SUPPLEMENTAL MATERIAL

Methods

Patient population

We consecutively recruited 190 unrelated patients with BrS (SADS-TW BrS registry)[1] from January 2000 to December 2016 in the Taiwanese population. Aborigines were excluded from this study. BrS was diagnosed by 2 independent cardiologists according to established criteria.[2] Demographic and clinical data, including age of onset, gender, clinical presentation, and family history of SCA or syncope, were recorded. In addition, the parameters of 12-lead ECGs, including heart rate, PR interval, QRS duration, QT interval, and QRS axis, were collected when patients were enrolled. Before enrolling patients with BrS, we ascertained that the SCA events were caused by ventricular fibrillation or polymorphic ventricular tachycardia which was successfully converted by an automated external defibrillator (AED) or direct current electrical shock. Syncope was defined as non-traumatic, abrupt, transient loss of consciousness with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, a short duration, and spontaneous complete recovery. It was reported by patients and/or bystanders and was ascertained by blinded and independent certificated cardiologists through careful history taking, physical examinations, and laboratory tests (e.g. ECG, 24 hours Holter monitoring, head-up tilt testing, electrophysiological studies, blood tests, etc.). This study was approved by the local ethical committee of National Taiwan University Hospital, and all participants gave informed consent before participating.

Datasets

We used a genome-wide SNP dataset which contains a total of 648,629 SNPs and 16,171 samples from a Taiwanese cohort, of which 190 samples were BrS patients from the SADS-TW registry. The remaining 15,981 samples were healthy controls from the Taiwan Biobank (TWB) project.[3] All samples were genotyped using the Affymetrix Axiom Genome-wide TWB array version 1.0. In order to obtain the genotypes of SNPs that were not examined in this microarray platform, an imputation approach was applied in which a reference panel was used to infer missing genotypes from the target genotype dataset for each study sample. In this study, the 1000 Genomes phase 3 dataset[4, 5] was used as the reference panel for imputation.

Quality control

To achieve high-quality imputation results, two quality control filters for performing a GWAS were applied to the target genotype dataset with the goal of excluding both low quality SNPs and samples. To deal with both per-SNP and per-individual filtering, we used Plink1.9[6] to remove SNPs with call rates <95% and samples with missing rates >95%, which removed 24,604 SNPs. All 16,171 samples passed the quality control steps, suggesting the high quality of the genotype data. The target genotype array data also includes rare variants with minor allele frequency (MAF) <1% and SNPs in the common (>5%) and low (1-5%) MAF ranges. We excluded very rare SNPs by removing variants with MAF <0.01%, which resulted in 4,264 SNPs being removed. Lastly, the remaining 619,761 SNPs were analyzed based on a processing pipeline including SHAPEIT 2[7] followed by imputation with IMPUTE 2.0[8] (**Figure 1**).

Candidate SNP selection, phasing, and imputation

The main objective in this study was to validate the 88 previously reported BrS- or ECG traits-associated SNPs[9] in Taiwanese BrS patients. For examples, these SNPs were in the following genes: *SCN5A*, *SCN10A*, *HEY2*, *NCOA7*, *HEATR5B*, *MEIS1*, *HAND1*, *SAP3OL*, *GJA1*, *FADS1*, *TBX3*, *TBX5*, *KLF12*, *MYH6*, and *KCNE*. The previously reported SNPs could be divided into 3 sets. The first set included the 3 most important SNPs previously associated with susceptibility to BrS and were included in the BrS-PRS: rs11708996 in *SCN5A*, rs10428132 in *SCN10A*, and rs9388451 near *HEY2*.[9] The second set included 12 SNPs reaching genome-wide significance in the GWAS from Dr. Bezzina et al. (rs6599240, rs11129801, rs9874633, rs10428132, rs7428167, rs10428168, rs12638572, rs7641844, rs7430439, and rs6599257 in *SCN10A*; rs1268070, rs9388451 in *HEY2/NCOA7*).[9] The third set included the 75 hit-SNPs associated with ECG traits identified from previous GWASs on ECG traits.[9-18] The list of SNPs in these 3 sets is shown in **Table S3**. The genotype calls from the microarrays were aligned to the forward strand, and the SHAPEIT2[7] algorithm was utilized to align alleles between the study samples and the reference panel, by inverting the alleles and/or the target set. Previous studies have demonstrated that the best strategy for imputing genotype data with IMPUTE2 is first to phase the study population with SHAPEIT2 and then impute the phased data with IMPUTE2.[19, 20] Therefore, samples analyzed in this study were compared with the 1000 Genomes phase 3 reference panel using SHAPEIT2, focusing on populations with East-Asian ancestry. The SHAPEIT2 algorithm iteratively updates each individual's haplotype estimation by conditioning upon the current haplotype estimates of all other individuals. The enormous amount of information present in the 1000 Genomes reference panel can be best exploited through phased haplotypes, which identify the SNPs that are co-located on the same

chromosome. The potential haplotypes are compared for each individual with all other observed haplotypes in the reference panel to impute missing genotypes using IMPUTE2 version 2.3.1 with default parameters. Imputation was performed by splitting the region of each of the chromosomes containing the gene of interest into 5 Mb chunks as recommended. The effective population size was set at 20,000 as recommended by the authors. To avoid margin effects while chunking genotypic regions, the IMPUTE2 algorithm uses an internal buffer region of 250 kb on either side of the analysis interval.

Single marker analysis and development of polygenic risk score models

A single marker test was performed to determine whether a DNA variant was enriched in BrS patients, and logistic regression was utilized accordingly. Considering the genetic effect of one variant is usually not strong, a polygenic risk score (PRS) that summarizes the effects of all variants was developed. The odds ratio (OR) for each variant was calculated by using an additive model, and these ORs in all variants were integrated through their logarithm transformed values after being divided by standard errors. Notably, the log-ORs divided by standard errors were set as the weights for these developed PRS models in this study. For the set 2 SNPs, a linkage disequilibrium (LD) association was calculated because many of the SNPs were located in chromosome 3 led by *SCN5A*. If a SNP pair has a high correlation (R^2> 0.7), only the SNP showing lowest p-value between BrS patients and healthy controls was kept for further analyses. In addition, we performed a condition analysis for each SNP located in chromosome 3 by conditioning on the most significant SNP, rs6599257, and only the significant SNPs ($P < 0.05$) were kept for further analyses. To stratify BrS patients, they were divided into two subgroups depending on whether they possessed a putative BrS1-associated variant in *SCN5A* or not. To determine the associations between the developed PRS models and three clinical outcomes (SCA, syncope, combined SCA and syncope) respectively, logistic regression models were utilized. Furthermore, we developed two weighting schemes by using the BrS patients with and without *SCN5A* variants versus healthy controls.

Statistical and survival analysis

Either Chi-square or Fisher exact tests were used to compare categorical variables. Student's t-test was applied for continuous variables. All continuous data are expressed as mean ± standard deviation and all categorical data are expressed as numbers and percentages. A two-

tailed *P*-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.). To remove the potential biases resulting from the left truncation and censoring of data, a Cox's proportional hazards model was utilized to evaluate the associations between a SNP and the 3 clinical outcomes (SCA, syncope, or both). The end date of this study date was set as December 31, 2018.

PCR and Sanger sequencing

With permission from study subjects, 10 mL of peripheral venous blood was drawn for genetic analysis. We used a DNA extraction kit (Qiagen, Germany) to extract DNA from the buffy coat of patients' peripheral blood. PCR experiments were performed in a total reaction volume of 50 μL, which contained 1 μg of genomic DNA from patient samples and 2.0 mM Mg^{2+} when used at a 1X concentration. The final concentration of dNTPs was 200μM of each deoxynucleotide. Each primer was used at a final concentration of 0.5 μM in the reaction. The concentration of Q5 Hot Start High-Fidelity DNA Polymerase in the 2X Master Mix has been optimized for best results under a wide range of conditions (New England BioLabs, USA). Conventional direct sequencing was performed on *SCN5A* using an ABI 3730 instrument (Applied Biosystems, Foster City, CA, USA). The candidate variants were classified as pathogenic or benign according to the definition of the American College of Medical Genetics and Genomics (ACMG).[21]

Supplementary Table 1. The p-value of the conditional analysis of each individual SNP from set 2 versus rs10428132.

CHR	SNP	P
3	rs6599240	0.4554
3	rs11129801	0.0373*
3	rs9874633	0.1876
3	rs7428167	0.0305*
3	rs10428168	0.0154*
3	rs7641844	0.0177*
3	rs7430439	0.0363*
3	rs6599257	0.0515
6	rs1268070	0.0233*
6	rs9388451	0.0009*

* indicates statistical significance ($p < 0.05$).

Supplementary Table 2. The odds ratios from the PRS models generated using the 3 sets of SNPs individually

Set 1 SNPs	***SCN5A* mutation-negative**	***SCN5A* mutation-positive**
PRS range		
0%-20%*	1	1
21%-40%	0.12 (0.03-0.38)‡	0.4 (0.08-2.06)
41%-60%	2.27 (1.43-3.61)‡	1.2 (0.37-3.93)
61%-80%	1.92 (1.19-3.1)‡	2.6 (0.93-7.3)
81%-100%	0.85 (0.48-1.5)	0.4 (0.08-2.06)
Set 2 SNPs		
PRS range		
0%-20%*	1	1
21%-40%	1.57 (0.8-3.08)	1.33 (0.3-5.96)
41%-60%	2.50 (1.34-4.66)‡	0.67 (0.11-3.99)
61%-80%	2.00 (1.05-3.81)‡	1.67 (0.4-6.98)
81%-100%	3.36 (1.84-6.11)‡	3.67 (1.02-13.16)‡
Set 3 SNPs		
PRS range		
0%-20%*	1	1
21%-40%	3.25 (1.06-10.03)‡	3 (0.6-14.94)
41%-60%	4.50 (1.52-13.37)‡	2 (0.37-10.96)
61%-80%	9.26 (3.28-26.13)‡	3 (0.6-14.94)
81%-100%	14.5 (5.24-40.16)‡	2.5 (0.48-12.93)

PRS: polygenic risk score; SNP: single nucleotide polymorphism

* Here showed the raw odds ratios. In order to make the axis symmetrical in **Figure 4**, we showed the ORs on a log scale in **Figure 4**.

† Reference group

‡ indicates statistical significance ($p < 0.05$).

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Supplementary Table 3. List of the 88 previously reported SNPs that were associated with BrS or reaching genome-wide significance or associated with ECG traits

Cause susceptibility to BrS (set 1)	Gene or nearest gene	Reaching genome-wide significance in the GWAS (set 2)	Gene or nearest gene	SNPs previously associated with ECG traits (set 3)	Gene or nearest gene
rs11708996	*SCN5A*	rs6599240	*SCN10A*	rs846111	*RNF207,NPHP4,CHDS,ACOT7,PLEKHG5,KLH20*
rs10428132	*SCN10A*	rs11129801	*SCN10A*	rs9436640	*NFIA*
rs9388451	*HEY2, NCOA7*	rs9874633	*SCN10A*	rs4074536	*CASQ2*
		rs10428132	*SCN10A*	rs2880058	*NOS1AP*
		rs7428167	*SCN10A*	rs12143842	*NOS1AP*
		rs10428168	*SCN10A*	rs10494366	*NOS1AP*
		rs12638572	*SCN10A*	rs16857031	*NOS1AP*
		rs7641844	*SCN10A*	rs12029454	*NOS1AP*
		rs7430439	*SCN10A*	rs4657178	*NOS1AP*
		rs6599257	*SCN10A*	rs10919071	*ATP1B1*
		rs1268070	*HEY2*	rs12731740	*CD46,CD34,PLXNA2PLXNA2*
		rs9388451	*HEY2, NCOA7*	rs2745967	*CD34*
				rs17391905	*C1orf185,RNF11,CDKN2C,FAF1*
				rs7562790	*CRIM1*
				rs17020136	*HEATR5B,STRN*
				rs10865355	*MEIS1*
				rs11897119	*MEIS1*
				rs2051211	*SCN5A,SCN10A*
				rs10865879	*SCN5A,SCN10A*
				rs11129795	*SCN5A,SCN10A*
				rs12053903	*SCN5A*
				rs3922844	*SCN5A,SCN10A*
				rs11708996	*SCN5A,SCN10A*

	rs6599222	*SCN5A,SCN10A*
	rs11710077	*SCN5A,SCN10A*
	rs9851724	*SCN5A,SCN10A*
	rs6795970	*SCN5A,SCN10A*
	rs6798015	*SCN5A,SCN10A*
	rs7627552	*SCN5A,SCN10A*
	rs4687718	*TKT*
	rs2242285	*LRIG-SLC25A26*
	rs7660702	*ARHGAP24*
	rs13165478	*HAND1,SAP30L*
	rs251253	*C5orf41,NKX2.5*
	rs1321311	*PI16,CDKN1A*
	rs281868	*C6orf204,SLC35F1,PLN,BRD7P3,ASF1A*
	rs11153730	*C6orf204,SLC35F1,PLN,BRD7P3,ASF1A*
	rs11970286	*C6orf204,SLC35F1,PLN,BRD7P3,ASF1A*
	rs12210810	*C6orf204,SLC35F1,PLN,BRD7P3,ASF1A*
	rs11154022	*GJA1*
	rs9398652	*GJA1*
	rs1362212	*TBX20*
	rs7784776	*IGFBP3*
	rs314370	*SLC12A9,UFSP1*
	rs3807989	*CAV1/CAV2*
	rs2968863	*KCNH2*
	rs4725982	*KCNH2*
	rs1733724	*DKK2*
	rs7342028	*VTI1A*
	rs2074238	*KCNQ1*
	rs12296050	*KCNQ1*
	rs12576239	*KCNQ1*

	rs174547	*FADS1*
	rs4944092	*WNT11*
	rs17287293	*SOX5,BCAT1*
	rs11047543	*SOX5,BCAT1*
	rs883079	*TBX3,TBX5*
	rs3825214	*TBX5*
	rs7312625	*TBX3,TBX5*
	rs1896312	*TBX3,TBX5*
	rs10850409	*TBX3,TBX5*
	rs885389	*GPR133*
	rs2478333	*TBX3,TBX5*
	rs1886512	*SUCLA2*
	rs365990	*KLF12*
	rs223116	*MYH6,MYH7,NDNG,ZFHX2*
	rs11848785	*MYH6,MYH7,NDNG,ZFHX2*
	rs8049607	*SIPA1L1*
	rs37062	*LITAF,CLEC16A,SNN,ZC3H7A,TNFRSF16*
	rs2074518	*CNOT1,GINS3,SLC38A7,GOT1*
	rs17608766	*LIG3,RFFL*
	rs9912468	*GOSR2*
	rs17779747	*PRKCA*
	rs991014	*KCNJ2*
	rs1805128	*SETBP1*

BrS: Brugada syndrome, SNP: single nucleotide polymorphism, ECG: electrocardiogram, GWAS: genome-wide association study

Supplementary Table 4. The associations between single SNP and composite clinical outcomes (SCA plus syncope).

SNP_ID	*SCN5A* mutation-		*SCN5A* mutation+		All BrS patients	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
rs4687718	1.95 (0.98-3.86)	0.057	12.99 (1.18-143.31)	0.036*	2.13 (1.11-4.08)	0.022*
rs7784776	1.54 (1.14-2.07)	0.005*	1.15 (0.44-2.99)	0.771	1.48 (1.12-1.96)	0.006*
rs2968863	0.50 (0.23-1.07)	0.075	0.28 (0.07-1.06)	0.061	0.41 (0.21-0.79)	0.008*

CI: confidence interval; HR: hazard ratio; SCA: sudden cardiac arrest; *P*<0.05 is highlighted in red color

* indicates statistical significance ($p < 0.05$).

Supplementary Table 5. Significant SNPs in the primary Taiwanese BrS-Control GWAS.

SNP	Chromosome	Location	Major allele	Minor allele	P-value
rs78412897	1	165186203	C	A	6.90E-32
rs9842169	3	77714832	G	A	1.60E-10
rs77867179	4	168402906	C	T	8.58E-48
rs77739912	5	42366688	G	A	5.97E-32
rs1360590	9	22041443	C	T	6.76E-12
rs1828774	15	29013164	G	A	3.41E-125
rs9925311	16	53767648	G	A	6.85E-20
rs162400	21	44950305	C	A	9.65E-18

Supplementary Table 6. Validation of the 88 previously reported SNPs in the Taiwanese BrS patients

	Chr. Position (Build 37)	Gene or nearest gene	Risk allele	Protective allele	RAF (case/control) in Taiwanese	RAF (case/control) in Caucasian	All BrS patients in Taiwan vs. Healthy controls	
SNPs causing susceptibility to Brugada syndrome[9] (set 1)							***P* value***	**Odds ratio**
rs11708996	Chr3:38633923	*SCN5A*	C	G	0.011/0.007	0.23/0.15	4.27E-01	1.5 (0.46-3.57)
rs10428132	Chr3:38777554	*SCN10A*	T	G	0.305/0.193	0.69/0.41	5.92E-08‡	1.84 (1.47-2.29)
rs9388451	Chr6:126090377	*HEY2, NCOA7*	C	T	0.818/0.742	0.65/0.50	7.94E-04‡	1.56 (1.21-2.05)
SNPs reaching genome-wide significance in the GWAS[9] (set 2)								
rs6599240	Chr3:38738717	*SCN10A*	A	G	0.195/0.138	NA/0.435	1.65E-03‡	1.51 (1.16-1.94)
rs11129801	Chr3:38750375	*SCN10A*	G	A	0.645/0.535	NA/0.72	8.91E-06‡	1.56 (1.28-1.89)
rs9874633	Chr3:38771994	*SCN10A*	A	G	0.789/0.784	NA/NA	9.94E-01	1 (0.79-1.28)
rs10428132	Chr3:38777554	*SCN10A*	T	G	0.305/0.193	NA/NA	5.92E-08‡	1.84 (1.47-2.29)
rs7428167	Chr3:38778191	*SCN10A*	T	C	0.521/0.396	NA/NA	1.08E-06‡	1.66 (1.35-2.03)
rs10428168	Chr3:38780059	*SCN10A*	T	C	0.663/0.669	NA/NA	8.08E-01	0.97 (0.79-1.21)
rs12638572	Chr3:38787797	*SCN10A*	A	G	0.318/0.205	NA/NA	9.04E-08‡	1.81 (1.45-2.25)
rs7641844	Chr3:38802251	*SCN10A*	A	G	0.447/0.318	NA/NA	1.05E-07‡	1.74 (1.42-2.13)
rs7430439	Chr3:38803639	*SCN10A*	G	A	0.418/0.294	NA/NA	1.91E-07‡	1.73 (1.4-2.12)
rs6599257	Chr3:38804588	*SCN10A*	C	T	0.226/0.13	NA/NA	4.78E-08‡	1.97 (1.54-2.5)
rs1268070	Chr6:126041164	*HEY2*	C	T	0.853/0.804	NA/NA	3.79E-02‡	1.33 (1.02-1.75)
rs9388451	Chr6:126090377	*HEY2, NCOA7*	C	T	0.818/0.742	NA/0.49	7.94E-04‡	1.56 (1.21-2.05)
SNPs previously associated with ECG traits[10-18, 22] (set 3)								
rs846111	Chr1:6279370	*RNF207,NPHP4 ,CHDS,ACOT7, PLEKHG5,KLH 20*	G	C	0.824/0.835	0.253/0.268	4.23E-01	0.9 (0.7-1.17)
rs9436640	Chr1:61873677	*NFIA*	T	G	1/1	0.468/0.448	9.76E-01	NA(0-Inf)†
rs4074536	Chr1:116310967	*CASQ2*	T	C	0.524/0.517	0.309/0.290	8.65E-01	1.02 (0.83-1.24)
rs2880058	Chr1:162014632	*NOS1AP*	A	G	0/0	0.358/0.337	NA	NA(0-Inf)†
rs12143842	Chr1:162033890	*NOS1AP*	C	T	0/0	0.274/0.254	NA	NA(0-Inf)†
rs10494366	Chr1:162085685	*NOS1AP*	G	T	0/0	0.399/0.365	NA	NA(0-Inf)†
rs16857031	Chr1:162112910	*NOS1AP*	C	G	0/0	0.146/0.145	NA	NA(0-Inf)†

rs12029454	Chr1:162133117	*NOS1AP*	G	A	0.231/0.217	0.176/0.165	5.46E-01	1.08 (0.84-1.36)
rs4657178	Chr1:162210610	*NOS1AP*	C	T	0/0	0.272/0.275	NA	NA(0-Inf)†
rs10919071	Chr1:169099483	*ATP1B1*	A	G	0/0	0.109/0.138	NA	NA(0-Inf)†
rs12731740	Chr1:208024820	*CD46,CD34,PLXNA2PLXNA2*	C	T	0/0	0.115/0.101	NA	NA(0-Inf)†
rs2745967	Chr1:208128722	*CD34*	G	A	0/0	0.372/0.371	NA	NA(0-Inf)†
rs17391905	Chr1:51546140	*C1orf185,RNF11,CDKN2C,FAF1*	G	A	0.079/0.059	NA/NA	1.08E-01	1.36 (0.92-1.95)
rs7562790	Chr2:36673555	*CRIM1*	T	G	0.379/0.378	0.396/0.406	9.57E-01	1.01 (0.81-1.24)
rs17020136	Chr2:37248015	*HEATR5B,STRN*	T	C	0.443/0.509	0.213/0.182	7.36E-03‡	0.76 (0.62-0.93)
rs10865355	Chr2:66764997	*MEIS1*	A	G	0.221/0.174	0.402/0.377	1.62E-02‡	1.35 (1.05-1.72)
rs11897119	Chr2:66772000	*MEIS1*	T	C	0.779/0.825	0.401/0.377	1.14E-02‡	0.73 (0.58-0.94)
rs2051211	Chr3:38559749	*SCN5A,SCN10A*	A	G	0.739/0.699	0.217/0.255	8.97E-02	1.22 (0.97-1.54)
rs10865879	Chr3:38577362	*SCN5A,SCN10A*	A	C	0.931/0.91	0.282/0.233	9.40E-02	1.37 (0.97-2.04)
rs11129795	Chr3:38589163	*SCN5A,SCN10A*	G	A	0.932/0.91	0.284/0.233	1.77E-17‡	3.89 (2.91-5.46)
rs12053903	Chr3:38593393	*SCN5A*	T	C	0.437/0.455	0.394/0.327	5.00E-01	0.93 (0.76-1.14)
rs3922844	Chr3:38624253	*SCN5A,SCN10A*	T	C	0.087/0.099	0.233/0.298	9.86E-01	1 (0.69-1.4)
rs11708996	Chr3:38633923	*SCN5A,SCN10A*	G	C	0.987/0.992	0.228/0.151	9.25E-02	0.56 (0.31-1.23)
rs6599222	Chr3:38648062	*SCN5A,SCN10A*	C	T	0/0.002	0.286/0.218	9.67E-01	0 (0-0.41)
rs11710077	Chr3:38657899	*SCN5A,SCN10A*	A	T	0.947/0.937	0.166/0.197	4.03E-01	1.21 (0.79-1.96)
rs9851724	Chr3:38719935	*SCN5A,SCN10A*	C	T	0.255/0.244	0.226/0.307	5.88E-01	1.07 (0.84-1.34)
rs6795970	Chr3:38766675	*SCN5A,SCN10A*	A	G	0.263/0.152	0.668/0.410	5.10E-09‡	1.98 (1.57-2.49)
rs6798015	Chr3:38798836	*SCN5A,SCN10A*	C	T	0.315/0.194	0.607/0.364	3.96E-09‡	1.92 (1.54-2.39)
rs7627552	Chr3:38666036	*SCN5A,SCN10A*	-	G	0/0	NA/NA	NA	NA(0-Inf)†
rs4687718	Chr3:53282303	*TKT*	A	G	0.029/0.036	0.120/0.118	4.47E-01	0.79 (0.41-1.37)
rs2242285	Chr3:66431602	*LRIG-SLC25A26*	A	G	0.171/0.166	0.436/0.400	8.02E-01	1.04 (0.78-1.34)
rs7660702	Chr4:86651464	*ARHGAP24*	T	C	0.074/0.081	0.277/0.303	6.35E-01	0.91 (0.61-1.31)
rs13165478	Chr5:153869040	*HAND1,SAP30L*	G	A	0.607/0.593	0.339/0.380	5.84E-01	1.06 (0.86-1.3)
rs251253	Chr5:172480336	*C5orf41,NKX2.5*	C	T	0.813/0.817	0.438/0.377	9.05E-01	0.98 (0.76-1.28)

rs1321311	Chr6:36622900	*PI16,CDKN1A*	C	A	0.811/0.839	0.267/0.248	1.45E-01	0.82 (0.64-1.08)
rs281868	Chr6:118574061	*C6orf204,SLC35F1,PLN,BRD7P3,ASF1A*	G	A	0.758/0.72	0.478/0.490	9.53E-02	1.22 (0.97-1.56)
rs11153730	Chr6:118667522	*C6orf204,SLC35F1,PLN,BRD7P3,ASF1A*	T	C	0/0	0.470/0.463	NA	NA(0-Inf)[†]
rs11970286	Chr6:118680374	*C6orf204,SLC35F1,PLN,BRD7P3,ASF1A*	C	T	0.247/0.258	0.427/0.422	6.72E-01	0.95 (0.75-1.2)
rs12210810	Chr6:118653204	*C6orf204,SLC35F1,PLN,BRD7P3,ASF1A*	T	C	0.262/0.27	NA/NA	2.08E-01	1.16 (0.92-1.44)
rs11154022	Chr6:121748542	*GJA1*	A	G	0.537/0.49	0.337/0.339	6.22E-02	1.21 (0.99-1.49)
rs9398652	Chr6:122146034	*GJA1*	C	A	0.526/0.539	0.085/0.099	6.50E-01	0.95 (0.78-1.17)
rs1362212	Chr7:35305306	*TBX20*	G	A	0.929/0.923	0.226/0.182	6.02E-01	1.11 (0.77-1.68)
rs7784776	Chr7:46620145	*IGFBP3*	A	G	0.229/0.243	0.430/0.420	5.26E-01	0.93 (0.72-1.17)
rs314370	Chr7:100453208	*SLC12A9,UFSP1*	T	C	0.928/0.955	0.176/0.189	2.65E-09[‡]	2.33 (1.8-3.15)
rs3807989	Chr7:116186241	*CAV1/CAV2*	A	G	0.263/0.248	0.471/0.401	4.87E-01	1.09 (0.86-1.36)
rs2968863	Chr7:150623137	*KCNH2*	C	T	0.974/0.964	0.245/0.277	2.84E-01	1.41 (0.8-2.82)
rs4725982	Chr7:150637863	*KCNH2*	C	T	0.352/0.373	0.221/0.204	3.76E-01	0.91 (0.73-1.12)
rs1733724	Chr10:54223977	*DKK2*	A	G	0.053/0.051	0.260/0.238	8.73E-01	1.04 (0.64-1.6)
rs7342028	Chr10:114479262	*VTI1A*	G	T	0.405/0.461	0.260/0.277	3.56E-02[‡]	0.8 (0.65-0.98)
rs2074238	Chr11:2484803	*KCNQ1*	T	C	0.024/0.026	0.093/0.079	9.58E-01	1.02 (0.48-1.88)
rs12296050	Chr11:2489342	*KCNQ1*	C	T	0.7/0.652	0.180/0.196	5.07E-02	1.24 (1-1.56)
rs12576239	Chr11:2502319	*KCNQ1*	C	T	0.916/0.899	0.124/0.134	2.45E-01	1.24 (0.88-1.81)
rs174547	Chr11:61570783	*FADS1*	T	C	0.45/0.411	0.329/0.305	1.30E-01	1.17 (0.95-1.43)
rs4944092	Chr11:75909619	*WNT11*	A	G	0.766/0.771	0.291/0.307	8.52E-01	0.98 (0.77-1.25)
rs17287293	Chr12:24770878	*SOX5,BCAT1*	A	G	0.892/0.876	0.171/0.158	3.22E-01	1.18 (0.86-1.65)
rs11047543	Chr12:24788339	*SOX5,BCAT1*	G	A	0.892/0.878	0.176/0.159	2.36E-01	1.21 (0.89-1.69)
rs883079	Chr12:114793240	*TBX3,TBX5*	C	T	0.542/0.548	0.356/0.280	8.64E-01	0.98 (0.8-1.2)
rs3825214	Chr12:114795443	*TBX5*	G	A	0.429/0.438	0.252/0.190	7.38E-01	0.97 (0.79-1.18)

rs7312625	Chr12:114799974	*TBX3,TBX5*	G	A	0.172/0.186	0.338/0.264	4.78E-01	0.91 (0.69-1.18)
rs1896312	Chr12:115346424	*TBX3,TBX5*	C	T	0.611/0.553	0.303/0.286	2.35E-02‡	1.27 (1.03-1.56)
rs10850409	Chr12:115381740	*TBX3,TBX5*	G	A	0.382/0.441	0.278/0.269	2.69E-02‡	0.79 (0.64-0.97)
rs885389	Chr12:131621762	*GPR133*	A	G	0.553/0.557	0.375/0.332	9.41E-01	0.99 (0.81-1.21)
rs2478333	Chr13:48162558	*SUCLA2*	C	A	0.932/0.933	0.252/0.190	9.70E-01	0.99 (0.68-1.52)
rs1886512	Chr13:74520186	*KLF12*	T	A	0.751/0.737	0.364/0.353	5.01E-01	1.08 (0.86-1.37)
rs365990	Chr14:23861811	*MYH6,MYH7,NDNG,ZFHX2*	A	G	0.834/0.825	0.363/0.378	6.10E-01	1.07 (0.82-1.42)
rs223116	Chr14:23977010	*MYH6,MYH7,NDNG,ZFHX2*	A	G	0.337/0.352	0.383/0.378	5.62E-01	0.94 (0.76-1.16)
rs11848785	Chr14:72057355	*SIPA1L1*	G	A	0.082/0.088	0.265/0.253	6.68E-01	0.92 (0.62-1.31)
rs8049607	Chr16:11691753	*LITAF,CLEC16A,SNN,ZC3H7A,TNFRSF16*	T	C	0.411/0.41	0.296/0.270	9.69E-01	1 (0.82-1.23)
rs37062	Chr16:58567238	*CNOT1,GINS3,SLC38A7,GOT1*	A	G	0.573/0.612	0.484/0.481	7.35E-02	0.83 (0.68-1.02)
rs2074518	Chr17:33324382	*LIG3,RFFL*	C	T	0.732/0.704	0.260/0.239	2.07E-01	1.16 (0.93-1.46)
rs17608766	Chr17:45013271	*GOSR2*	T	C	1/1	0.479/0.456	9.68E-01	NA(0-Inf)†
rs9912468	Chr17:64318357	*PRKCA*	G	C	0.474/0.437	0.136/0.135	1.76E-01	1.15 (0.94-1.41)
rs17779747	Chr17:68494992	*KCNJ2*	G	T	0.924/0.936	0.473/0.454	3.85E-01	0.84 (0.59-1.26)
rs991014	Chr18:42439886	*SETBP1*	C	T	0.666/0.642	0.353/0.332	3.08E-01	1.12 (0.9-1.39)
rs1805128	Chr21:35821680	*KCNE1*	T	C	0.003/0.004	0.405/0.403	7.06E-01	0.69 (0.04-3.03)

NA: only one genotype exists

**P*-value was obtained by using logistic regression.

† Unable to estimate due to extremely imbalanced sample distributions

‡ indicates statistical significance ($p < 0.05$).

Supplementary Table 7. Comparisons of the 88 previously reported SNPs between BrS patients with and without *SCN5A* mutations

	Without *SCN5A* mutations		With *SCN5A* mutations	
SNPs (set 1)	**P-value***	**OR**	**P-value***	**OR**
rs11708996	2.66E-01	1.76 (0.54-4.22)	9.85E-01	NA(0-Inf)‡
rs10428132	1.97E-06†	1.79 (1.4-2.27)	6.68E-03†	2.16 (1.21-3.72)
rs9388451	5.69E-04†	1.66 (1.25-2.24)	6.57E-01	1.15 (0.64-2.22)
SNPs (set 2)				
rs6599240	3.79E-03†	1.51 (1.13-1.97)	2.10E-01	1.53 (0.75-2.84)
rs11129801	7.81E-05†	1.53 (1.24-1.89)	3.68E-02†	1.73 (1.04-2.93)
rs9874633	8.36E-01	0.97 (0.76-1.27)	6.32E-01	1.17 (0.64-2.37)
rs10428132	1.97E-06†	1.79 (1.4-2.27)	6.68E-03†	2.16 (1.21-3.72)
rs7428167	2.69E-05†	1.6 (1.28-1.99)	8.81E-03†	2.03 (1.2-3.48)
rs10428168	7.45E-01	0.96 (0.77-1.22)	8.81E-01	1.04 (0.61-1.87)
rs12638572	1.68E-06†	1.78 (1.4-2.25)	1.47E-02†	2 (1.12-3.43)
rs7641844	2.68E-06†	1.7 (1.36-2.12)	9.60E-03†	2 (1.18-3.39)
rs7430439	3.64E-06†	1.69 (1.35-2.11)	1.41E-02†	1.94 (1.13-3.28)
rs6599257	5.81E-07†	1.96 (1.49-2.53)	2.51E-02†	2.04 (1.05-3.69)
rs1268070	1.00E-02†	1.49 (1.11-2.04)	4.21E-01	0.79 (0.45-1.47)
rs9388451	5.69E-04†	1.66 (1.25-2.24)	6.57E-01	1.15 (0.64-2.22)
SNPs (set 3)				
rs846111	3.51E-01	0.88 (0.67-1.17)	8.77E-01	1.06 (0.55-2.29)
rs9436640	9.76E-01	NA(0-Inf)‡	9.86E-01	NA(0-Inf)‡
rs4074536	6.36E-01	1.05 (0.85-1.31)	4.86E-01	0.83 (0.49-1.4)
rs2880058	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs12143842	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs10494366	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs16857031	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs12029454	3.50E-01	1.13 (0.87-1.45)	4.99E-01	0.79 (0.38-1.5)
rs4657178	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs10919071	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs12731740	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs2745967	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs17391905	2.62E-01	1.27 (0.81-1.89)	1.36E-01	1.91 (0.73-4.15)
rs7562790	7.61E-01	1.04 (0.82-1.3)	5.54E-01	0.85 (0.48-1.45)
rs17020136	2.72E-03†	0.71 (0.57-0.89)	8.11E-01	1.07 (0.63-1.8)
rs10865355	6.72E-03†	1.44 (1.1-1.86)	7.92E-01	0.91 (0.42-1.77)
rs11897119	3.99E-03†	0.69 (0.54-0.89)	7.30E-01	1.13 (0.59-2.47)
rs2051211	1.06E-01	1.23 (0.96-1.58)	5.92E-01	1.17 (0.67-2.18)
rs10865879	1.27E-01	1.37 (0.94-2.1)	4.85E-01	1.42 (0.61-4.57)
rs11129795	3.95E-15†	3.9 (2.85-5.66)	1.06E-03†	3.77 (1.94-10.24)
rs12053903	2.54E-01	0.88 (0.7-1.1)	3.23E-01	1.3 (0.77-2.2)

rs3922844	7.30E-01	1.07 (0.72-1.53)	3.83E-01	0.6 (0.15-1.61)
rs11708996	3.85E-02†	0.49 (0.27-1.08)	9.83E-01	NA(0-Inf)‡
rs6599222	9.68E-01	NA(0-Inf)‡	9.88E-01	NA(0-Inf)‡
rs11710077	4.32E-01	1.22 (0.77-2.06)	7.69E-01	1.19 (0.44-4.86)
rs9851724	5.06E-01	1.09 (0.84-1.39)	8.48E-01	0.94 (0.49-1.69)
rs6795970	1.79E-07†	1.94 (1.51-2.48)	6.83E-03†	2.22 (1.21-3.89)
rs6798015	1.54E-07†	1.88 (1.48-2.38)	5.98E-03†	2.17 (1.22-3.73)
rs7627552	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs4687718	6.02E-01	0.85 (0.42-1.5)	4.73E-01	0.49 (0.03-2.18)
rs2242285	8.65E-01	1.03 (0.76-1.36)	8.04E-01	1.09 (0.52-2.07)
rs7660702	9.93E-01	1 (0.65-1.46)	2.36E-01	0.43 (0.07-1.36)
rs13165478	1.83E-01	1.16 (0.93-1.46)	7.68E-02	0.63 (0.37-1.05)
rs251253	6.95E-01	1.06 (0.8-1.42)	2.11E-01	0.68 (0.38-1.29)
rs1321311	1.98E-01	0.83 (0.63-1.11)	4.82E-01	0.79 (0.42-1.61)
rs281868	2.19E-01	1.17 (0.91-1.52)	1.64E-01	1.6 (0.86-3.25)
rs11153730	NA	NA(0-Inf)‡	NA	NA(0-Inf)‡
rs11970286	8.75E-01	0.98 (0.76-1.25)	4.68E-01	0.79 (0.4-1.44)
rs12210810	8.04E-02	1.24 (0.97-1.57)	3.53E-01	0.73 (0.35-1.36)
rs11154022	1.31E-01	1.18 (0.95-1.48)	2.17E-01	1.4 (0.82-2.4)
rs9398652	9.41E-01	1.01 (0.81-1.26)	1.74E-01	0.7 (0.41-1.17)
rs1362212	4.91E-01	1.16 (0.78-1.84)	7.64E-01	0.87 (0.39-2.48)
rs7784776	8.72E-01	1.02 (0.79-1.31)	4.61E-02†	0.45 (0.19-0.92)
rs314370	1.92E-08†	2.48 (1.85-3.5)	5.68E-02	1.78 (1.05-3.57)
rs3807989	3.19E-01	1.13 (0.88-1.45)	5.59E-01	0.83 (0.41-1.52)
rs2968863	1.56E-01	1.72 (0.88-4)	5.18E-01	0.69 (0.26-2.78)
rs4725982	3.88E-01	0.9 (0.72-1.13)	8.18E-01	0.94 (0.53-1.61)
rs1733724	3.72E-01	1.23 (0.75-1.9)	9.83E-01	NA(0-Inf)‡
rs7342028	2.82E-02†	0.78 (0.62-0.97)	8.42E-01	0.95 (0.56-1.6)
rs2074238	8.65E-01	1.06 (0.48-2.03)	7.86E-01	0.76 (0.04-3.56)
rs12296050	1.10E-01	1.21 (0.96-1.54)	2.11E-01	1.46 (0.83-2.71)
rs12576239	2.60E-01	1.25 (0.86-1.9)	7.45E-01	1.16 (0.52-3.32)
rs174547	1.60E-01	1.17 (0.94-1.46)	5.69E-01	1.17 (0.68-1.97)
rs4944092	7.50E-01	0.96 (0.75-1.25)	7.79E-01	1.1 (0.6-2.17)
rs17287293	8.28E-02	1.39 (0.97-2.07)	1.12E-01	0.59 (0.32-1.19)
rs11047543	5.95E-02	1.43 (1-2.11)	1.46E-01	0.62 (0.34-1.24)
rs883079	8.19E-01	0.97 (0.78-1.21)	9.16E-01	1.03 (0.61-1.75)
rs3825214	9.78E-01	1 (0.8-1.25)	3.49E-01	0.77 (0.44-1.31)
rs7312625	3.19E-01	0.86 (0.64-1.14)	5.81E-01	1.2 (0.61-2.18)
rs1896312	1.46E-02†	1.32 (1.06-1.66)	9.81E-01	1.01 (0.6-1.71)
rs10850409	1.95E-02†	0.76 (0.61-0.96)	8.80E-01	0.96 (0.56-1.62)
rs885389	9.41E-01	0.99 (0.8-1.23)	9.88E-01	1 (0.59-1.69)
rs2478333	6.60E-01	1.11 (0.72-1.8)	2.50E-01	0.61 (0.28-1.58)
rs1886512	2.22E-01	1.17 (0.91-1.52)	2.37E-01	0.72 (0.42-1.27)
rs365990	5.65E-01	1.09 (0.82-1.48)	9.58E-01	0.98 (0.52-2.06)
rs223116	5.04E-01	0.92 (0.73-1.16)	9.24E-01	1.03 (0.58-1.76)

rs11848785	9.29E-01	0.98 (0.65-1.43)	3.69E-01	0.59 (0.14-1.6)
rs8049607	4.51E-01	0.92 (0.73-1.15)	5.73E-02	1.67 (0.98-2.84)
rs37062	2.95E-01	0.89 (0.71-1.11)	3.30E-02†	0.57 (0.33-0.95)
rs2074518	2.52E-02†	1.34 (1.04-1.74)	3.68E-02†	0.57 (0.34-0.98)
rs17608766	9.79E-01	NA(0-Inf)‡	9.88E-01	NA(0-Inf)‡
rs9912468	3.38E-01	1.11 (0.89-1.38)	2.23E-01	1.38 (0.82-2.35)
rs17779747	2.78E-01	0.8 (0.55-1.23)	7.26E-01	1.23 (0.45-5.05)
rs991014	4.56E-01	1.09 (0.87-1.38)	3.85E-01	1.29 (0.74-2.33)
rs1805128	9.71E-01	NA(0-Inf)‡	1.28E-01	4.52 (0.26-19.8)

SNP: single nucleotide polymorphism; OR, odds ratio

NA: only one genotype exists

* *P*-value was obtained by using logistic regression;

† indicates statistical significance ($p < 0.05$).

‡ Unable to estimate due to extremely imbalanced sample distributions

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