Common variants at *SCN5A*/*SCN10A* and *HEY2* are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death

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SUPPLEMENTARY INFORMATION

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Supplementary Table 1: Summarized clinical information on 1,114 patients with Brugada syndrome

Clinical Centre	*n*	*Males*	*Age at diagnosis*	*Baseline Type-I ECG*	*Symptoms* [1]	*SCN5A carriers*
Nantes (FR)	422	323 (77%)	48 (+/-13)	295 (46%)	153 (36%)	71 (17%)
Pavia (IT)	126	105 (83%)	42 (+/-14)	46 (37%)	16 (13%)	20 (16%)
Amsterdam (NL)	101	84 (83%)	48 (+/-13)	46 (46%)	52 (51%)	23 (23%)
Paris (FR)	93	84 (90%)	44 (+/-13)	56 (60%)	28 (30%)	15 (16%)
Utica (US)	74	49 (66%)	42 (+/-17)	24 (32%)	41 (55%)	10 (14%)
Other Centers [2]	90	71 (79%)	44 (+/-14)	47 (52%)	42 (47%)	21 (23%)
Japan [3]	208	190 (91%)	46 (+/-15)	95 (46%)	84 (40%)	29 (14%)

[1] Ventricular tachycardia, ventricular fibrillation, syncope and near syncope

[2] Munster (DE), London (UK), Copenhagen (DK), Munich (DE), Nashville (US)

[3] Osaka, Nagasaki, Shiga

Supplementary Table 2: List of SNPs reaching genome-wide significance in the GWAS

SNP	Chromosome	Position	closest gene(s)	Risk allele	Protective allele	P-value	Odds ratio (95% CI)
rs6599240	3	38738717	*SCN10A*	A	G	1,20E-13	2.0696 [1.7076-2.5084]
rs11129801	3	38750375	*SCN10A*	G	A	2,77E-08	1.9969 [1.5645-2.5487]
rs9874633	3	38771994	*SCN10A*	A	G	1,66E-13	2.7009 [2.0742-3.5169]
rs10428132	3	38777554	*SCN10A*	T	G	6,79E-26	3.0026 [2.4465-3.6851]
rs7428167	3	38778191	*SCN10A*	T	C	1,22E-22	2.8625 [2.3191-3.5331]
rs10428168	3	38780059	*SCN10A*	T	C	2,36E-15	2.6190 [2.0636-3.3238]
rs12638572	3	38787797	*SCN10A*	A	G	2,48E-10	2.1155 [1.6773-2.6680]
rs7641844	3	38802251	*SCN10A*	A	G	3,80E-08	2.0198 [1.5722-2.5947]
rs7430439	3	38803639	*SCN10A*	G	A	1,10E-08	1.7533 [1.4460- 2.1258]
rs6599257	3	38804588	*SCN10A*	C	T	1,01E-14	2.1738 [1.7858-2.6460]
rs1268070	6	126041164	*HEY2*	C	T	5,13E-09	1.8030 [1.4795-2.1973]
rs9388451	6	126090377	*HEY2, NCOA7*	C	T	8,85E-10	1.8325 [1.5099-2.2240]

Supplementary Table 3: GWAS results for hit-SNPs from previously associated with ECG traits

SNP	Cyto Band	Nearest genes	MAF	General trait	allele_A	allele_B	cases_maf	controls_maf	tinfo	beta	se	P-value
rs846111	1p36.31	RNF207,NPHP4,CHDS,ACOT7,PLEKHG5,KLH20	0.26	QTc	G	C	0,253	0,268	0,493	-0,126	0,148	3,94E-01
rs9436640	1p31.3p31.2	NFIA	0.48	QRS	T	G	0,468	0,448	0,950	0,078	0,095	4,09E-01
rs4074536	1p13.3p11	CASQ2	0.30	QRS	T	C	0,309	0,290	1,000	0,080	0,101	4,31E-01
rs2880058	1q23.3	NOS1AP	0.26	QTc	A	G	0,358	0,337	0,893	0,146	0,103	1,56E-01
rs12143842	1q23.3	NOS1AP	0.16	QTc	C	T	0,274	0,254	1,000	0,157	0,107	1,41E-01
rs10494366	1q23.3	NOS1AP	0.33	QTc	G	T	0,399	0,365	1,000	-0,159	0,095	9,59E-02
rs16857031	1q23.3	NOS1AP	0.15	QTc	C	G	0,146	0,145	1,000	0,054	0,131	6,82E-01
rs12029454	1q23.3	NOS1AP	0.11	QTc	G	A	0,176	0,165	1,000	0,107	0,126	3,96E-01
rs4657178	1q23.3	NOS1AP	0.18	QTc	C	T	0,272	0,275	1,000	0,026	0,103	8,03E-01
rs10919071	1q24.2	ATP1B1	0.11	QTc	A	G	0,109	0,138	1,000	-0,241	0,140	8,47E-02
rs12731740	1q32.2	CD46,CD34,PLXNA2PLXNA2	0.09	Heart rate	C	T	0,115	0,101	1,000	0,127	0,149	3,94E-01
rs2745967	1q32	CD34	0.49	Heart rate	G	A	0,372	0,371	1,000	0,035	0,095	7,17E-01
rs17391905	1p32.3	C1orf185,RNF11,CDKN2C,FAF1	0.03	QRS	NA	NA	NA	NA	NA	NA	NA	NA
rs7562790	2p21	CRIM1	0.36	QRS	T	G	0,396	0,406	0,998	-0,028	0,095	7,68E-01
rs17020136	2p22.2	HEATR5B,STRN	0.23	QRS	T	C	0,213	0,182	0,998	0,206	0,119	8,32E-02
rs10865355	2p14	MEIS1	0.46/0.48*	PR	A	G	0,402	0,377	0,999	-0,064	0,099	5,14E-01
rs11897119	2p14	MEIS1	0.46	PR	T	C	0,401	0,377	0,997	0,057	0,099	5,63E-01
rs2051211	3p22.2	SCN5A,SCN10A	0.19	QRS	A	G	0,217	0,255	0,995	-0,205	0,108	5,88E-02
rs10865879	3p22.2	SCN5A,SCN10A	0.26	QRS	A	C	0,282	0,233	0,949	0,246	0,112	2,81E-02
rs11129795	3p22.2	SCN5A,SCN10A	0.25	QRS	G	A	0,284	0,233	0,960	0,255	0,111	2,18E-02
rs12053903	3p22.2	SCN5A	0.29	QTc	T	C	0,394	0,327	0,950	0,298	0,101	3,15E-03
rs3922844	3p22.2	SCN5A,SCN10A	0.26/0.68*	PR	T	C	0,233	0,298	0,967	0,344	0,107	1,29E-03
rs11708996	**3p22.2**	**SCN5A,SCN10A**	**0.17**	**PR/QRS**	**G**	**C**	**0,228**	**0,151**	**1,000**	**0,540**	**0,121**	**8,65E-06**
rs6599222	3p22.2	SCN5A,SCN10A	0.23/0.29*	PR	C	T	0,286	0,218	0,897	-0,411	0,114	3,19E-04
rs11710077	3p22.2	SCN5A,SCN10A	0.18	QRS	A	T	0,166	0,197	0,682	-0,266	0,146	6,79E-02
rs9851724	3p22.2	SCN5A,SCN10A	0.28	QRS	C	T	0,226	0,307	0,981	0,387	0,102	1,56E-04
rs6795970	**3p22.2**	**SCN5A,SCN10A**	**0.42**	**PR/QRS**	**A**	**G**	**0,668**	**0,410**	**0,968**	**-0,993**	**0,091**	**1,11E-27**
rs6798015	**3p22.2**	**SCN5A,SCN10A**	**0.38/0.06***	**PR**	**C**	**T**	**0,607**	**0,364**	**0,952**	**-0,985**	**0,093**	**3,53E-26**
rs7627552	3p22.2	SCN5A,SCN10A	0.18*	PR	NA	NA	NA	NA	NA	NA	NA	NA
rs4687718	3p14.3	TKT,PRKCD,CACNA1D	0.13	QRS	A	G	0,120	0,118	0,949	0,005	0,146	9,74E-01
rs2242285	3p14.1	LRIG-SLC25A26	0.37	QRS	A	G	0,436	0,400	0,988	-0,130	0,097	1,81E-01
rs7660702	4q22.1	ARHGAP24	0.25	PR	T	C	0,277	0,303	1,000	-0,121	0,101	2,27E-01
rs13165478	5q33	HAND1,SAP30L	0.33	QRS	G	A	0,339	0,380	0,993	-0,204	0,097	3,60E-02
rs251253	5q35.1	C5orf41,NKX2.5	0.38	PR	C	T	0,438	0,377	0,937	-0,276	0,097	4,58E-03
rs1321311	6p21.2	PI16,CDKN1A	0.31	QRS	C	A	0,267	0,248	0,986	0,083	0,106	4,35E-01
rs281868	6q22.31	C6orf204,SLC35F1,PLN,BRD7P3,ASF1A	0.48	Heart rate	G	A	0,478	0,490	0,995	-0,057	0,092	5,34E-01
rs11153730	6q22.31	C6orf204,SLC35F1,PLN,BRD7P3,ASF1A	0.48	QRS	T	C	0,470	0,463	0,982	0,020	0,094	8,30E-01
rs11970286	6q22.1-6q22.31	C6orf204,SLC35F1,PLN,BRD7P3,ASF1A	0.47	QTc	C	T	0,427	0,422	0,985	-0,001	0,094	9,89E-01
rs12210810	6q22.1-6q22.31	C6orf204,SLC35F1,PLN,BRD7P3,ASF1A	0.08	QTc	NA	NA	NA	NA	NA	NA	NA	NA
rs11154022	6q21q23.2	GJA1	0.29	Heart rate	A	G	0,337	0,339	0,998	-0,024	0,097	8,02E-01
rs9398652	6q21q23.2	GJA1	0.07	Heart rate	C	A	0,085	0,099	0,991	-0,146	0,161	3,64E-01
rs1362212	7p14.3	TBX20	0.13	QRS	G	A	0,226	0,182	0,999	0,319	0,116	6,02E-03
rs7784776	7p12.3	IGFBP3	0.48	QRS	A	G	0,430	0,420	0,984	0,067	0,097	4,87E-01
rs314370	7q22	SLC12A9,UFSP1	0.22	Heart rate	T	C	0,176	0,189	0,930	-0,128	0,122	2,94E-01
rs3807989	7q31.1	CAV1/CAV2	0.43	PR	A	G	0,471	0,401	1,000	-0,273	0,092	2,94E-03
rs2968863	7q36.1	KCNH2	0.26	QTc	C	T	0,245	0,277	0,989	-0,112	0,106	2,92E-01
rs4725982	7q36.1	KCNH2	0.18	QTc	C	T	0,221	0,204	0,955	0,124	0,117	2,90E-01
rs1733724	10q11.2	DKK2	0.23	QRS	A	G	0,260	0,238	0,996	-0,121	0,106	2,56E-01
rs7342028	10q25.2	VTI1A	0.27	QRS	G	T	0,260	0,277	0,981	-0,058	0,103	5,75E-01
rs2074238	11p15.5	KCNQ1	0.08	QTc	T	C	0,093	0,079	0,480	-0,499	0,245	4,17E-02
rs12296050	11p15.5	KCNQ1	0.23	QTc	C	T	0,180	0,196	0,780	-0,145	0,132	2,73E-01
rs12576239	11p15.5	KCNQ1	0.16	QTc	C	T	0,124	0,134	0,848	-0,136	0,146	3,52E-01
rs174547	11q12.2q13.1	FADS1	0.38	Heart rate	T	C	0,329	0,305	0,994	0,069	0,099	4,90E-01
rs4944092	11q13.5	WNT11	0.29	PR	A	G	0,291	0,307	0,609	-0,117	0,128	3,61E-01
rs17287293	12p12.1	SOX5,BCAT1	0.15	Heart rate	A	G	0,171	0,158	0,997	0,144	0,127	2,56E-01
rs11047543	12p12.1	SOX5,BCAT1	0.15	PR	G	A	0,176	0,159	1,000	0,177	0,125	1,57E-01
rs883079	12q24.21	TBX3,TBX5	0.28	QRS	C	T	0,356	0,280	1,000	-0,356	0,101	3,97E-04
rs3825214	12q24.21	TBX5	0.22	QTc	G	A	0,252	0,190	1,000	-0,367	0,115	1,38E-03
rs7312625	12q24.21	TBX3,TBX5	0.27/0.25*	PR	G	A	0,338	0,264	0,995	-0,352	0,102	5,46E-04
rs1896312	12q24.21	TBX3,TBX5	0.38	PR	C	T	0,303	0,286	0,990	-0,054	0,102	6,00E-01
rs10850409	12q24.21	TBX3,TBX5	0.32	QRS	G	A	0,278	0,269	0,969	0,031	0,104	7,69E-01
rs885389	12q24.33	GPR133	0.29	Heart rate	A	G	0,375	0,332	0,971	-0,171	0,099	8,33E-02
rs3825214	12q24.21	TBX3,TBX5	0.22	PR/QRS, QTc	G	A	0,252	0,190	1,000	-0,367	0,115	1,38E-03
rs2478333	13q12.2q13.3	SUCLA2	0.35	QTc	C	A	0,364	0,353	1,000	0,026	0,096	7,84E-01
rs1886512	13q22	KLF12	0.33	QRS	T	A	0,363	0,378	0,994	-0,072	0,094	4,45E-01
rs365990	14q11.2	MYH6,MYH7,NDNG,ZFHX2	0.31	Heart rate	A	G	0,383	0,378	0,613	0,047	0,123	7,05E-01
rs223116	14q11.2	MYH6,MYH7,NDNG,ZFHX2	0.25	Heart rate	A	G	0,265	0,253	0,770	-0,101	0,120	4,02E-01
rs11848785	14q24.2	SIPA1L1	0.30	QRS	G	A	0,296	0,270	0,991	-0,160	0,107	1,34E-01
rs8049607	16p13.13	LITAF,CLEC16A,SNN,ZC3H7A,TNFRSF16	0.49	QTc	T	C	0,484	0,481	0,940	0,018	0,099	8,58E-01
rs37062	16q21	CNOT1,GINS3,SLC38A7,GOT1	0.27	QTc	A	G	0,260	0,239	0,997	0,081	0,107	4,48E-01
rs2074518	17q11.2q12	LIG3,RFFL	0.49	QTc	C	T	0,479	0,456	0,994	0,059	0,093	5,27E-01
rs17608766	17q21	GOSR2	0.09	QRS	T	C	0,136	0,135	1,000	0,031	0,133	8,14E-01
rs9912468	17q22q23.2	PRKCA	0.42	QRS	G	C	0,473	0,454	1,000	-0,099	0,090	2,73E-01
rs17779747	17q24.3	KCNJ2	0.32	QTc	G	T	0,353	0,332	0,995	0,109	0,097	2,63E-01
rs991014	18q21.1	SETBP1	0.41	QRS	C	T	0,405	0,403	1,000	0,004	0,095	9,66E-01
rs1805128	21q22.12	KCNE1	0.03	QTc	NA	NA	NA	NA	NA	NA	NA	NA

Supplementary Table 4 : Cumulative effect of the three associated SNPs on susceptibility to Brugada syndrome, in Europe and Japan

	Europe			Japon		
Nb of at-risk alleles	% controls	% cases	OR	% controls	% cases	OR
0-1	27.8	9.7	1	40.0	15.4	1
2	35.8	21.8	1.69 [1.27-2.26]	40.9	37.0	2.35 [1.52-3.63]
3	25.5	33.6	3.69 [2.78-4.89]	15.2	30.3	5.18 [3.26-8.25]
4	9.4	26.2	7.89 [5.75-10.81]	3.7	14.4	10.14 [5.56-18.49]
5-6	1.5	8.7	19.89 [11.68-33.86]	0.1	2.9	75.00 [8.76-642.2]

Supplementary Table 5: Subset analyses testing for association with symptoms, baseline type-1 ECG and SCN5A mutation status

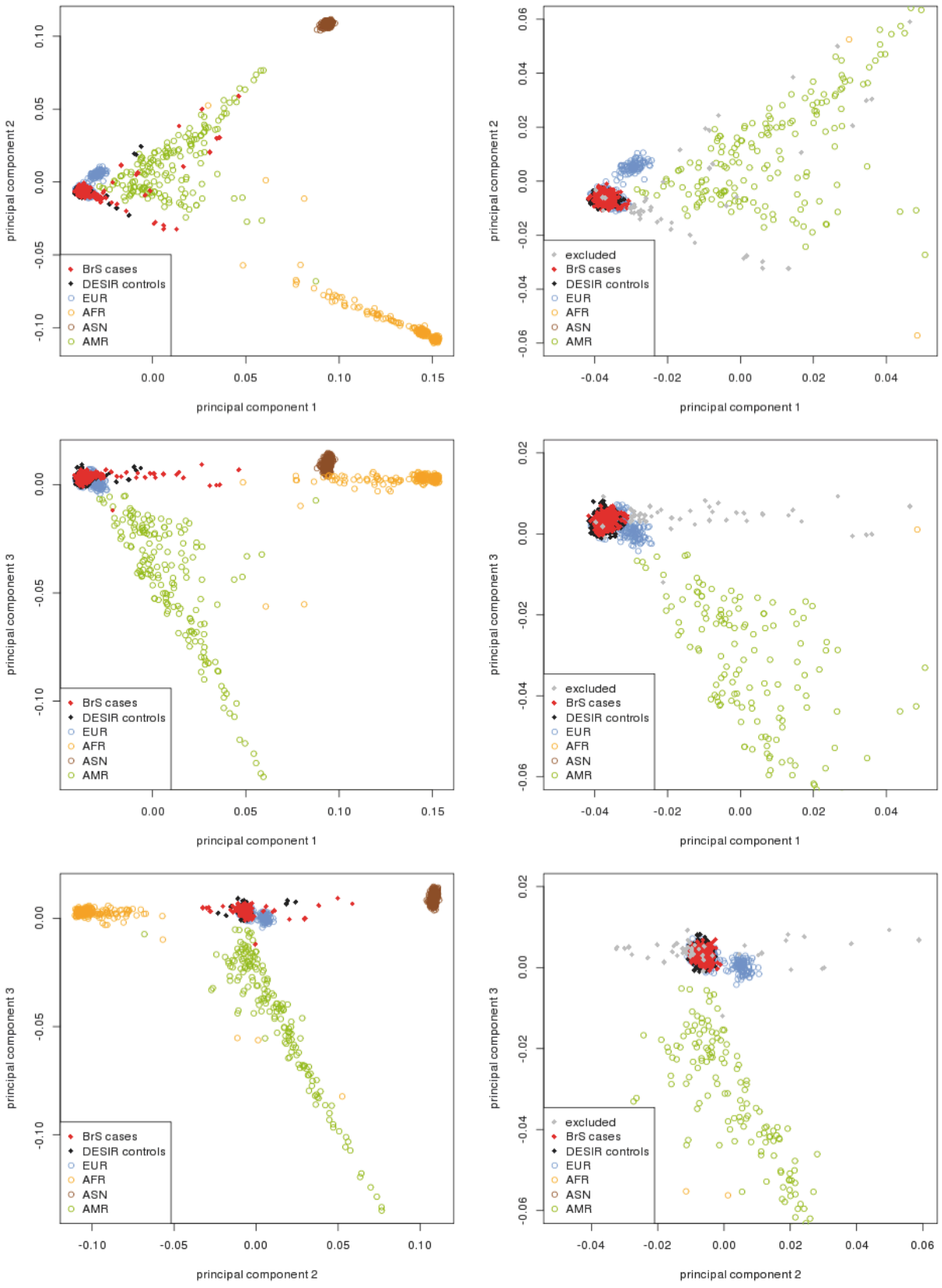
Trait	SNP	Population	Affected (PP	PR	RR)	Non aff. (PP	PR	RR)	**beta add**	**p add**
Symptoms	rs11708996_C	Europe	200	110	15	317	198	33	**-0,163**	**0,172**
		Japan	66	15	3	105	16	0	**0,630**	**0,066**
		All	266	125	18	422	214	33	**-0,074**	**0,509**
	rs10428132_T	Europe	31	138	162	76	240	232	**0,277**	**0,009**
		Japan	32	34	17	37	56	28	**-0,205**	**0,293**
		All	63	172	179	113	296	260	**0,170**	**0,065**
	rs9388451_C	Europe	48	157	123	99	240	218	**0,027**	**0,783**
		Japan	8	38	37	9	44	68	**-0,337**	**0,132**
		All	56	195	160	108	284	286	**-0,032**	**0,722**
Baseline BrS ECG	rs11708996_C	Europe	250	134	24	274	179	25	**-0,102**	**0,377**
		Japan	76	15	3	97	16	0	**0,414**	**0,228**
		All	326	149	27	371	195	25	**-0,045**	**0,682**
	rs10428132_T	Europe	46	185	179	63	198	220	**-0,003**	**0,974**
		Japan	30	43	22	40	47	24	**0,095**	**0,620**
		All	76	228	201	103	245	244	**0,020**	**0,822**
	rs9388451_C	Europe	64	189	157	86	213	189	**0,009**	**0,926**
		Japan	7	37	50	10	45	57	**0,093**	**0,678**
		All	71	226	207	96	258	246	**0,028**	**0,755**
SCN5A mutation	rs11708996_C	Europe	100	50	8	419	262	40	**-0,134**	**0,385**
		Japan	24	3	1	149	28	2	**-0,093**	**0,855**
		All	124	53	9	568	290	42	**-0,127**	**0,391**
	rs10428132_T	Europe	19	79	62	89	299	336	**-0,215**	**0,097**
		Japan	15	12	2	55	78	44	**-0,839**	**0,010**
		All	34	91	64	144	377	380	**-0,306**	**0,009**
	rs9388451_C	Europe	24	76	60	125	325	281	**0,061**	**0,633**
		Japan	2	9	17	15	73	90	**0,305**	**0,365**
		All	26	85	77	140	398	371	**0,095**	**0,423**

* PP: homozygous for the protective allele ; PR : heterozygous ; RR: homozygous for the risk alleles

Supplementary Table 6: Independent heterozygote effects for the three associated SNPs

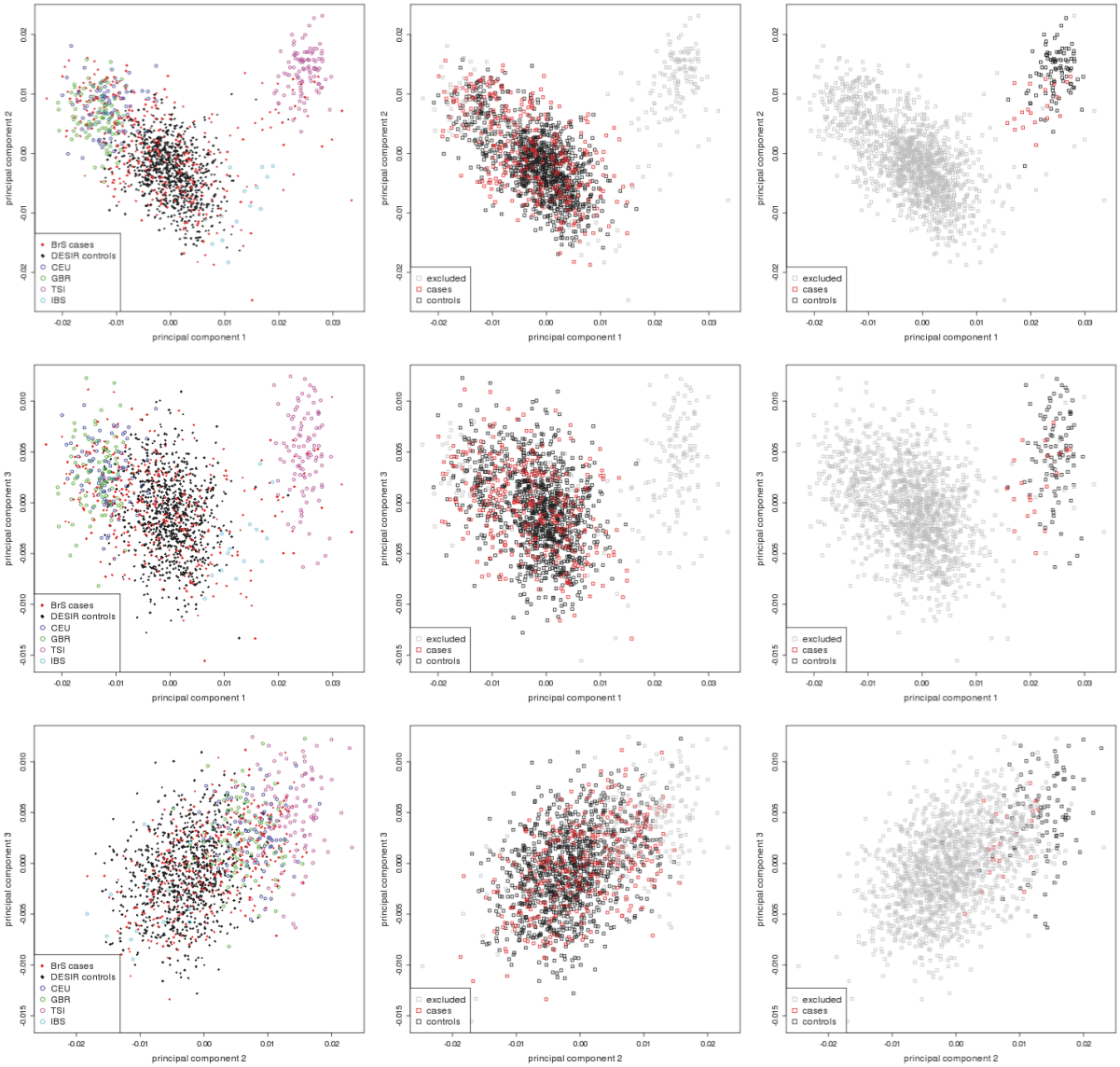
SNP	OR	Z score	p-value
rs11708996	1.01 [0.79-1.29]	0.07	9.46E-01
rs10428132	0.92 [0.79-1.07]	-1.06	2.90E-01
rs9388451	0.86 [0.74-1.01]	-1.84	6.55E-02

Supplementary Figure 1: Multidimensional scaling (MDS) identifies 42 samples of non-European descent
On the left-panels, the first 3 principal components are plotted against one another for combined genotype data from cases, D.E.S.I.R. controls, and individuals from the 1000 Genomes Project (EUR, European; AFR, African; ASN, East Asian; AMR, Admixed American). The right-panels are zoomed views from the same plots, where 42 samples of Non-European descent, which were excluded from the GWAS study, are displayed in grey.



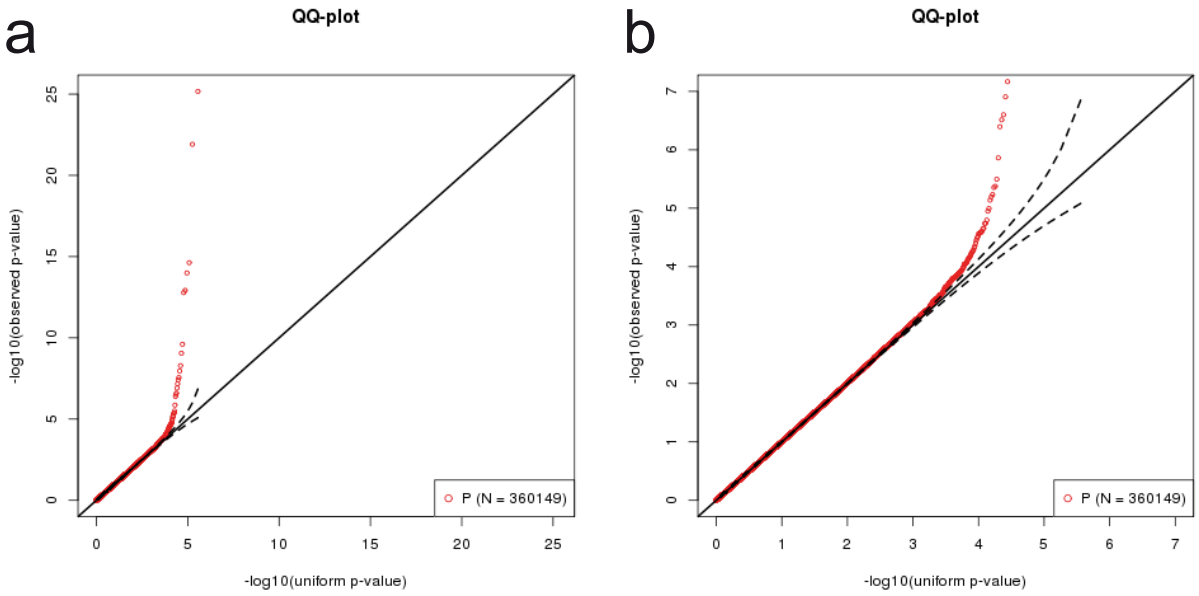
Supplementary Figure 2: MDS on samples of European ancestry defines 2 homogeneous case-control sets suitable for GWAS

MDS including genotype data of European descent individuals drawn from 1000 Genomes Project indicates, as displayed in the left-panels, that the corresponding individuals can be used as additional controls in the present study. The GWAS was conducted separately on the two homogeneous case-control groups thus identified (shown respectively on the middle- and right-panels). The association data obtained on both groups were subsequently combined in a meta-analysis, which included a total of 312 cases and 1,115 ancestry-matched controls. CEU, Utah residents (CEPH) with Northern and Western European ancestry; GBR, British from England and Scotland; TSI, Tuscan from Italy; IBS, Iberian populations from Spain.



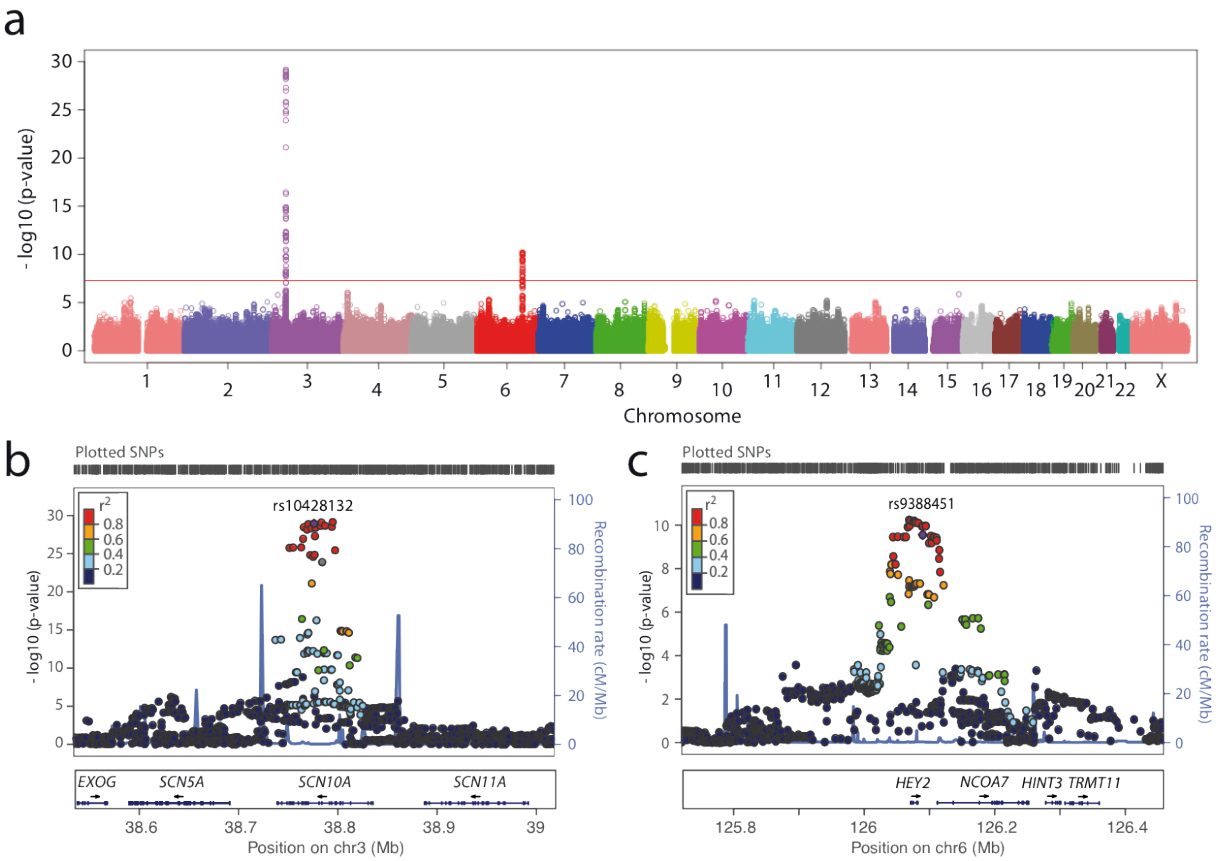
Supplementary Figure 3: Quantile-quantile plot for the genome-wide association results

(a) Q-Q plot of association results (inverse normal meta-analysis) for 360,149 SNPs in 312 cases and 1,115 ancestry-matched controls. The horizontal axis shows (–log10 transformed) expected p values while the vertical axis indicates (–log10 transformed) observed p values. Straight line indicates expected results under null hypothesis. **(b)** Zoomed view of the same Q-Q plot, indicating no widespread small differences in allele frequencies between cases and controls.



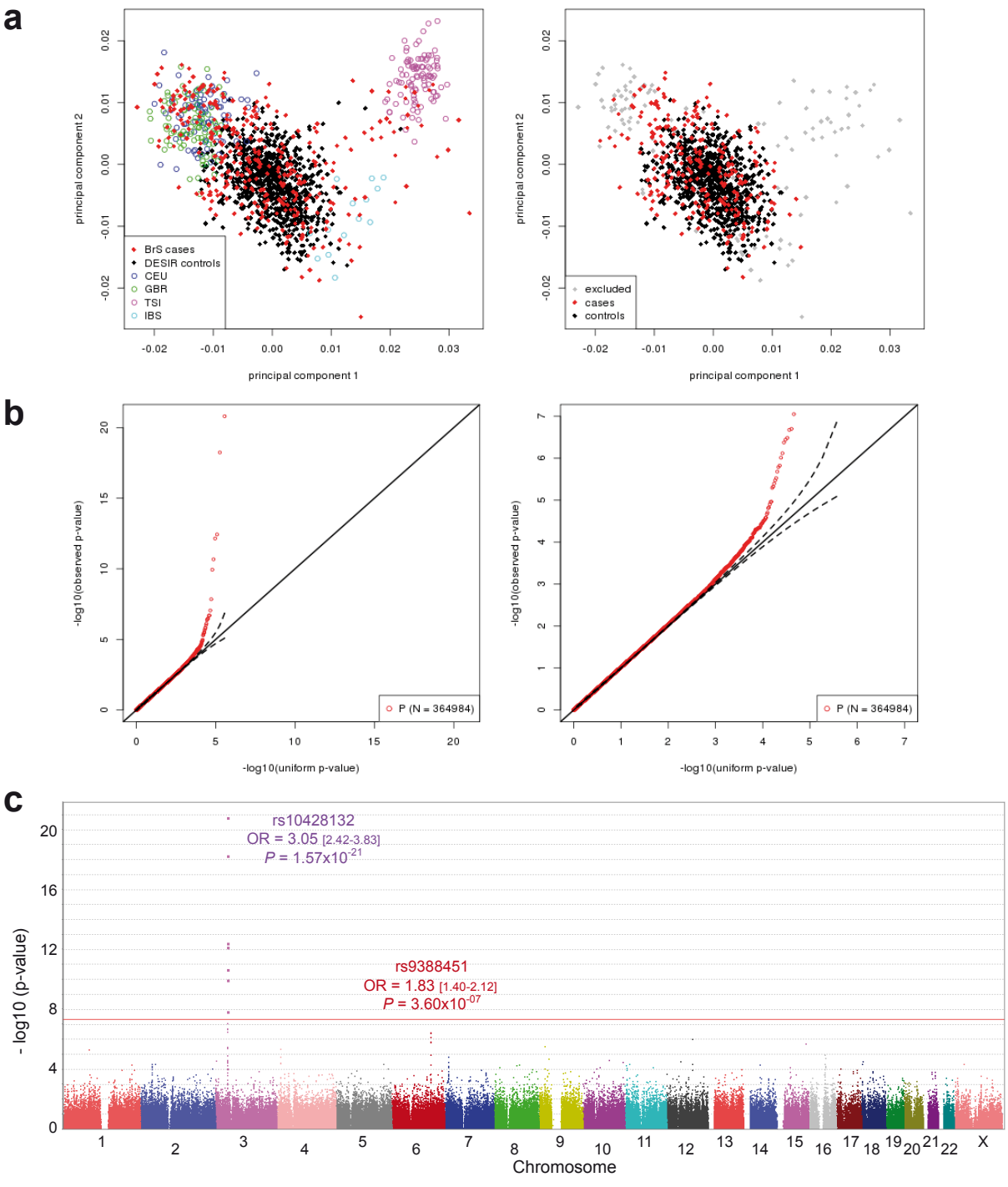
Supplementary Figure 4: Manhattan plot and association results at each significantly associated locus after genome-wide imputation of non-genotyped alleles

(**a**) Manhattan plot showing the association of SNPs with Brugada syndrome in a GWAS of 312 cases versus 1,115 controls, after imputation of the 1000 Genome Project variants (CEU population). The red horizontal line marks the threshold for genome-wide significance ($P = 5 \times 10^{-8}$). Two loci reached genome-wide significance, on chromosomes 3 and 6. (**b**) Association plots at 3q22.2 (left panel) and 6q22.32 (right panel). Each SNP is plotted with respect to its chromosomal location (x-axis) and its P value (y-axis on the left). SNPs are coloured according to their degree of linkage disequilibrium (R^2), with the leading variant highlighted with a purple square and displayed by name. The tall blue spikes indicate the recombination rate (y-axis on the right) at that region of the chromosome. The blue-outlined triangles indicate coding region SNPs. Coordinates are given according to NCBI build 37.



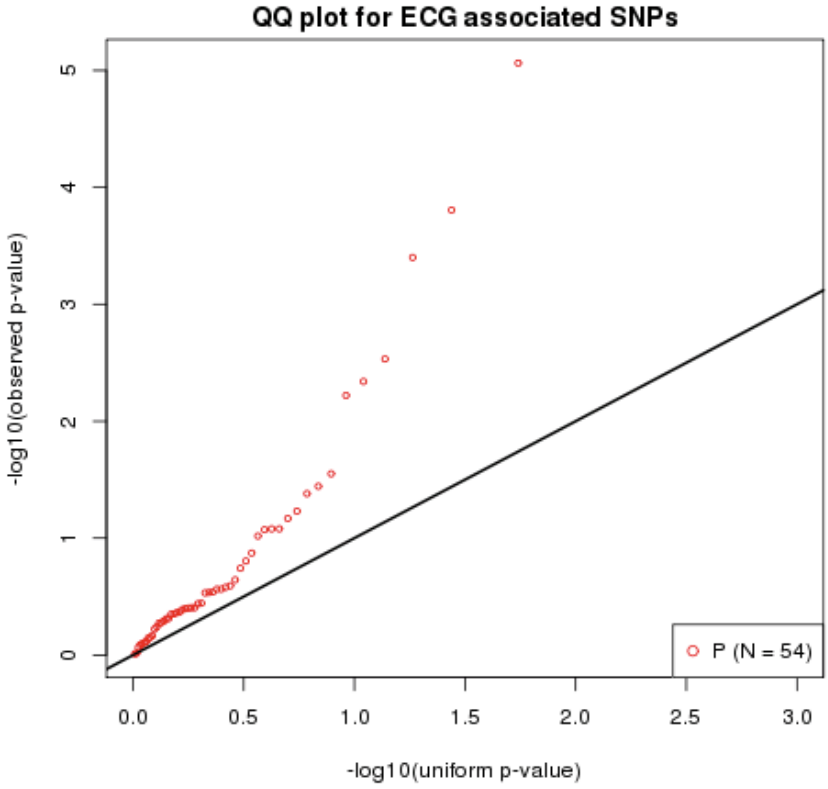
Supplementary Figure 5: Restricting the GWAS to D.E.S.I.R. controls and ancestry-matched cases with Brugada syndrome by stringent MDS criteria confirms both association hits

(a) On the left-panel, the first two principal components are plotted against one another for combined genotype data from the cases, D.E.S.I.R. controls, and European descent individuals from the 1000 Genomes Project (CEU, Utah residents (CEPH) with Northern and Western European ancestry; GBR, British from England and Scotland; TSI, Tuscan from Italy; IBS, Iberian populations from Spain). The right-panel displays the first two principal components for genotype data pertaining to the 856 D.E.S.I.R. controls and 254 cases used in the subsequent GWAS: the samples in grey were excluded from subsequent GWAS by applying stringent exclusion criteria. **(b)** The left-panel displays the Q-Q plot of association results for 364,984 SNPs in the 254 cases and the 856 ancestry-matched controls. The right-panel is a zoomed view of the same plot, indicating no widespread small differences in allele frequencies between cases and controls. **(c)** Manhattan plot showing SNP association with Brugada syndrome. The red horizontal line marks the threshold for genome-wide significance (P=5×10^{-8}).



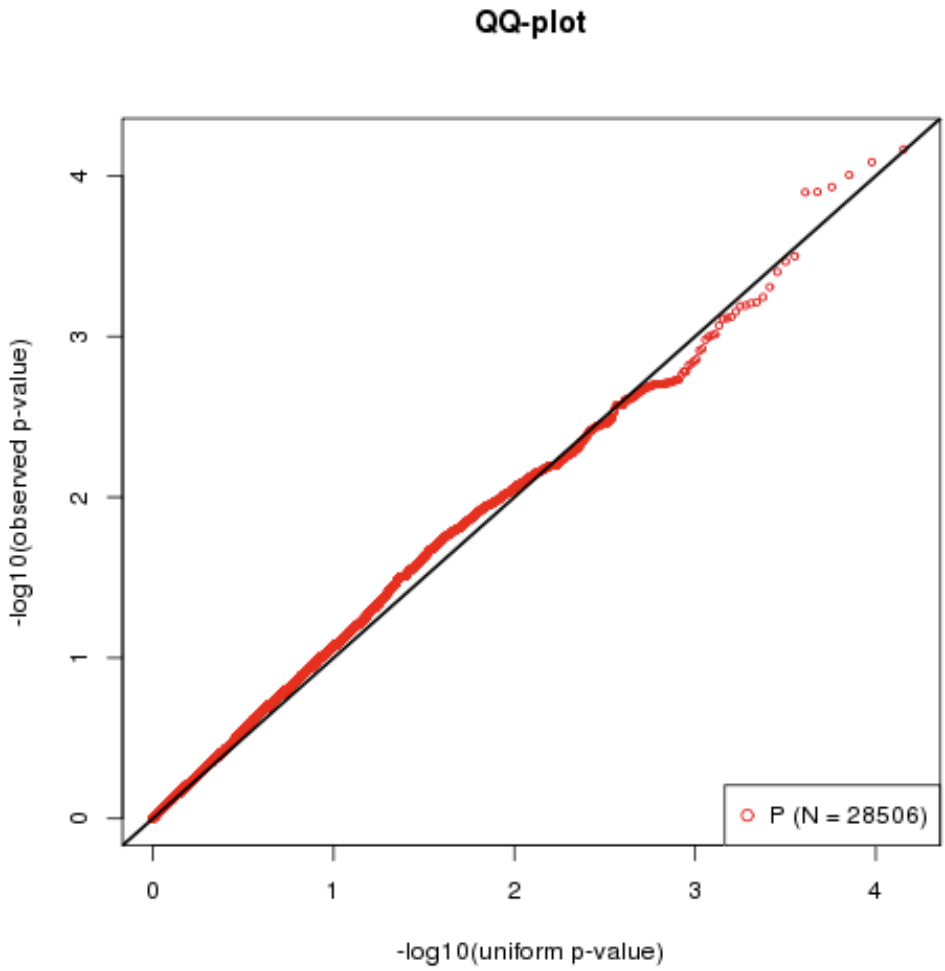
Supplementary Figure 6: Q-Q plot for ECG-associated SNPs

The analysis of 54 independent SNPs previously associated with ECG traits (after exclusion of the haplotype including rs10428132) results in a significant enrichment in association signals (P=5.0x10^{-8}). Note that, when all SNPs from the SCN5A/SCN10A locus were removed, a large decrease in statistical significance (P=0.0011) was observed. The horizontal axis shows (–log10 transformed) expected P values, the vertical axis (–log10 transformed) observed p values. The straight line indicates expected results under the null hypothesis.



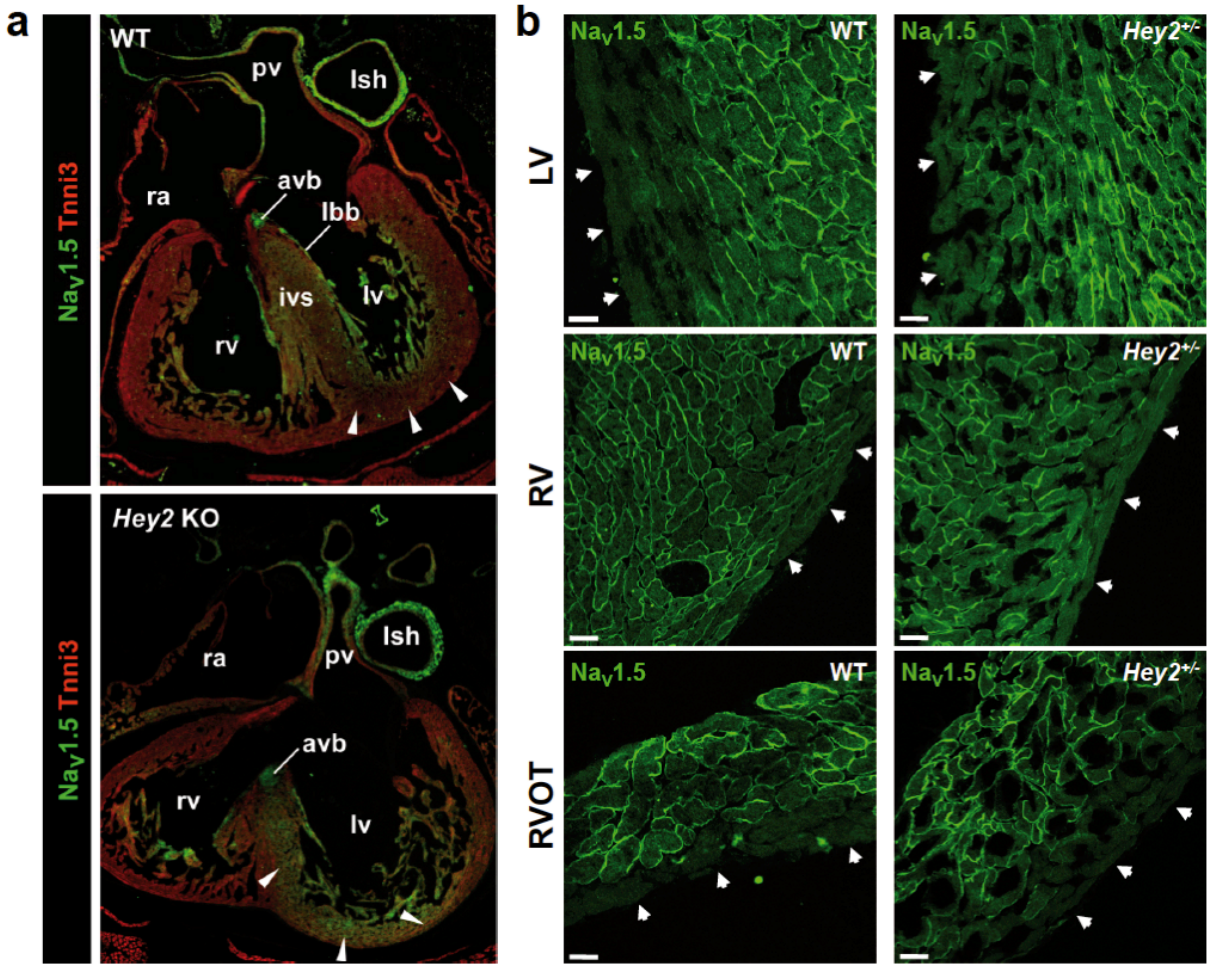
Supplementary Figure 7: Q-Q plot for SNPs located at loci harboring susceptibility genes for Brugada syndrome

The horizontal axis shows (–log10 transformed) expected p values while the vertical axis indicates (–log10 transformed) observed p values. Straight line indicates expected results under the null hypothesis.



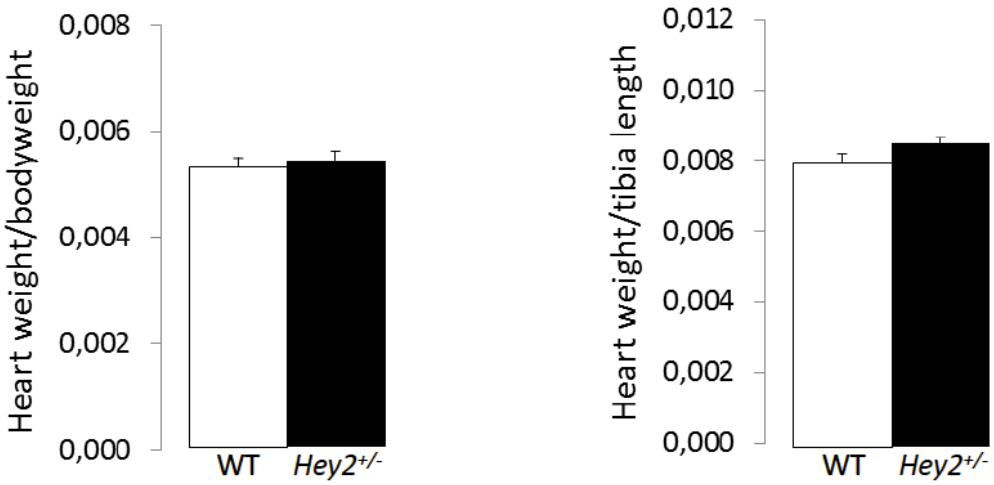
Supplementary Figure 8: $Na_V1.5$ patterning across the ventricular wall in *Hey2* knockout embryos and adult *Hey2*$^{+/-}$ hearts

(**a**) Immunohistochemical staining displaying expanded expression of $Na_V1.5$ in the compact zone of the ventricular myocardium (white arrowheads) in embryonic hearts (ED16.5) of *Hey2* knockout mice. Tnni3 (troponin I) is used as cardiomyocyte marker. Note the thinner (hypoplastic) left and right ventricular compact walls and the smaller and deformed right ventricle in knockout mice. La, left atrium; ra, right atrium; ivs, inter-ventricular septum; lv, left ventricle; rv, right ventricle; lbb, left bundle branch; avb, atrioventricular bundle; pv, pulmonary vein; lsh, left sinus horn. (**b**) Immunohistochemical staining of $Na_V1.5$ in left ventricle (LV), right ventricle (RV) and right ventricular outflow tract (RVOT) regions of adult wild-type (WT) and *Hey2*$^{+/-}$ hearts. No differences in $Na_V1.5$ distribution across the myocardial wall were detected between adult WT and *Hey2*$^{+/-}$ hearts (sub-epicardial layers are indicated by white arrowheads; scale bar: 25 µm).



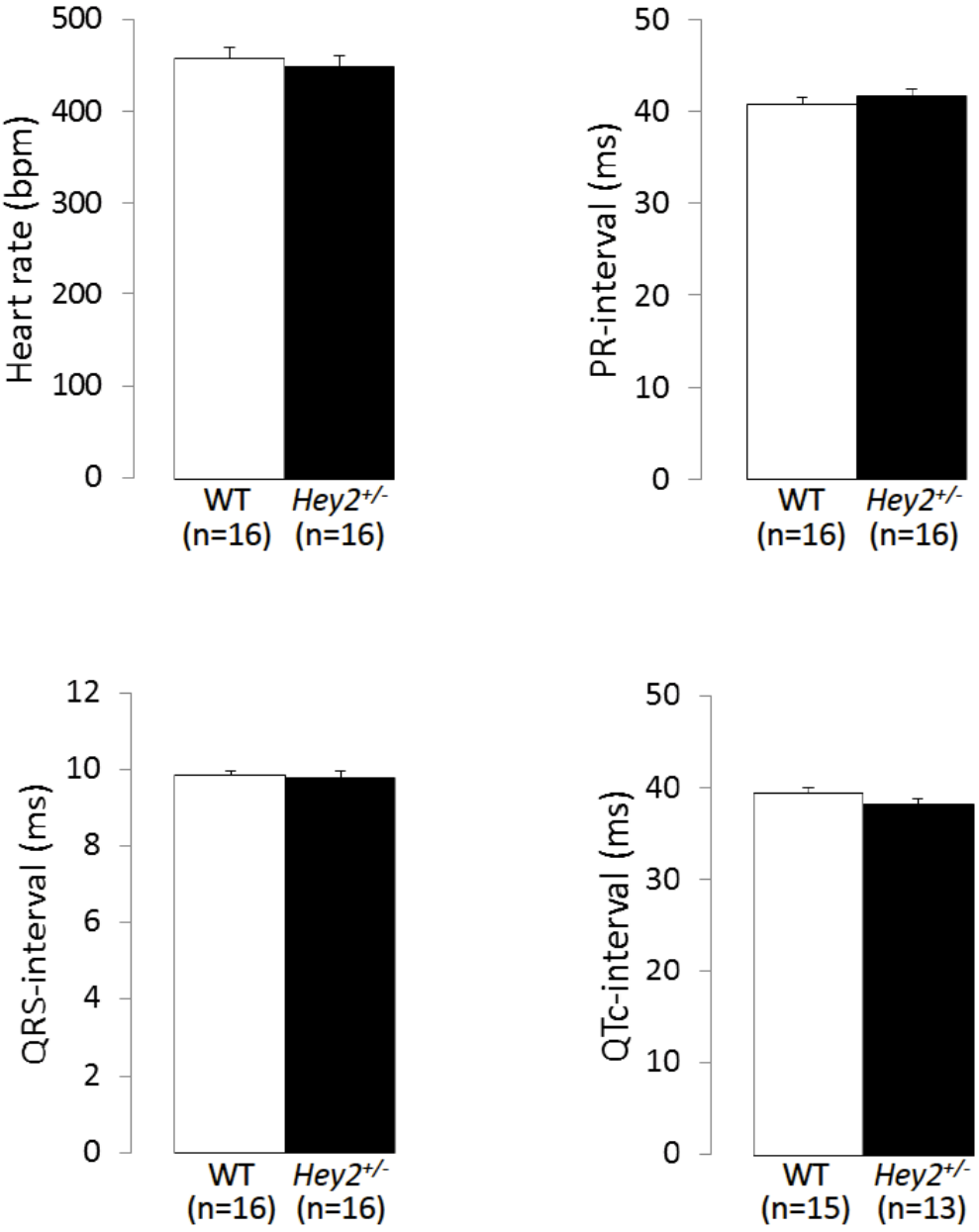
Supplementary Figure 9: Heart weight in adult WT and *Hey2*$^{+/-}$ mice.

Heart weight to body weight ratios (left) and heart weight to tibia length ratios (right) were similar in adult wild-type (WT, n=8) and *Hey2*$^{+/-}$ (n=8) mice.



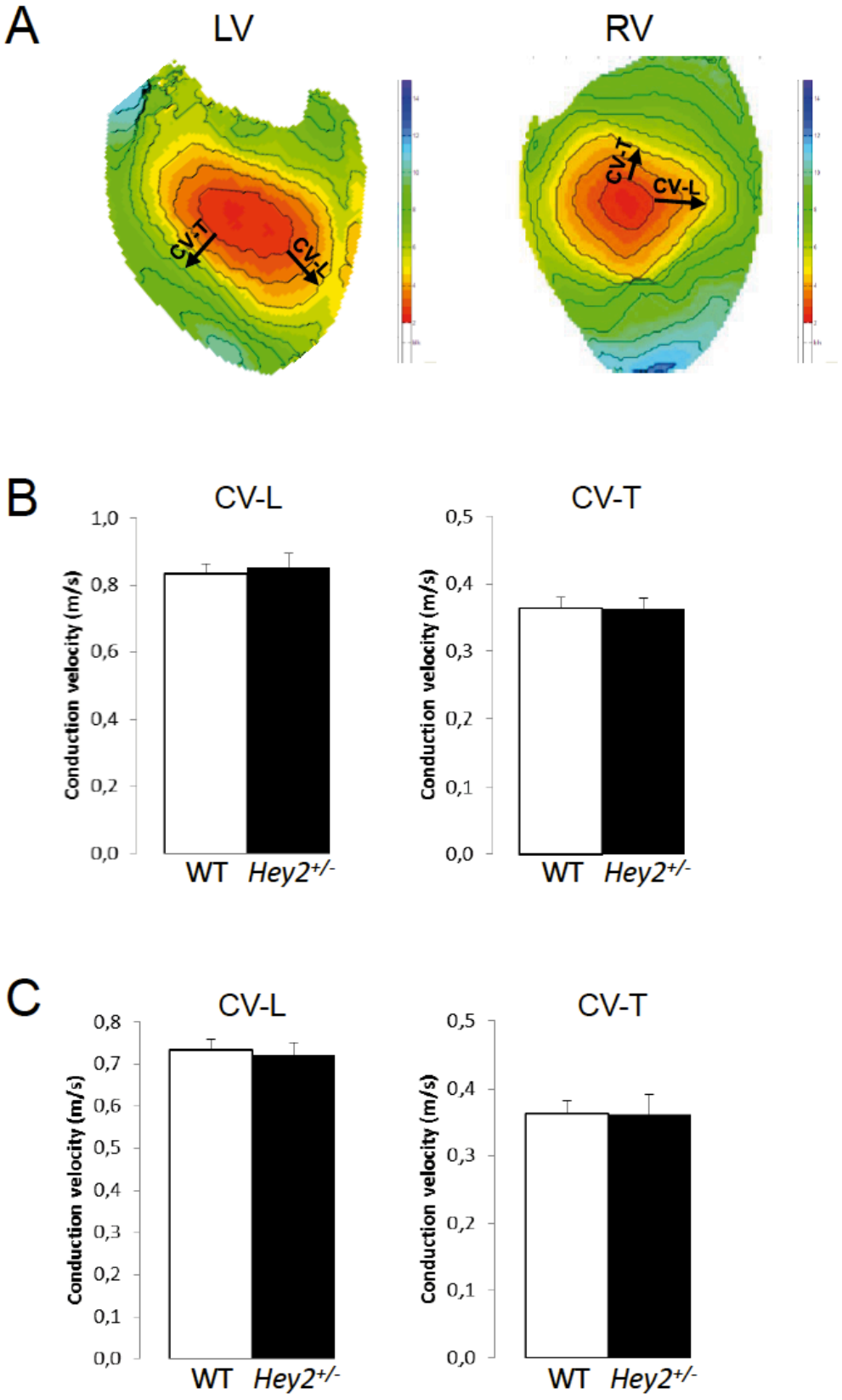
Supplementary Figure 10: ECG data in adult WT and *Hey2*$^{+/-}$ mice.

Surface ECG parameters measured from anaesthetized (isoflurane) adult wild-type (WT) and *Hey2*$^{+/-}$ mice. No significant differences in heart rate or PR-, QRS-, and QTc-intervals were observed between WT and *Hey2*$^{+/-}$ mice.



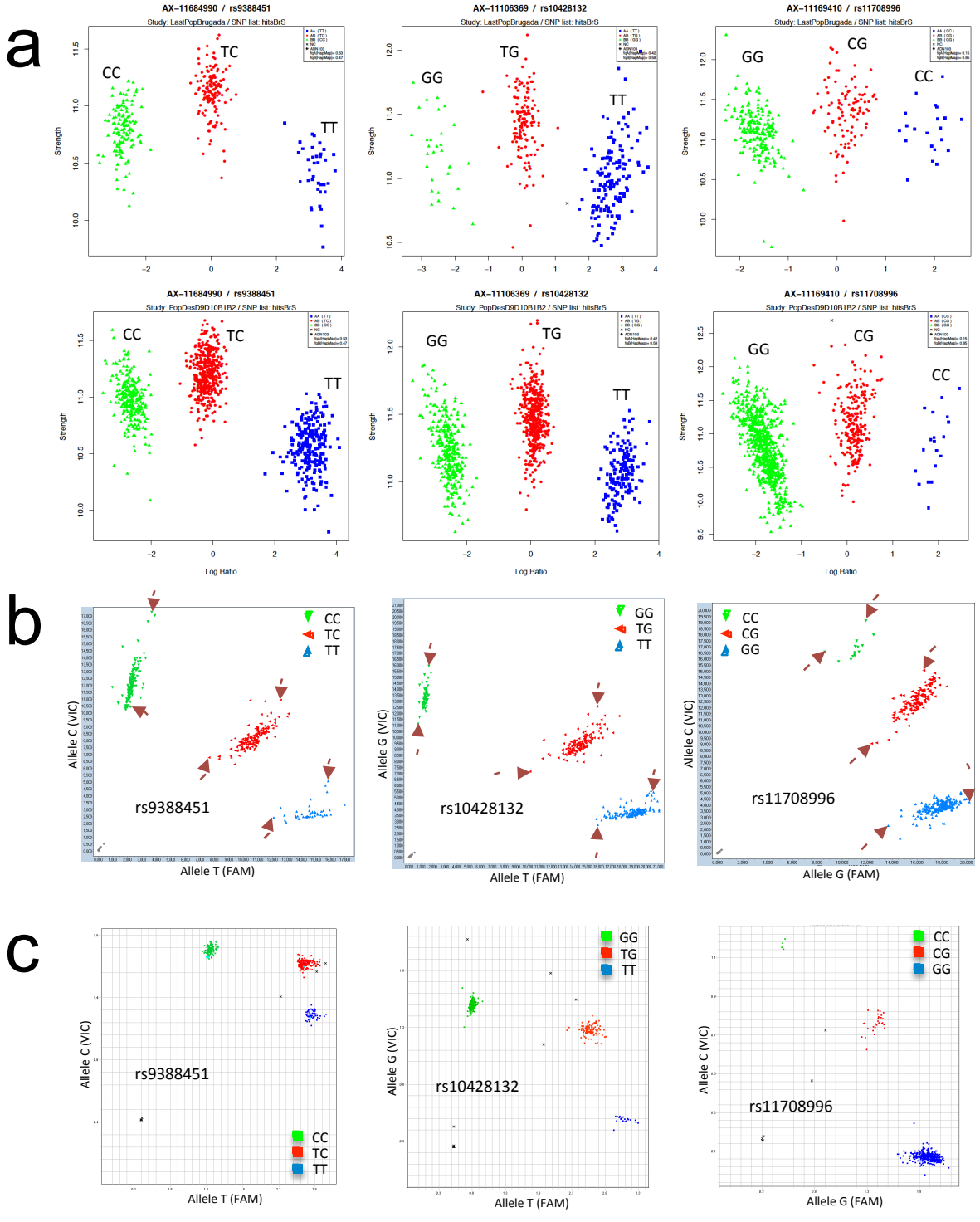
Supplementary Figure 11: RV and LV conduction velocities in WT and *Hey2*$^{+/-}$ hearts.

(**a**) Representative optical activation maps measured in right (RV) and left ventricle (LV) of isolated adult hearts. Hearts were stimulated at a basic cycle length of 120 ms, and longitudinal (CV-L) and transversal conduction velocities (CV-T) were measured as indicated. (**b**) Average longitudinal (CV-L) and transversal conduction velocities (CV-T) in LV and (**c**) RV were similar in WT and *Hey2*$^{+/-}$ hearts.



Supplementary Figure 12: Genotyping plots for the three SNPs associated with Brugada syndrome

(a) Cluster plots of the SNPs rs9388451, rs10428132 and rs11708996 genotyped on Affymetrix Axiom CEU-1 arrays for cases (top-panel) and controls (bottom-panel). Blue squares, red circles and green triangles indicated AA, AB and BB genotypes, respectively; "x" symbols indicate missing genotype calls. **(b)** Scatter plot analysis of TaqMan® Endpoint genotyping assay using a LightCycler® 480 Real-Time PCR System (Roche, Mannheim, Germany). **(c)** Scatter plot analysis of TaqMan® Endpoint genotyping assay using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA). The X-axis reports the FAM-fluorescence intensity; the Y-axis the VIC-fluorescence intensity. Green/blue triangles indicate homozygote genotypes; red triangles heterozygote samples; grey circles or "x" symbols missing genotype calls. Arrows indicate the samples for which genotypes were validated by capillary sequencing.



Supplementary Figure 13: Quality control of imputed risk allele dosages

(**a**) Distribution of imputed risk allele dosages for the control population (n=806) used in the European replication set. (**b**) Comparison of the genetic scores obtained with imputed *versus* typed SNPs for 49 individuals.