	rs6882076	TC (LDL, TG)	156390297	T	0.38	0.37	0.94	0.79 - 1.10	0.42
6	*PHACTR1*	rs12526453	CAD	12927544	G	0.33	0.33	1.01	0.85 - 1.19	0.94
	ANKS1A	rs17609940	CAD	35034800	C	0.22	0.22	1.00	0.82 - 1.22	0.82
		rs9370138	AAA	52532308	T	0.23	0.17	0.69	0.56-0.84	2.6×10^{-4}
7	*MLXIPL*	rs17145738	TG (HDL)	72982874	T	0.13	0.13	1.03	0.81 - 1.31	0.81
	ZC3HC1	rs11556924	CAD	129450732	T	0.41	0.36	0.83	0.70 – 0.98	0.99
8	*PP1R3B*	rs9987289	HDL (TC, LDL)	9183358	A	0.07	0.08	1.22	0.90 - 1.65	0.19
	LPL	rs12678919	TG (HDL)	19844222	G	0.11	0.09	0.78	0.59 - 1.02	0.07
	TR1B1	rs2954029	TG (TC, LDL, HDL)	126490972	T	0.45	0.46	1.03	0.87 - 1.21	0.72
9	*CDKN2B-AS1*	rs4977574	CAD	22098574	A	0.51	0.46	0.80	0.68 - 0.95	0.01
	ABO	rs579459	CAD	136154168	C	0.19	0.20	1.03	0.85 – 1.26	0.75
		rs35536860	AAA	136143120	G	0.25	0.19	0.73	0.58 - 0.92	6.1×10^{-3}
10	*CXCL12*	rs1746048	CAD	44775824	T	0.13	0.14	1.10	0.87 - 1.39	0.44

	CYP17A1	rs12413409	CAD	104719096	A	0.08	0.07	0.88	0.65 - 1.18	0.39
11	*FADS1-2-3*	rs174546	TG (TC, LDL, HDL)	61569830	T	0.37	0.36	0.94	0.79 - 1.11	0.44
	APOA1	rs964184	CAD, TG (TC, LDL, HDL)	116648917	G	0.14	0.15	1.12	0.89 - 1.41	0.33
12	*SH2B3*	rs3184504	CAD	111884608	T	0.47	0.51	1.18	0.64 -0.96	0.07
	HNF1A	rs1169288	TC (LDL)	121416650	C	0.30	0.32	1.10	0.91 - 1.32	0.32
13	*COL4A1*	rs4773144	CAD	110960712	G	0.44	0.44	0.97	0.83 - 1.14	0.72
15	*LIPC*	rs1532085	HDL (TC, TG)	58683366	A	0.40	0.39	0.96	0.81- 1.13	0.62
		rs4775049	AAA	58748906	G	0.46	0.40	0.79	0.67 - 0.92	3.4×10^{-3}
	ADAMTS7	rs3825807	CAD	79089111	G	0.43	0.44	1.07	0.90 - 1.25	0.45
		rs1564499	AAA	79084808	A	0.27	0.23	0.81	0.68 - 0.98	0.03
16	*CETP*	rs3764261	HDL (TC, LDL, TG)	56993324	T	0.34	0.32	0.92	0.77 - 1.09	0.33
	LCAT	rs16942887	HDL	67928042	A	0.09	0.10	1.22	0.93 - 1.60	0.16
	HPR	rs2000999	TC (LDL)	72108093	G	0.20	0.19	0.94	0.77 - 1.16	0.57
17	*SMG6*	rs216172	CAD	2126504	C	0.34	0.33	0.94	0.80 - 1.12	0.50
	RASD1	rs12936587	CAD	17543722	A	0.48	0.45	0.91	0.78 - 1.07	0.26
	UBE2Z	rs46522	CAD	46988597	C	0.51	0.48	0.87	0.74 - 1.02	0.09
18	*LIPG*	rs7241918	HDL (TC)	47160953	G	0.18	0.19	1.08	0.88 - 1.33	0.46
19	*LDLR*	rs1122608	CAD LDL	11163601	T	0.25	0.22	0.85	0.70 -1.02	0.08
		rs3786728	AAA	11168029	C	0.25	0.22	0.82	0.67- 0.99	0.04
	APOE	rs4420638	LDL (TC, TG)	45422946	G	0.17	0.21	1.29	1.06 -1.59	0.01
20	*PLTP*	rs6073966	HDL, TG	44570192	T	0.19	0.15	0.78	0.63 - 0.97	0.03
21	*MRPS6*	rs9982601	CAD	35599128	T	0.12	0.12	0.96	0.75 -1.22	0.73

Table S2. Genotyping of dyslipidemia and CAD genetic markers in the NZ AAA GWAS discovery population. The leading SNPs in each candidate locus are listed. The associated phenotypes for each SNP are coronary artery disease (CAD), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglycerides (TG). In addition, the leading aneurysm (AAA) SNP ($p<0.05$) in these loci is also shown. The discovery Affymetrix SNP6.0 dataset was filtered to exclude low SNP and individual call rate (<0.98). Imputation was performed using the 1000 Genome June 2011, and then imputation quality filtered (>0.9). ⁎Probable SORT1 functional SNP (1).

1. Musunuru, K., Strong, A., Frank-Kamenetsky, M., Lee, N.E., Ahfeldt, T., Sachs, K.V., Li, X., Li, H., Kuperwasser, N., Ruda, V.M. *et al.* (2010) From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. *Nature*, **466**, 714-719.

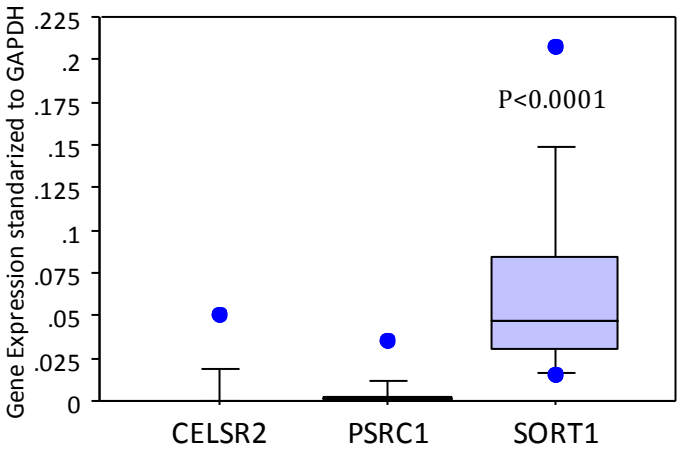
Supplementary Table S3. Validation genotyping of putative genetic markers in NZ AAA populations.

Locus/leading SNP	Group	Allele	Allele Odds Ratio (95%CI)	p-value	HWE
PCSK9; 1p32, rs2479394		T>C	C		
NZ discovery	Case Control	297 (0.258) 378 (0.326)	0.72 (0.60-0.86)	2.9 x10^{-4}	0.06 0.75
NZ validation	Case Control	403 (0.288) 1056 (0.295)	0.97 (0.84-1.11)	0.63	0.58 0.16
PPAP2B; 1p22, rs1261411		A>G	G		
NZ discovery	Case Control	455 (0.397) 474 (0.419)	0.91 (0.77-1.07)	0.28	0.002 0.66
NZ validation	Case Control	567 (0.411) 1408 (0.402)	1.04 (0.92-1.18)	0.56	0.10 0.08
***SORT1*; 1p13.3, rs599839**		**A>G**	**G**		
NZ (GWAS) discovery	**Case Control**	**219 (0.180) 305 (0.249)**	**0.66 (0.54-0.81)**	**3.3 x10^{-5}**	**0.40 0.81**
NZ validation	**Case Control**	**272 (0.191) 848 (0.240)**	**0.75 (0.64-0.88)**	**2.4 x10^{-4}**	**0.49 0.97**
MOSC1; 1q41, rs17649913		A>G	G		
NZ discovery	Case Control	198 (0.169) 256 (0.221)	0.71 (0.58-0.88)	1.4 x10-3	0.83 0.93
NZ validation	Case Control	330 (0.236) 580 (0.207)	1.19 (1.01-1.38)	0.03	0.21 0.07
ABCG5/8; 2p21, rs4245791		T>C	C		
NZ discovery	Case Control	408 (0.348) 333 (0.301)	1.24 (1.04-1.48)	0.015	0.046 0.42
NZ validation	Case Control	490 (0.343) 1184 (0.329)	1.06 (0.94-1.22)	0.32	0.61 0.71
IRS1; 2q36, rs10933136		G>C	C		
NZ discovery	Case Control	303 (0.259) 225 (0.193)	1.46 (1.20-1.78)	1.4 x10^{-4}	0.64 0.25
NZ validation	Case Control	312 (0.219) 734 (0.206)	1.08 (0.93-1.26)	0.30	0.86 0.17
ZC3HC1; 7q32, rs11556924					
NZ discovery	Case Control	398 (0.357) 449 (0.405)	0.81 (0.69-0.97)	0.02	0.04 0.26
NZ validation	Case Control	603 (0.397) 518 (0.384)	1.06 (0.91-1.23)	0.48	0.73 0.46
***CDKN2B-AS1*; 9p21, rs4977574**		**A>G**	**G**		
NZ discovery	**Case Control**	**518 (0.446) 594 (0.489)**	**0.77 (0.65-0.91)**	**1.6 x10^{-3}**	**0.68 0.04**
NZ validation	**Case Control**	**636 (0.450) 1723 (0.479)**	**0.89 (0.79-1.01)**	**0.067**	**0.09 0.94**
ABO; 9q34, rs612169		A>G	G		
NZ discovery	Case Control	331 (0.281) 373 (0.325)	0.81 (0.68-0.96)	0.022	0.77 0.65
NZ validation	Case Control	447 (0.318) 1148 (0.323)	0.98 (0.86-1.12)	0.77	0.40 0.15
SH2B3; 12q24, rs28362508					
NZ discovery	Case Control	215 (0.193) 260 (0.233)	0.78 (0.64-0.96)	0.02	0.15 0.94
NZ validation	Case	270 (0.190)	0.93	0.40	0.38

	Control	576 (0.201)	(0.80-1.10)		0.90
***LIPC*; 15q21, rs4775049**		**G>T**	**T**		
NZ discovery	**Case**	**459 (0.405)**	**0.80**	**8.7 x10^{-3}**	**0.08**
	Control	**512 (0.460)**	**(0.68-0.95)**		**0.95**
NZ validation	**Case**	**611 (0.443)**	**0.90**	**0.10**	**0.91**
	Control	**1599 (0.469)**	**(0.79-1.02)**		**0.13**
ADAMTS7; 15q24, rs1564499		G>A	A		
NZ discovery	Case	268 (0.232)	0.76	4.9 x10^{-3}	0.65
	Control	325 (0.283)	(0.63-0.92)		0.15
NZ validation	Case	355 (0.249)	0.97	0.65	0.67
	Control	907 (0.255)	(0.84-1.12)		0.66
LDLR; 19p13, rs3786727		C>T	T		
NZ discovery	Case	317 (0.296)	0.99	0.90	0.70
	Control	322 (0.298)	(0.82-1.19)		0.68
NZ validation	Case	431 (0.311)	1.06	0.44	0.99
	Control	875 (0.299)	(0.92-1.21)		0.05
APOE; 19q13, rs4420638		A>G	G		
NZ discovery	Case	248 (0.216)	1.28	0.021	0.24
	Control	198 (0.177)	(1.04-1.58)		0.90
NZ validation	Case	291 (0.211)	1.11	0.16	0.02
	Control	676 (0.193)	(0.95-1.30)		0.04
PLTP; 20q13, rs6073966		C>T			
NZ discovery	Case	177 (0.157)	0.74	0.006	0.54
	Control	223 (0.202)	(0.59-0.92)		0.51
NZ validation	Case	236 (0.168)	1.02	0.98	0.74
	Control	466 (0.165)	(0.86-1.21)		0.39

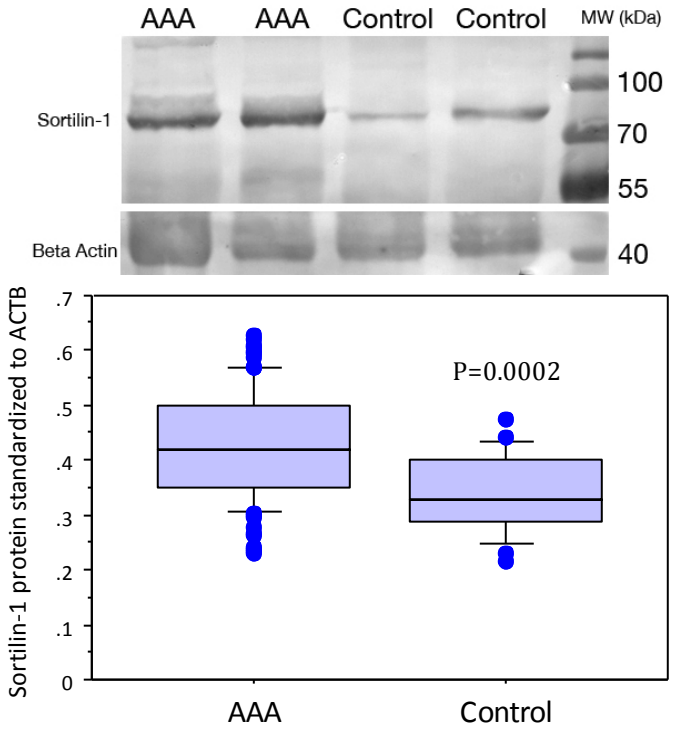
Putative SNPs from the *in silico* screen of the NZ AAA discovery cohort were re-genotyped in both the discovery and validation cohorts using allele specific Taqman probes. Three loci, 1p13.3 *SORT1*, 9p21 *CDKN2BAS1* and 15q21 *LIPC* appeared to show suggestive replicated association.

Supplementary Figure 1. Relative expression of 1p13 genes (standardized to GAPDH) in aortic aneurysm tissue.



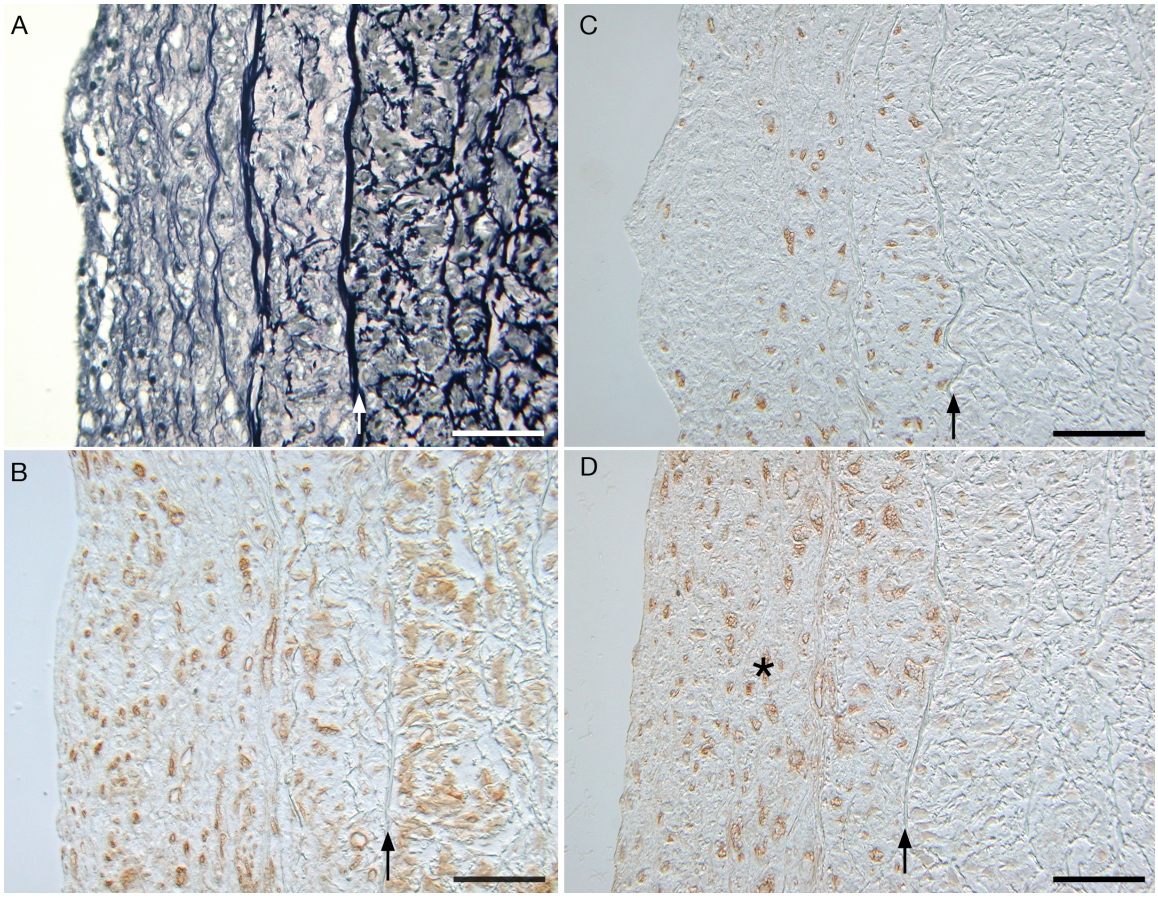
SORT1 gene expression was observed in all 11 aortic aneurysm specimens examined. Box and whiskers plots, showing median, 25th and 75th percentile (box) and 10th and 90th percentile (bars).

Supplementary Figure 2. Sortilin-1 abdominal aortic wall protein expression.



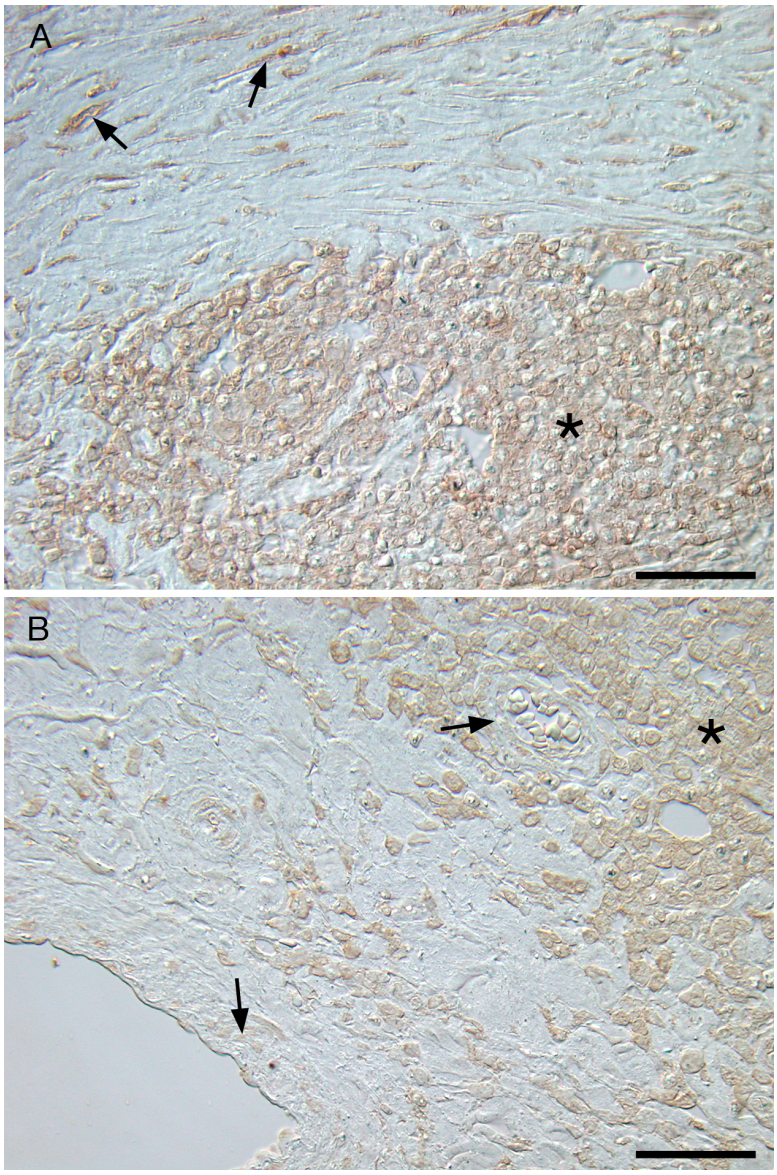
Western blot quantification of sortilin-1 (cytoplasmic domain) in control (n=20) and AAA (n=98) tissue (predicted molecular weight 92 kDa), standardized against ACTB (predicted molecular weight 42 kDa). Box and whiskers plots, showing median, 25th and 75th percentile (box) and 10th and 90th percentile (bars).

Supplementary Figure 3. Immunohistochemistry for Sortilin-1. Non-aneurysmal infrarenal aorta (male, 32 years).



(A) Verhoeff's elastic stain and van Gieson's counterstain, (B) anti-smooth muscle alpha actin, (C) anti-T-cell, (D) anti-sortilin-1 (cytoplasmic domain) immunostaining (brown) with differential interference contrast microscopy. The luminal aortic surface is to the left hand side and the internal elastic lamina (IEL), indicating the intimal medial border, is indicated by an arrow in each panel. (B) Smooth muscle cells (SMCs) and (C) T-cells within the thickened intima were immuno-positive for sortilin-1 (asterisk in D), while the medial SMCs (to the right of the IEL) were very weakly stained, near the intimal medial border or negative (deep media). Regions of intimal thickening without a significant T-cell accumulation were weakly stained for sortilin-1. Negative (no primary antibody) controls were free of background staining. Scale bars equal 50 µm.

Supplementary Figure 4. Immunohistochemistry for Sortilin-1. Anterior aortic wall from a large (11.2cm) abdominal aortic aneurysm (male, 78 years).



(A) Residual atrophic medial SMCs (arrows) and (T-cell positive) lymphoid aggregates (asterisks) were positively stained for sortilin-1. (B) SMCs surrounding adventitial vasa vasorum (arrows) were only weakly stained compared to intimal or atrophic medial SMCs, suggesting that SMC sortillin-1 expression may be associated with transformed (synthetic) rather than contractile muscle cells. Anti-sortilin-1 (cytoplasmic domain) immunostaining (brown) with differential interference contrast microscopy. Scale bars equal 50 μm.