

Genome-wide association analyses identify novel Brugada syndrome risk loci and highlight a new mechanism of sodium channel regulation in disease susceptibility

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Brugada syndrome is a cardiac arrhythmia disorder associated with sudden death in young adults. With the exception of *SCN5A*, encoding the cardiac sodium channel Nav1.5, susceptibility genes remain largely unknown. Here we performed a genome-wide association meta-analysis comprising 2,820 unrelated cases with Brugada syndrome and 10,001 controls and identified 21 association signals at 12 loci (10 novel). SNP-heritability estimates indicate a strong polygenic influence. Polygenic risk score analyses based on the 21 susceptibility variants demonstrate varying cumulative contribution of common risk alleles among different patient sub-groups, as well as genetic associations with cardiac electrical traits and disorders in the general population. The predominance of cardiac transcription factor loci indicates that transcriptional regulation is a key feature of Brugada syndrome pathogenesis. Furthermore, functional studies conducted on *MAPRE2*, encoding the microtubule plus-end-binding protein EB2, point to microtubule-related trafficking effects on Nav1.5 expression as a novel underlying molecular mechanism. Taken together, these findings broaden our understanding of the genetic architecture of Brugada syndrome and provide new insights into its molecular underpinnings.

Brugada syndrome (BrS) is a cardiac disorder characterized by hallmark ST-segment elevation in the right precordial leads of the electrocardiogram (ECG) and increased risk of sudden death in young adults^{1,2}. Rare coding variants in *SCN5A*, encoding the cardiac sodium channel Nav1.5 that underlies the sodium current (I_{Na}), are reported in approximately 20% of cases^{3,4}. Other susceptibility genes contributing to the disorder remain largely unknown. In a genome-wide association study (GWAS) conducted in 312 individuals with BrS, we previously identified three common susceptibility variants and provided evidence for a complex genetic architecture⁵. Here we extended this original association scan to a large meta-analysis comprising 2,820 unrelated cases and 10,001 controls of European ancestry (**Supplementary Tables 1 and 2 and Supplementary Note**), testing 6,990,521 variants with a minor allele frequency (MAF) ≥ 0.01 (**Fig. 1 and Supplementary Figs. 1 and 2**). A total of 12 loci (10 novel) reached the genome-wide statistical significance threshold of $P < 5 \times 10^{-8}$ (**Table 1 and Supplementary Fig. 3a-l**). Conditional analysis uncovered seven additional association signals at genome-wide significance at the chromosome 3 locus, and an additional signal at the chromosome 6 and chromosome 7 loci (**Table 1 and Supplementary Fig. 3m-u**). Analysis of SNP-based heritability (h^2_{SNP}) demonstrated that a substantial portion of susceptibility to BrS is attributable to common genetic variation. h^2_{SNP} estimates ranged from 0.17 (standard error, (s.e.) 0.035) using LDSC⁶ to 0.34 (s.e. 0.02) using GREML⁷, assuming a disease prevalence of 0.05%⁸, with 24% of the total SNP-based heritability being explained by the 12 loci reaching genome-wide significance (**Supplementary Table 4**).

Seven association signals (defined by the lead SNP and SNPs with $r^2 \geq 0.6$) at the chromosome 3 locus overlapped *SCN5A* and one overlapped the neighboring *SCN10A* gene encoding the sodium channel isoform Nav1.8 (**Supplementary Fig. 4a-h**). While previous work⁹ proposed that the latter signal may act through regulation of *SCN5A* expression, a possible involvement of *SCN10A* itself is suggested by a significant eQTL in left ventricular tissue ($P = 5.29 \times 10^{-6}$, colocalization posterior probability (CLPP) = 0.16) (**Supplementary Fig. 4h and Supplementary Table 3**), whereas no eQTL was detected for *SCN5A* ($P = 0.27$). Notably, six association signals overlapped genes encoding cardiac developmental transcription factors (*HEY2*, *TBX20*, *ZFPM2*, *GATA4*, *WT1*, *TBX5*) and four were < 300 kb from

such genes (*TBX20*, *IRX3/IRX5*, *HEY2*)¹⁰. In support for the involvement of transcription factor genes, an enrichment in genes encoding DNA binding proteins was found at BrS GWAS loci by permutation testing (one-tailed permutation $P = 1 \times 10^{-4}$; **Extended Data Fig. 1**). The transcription factors HEY2, TBX20, GATA4, TBX5 and IRX3/IRX5 are established regulators of ion channel expression in the adult heart, including that of Nav1.5^{11–15}, suggesting that modulation of ion channel expression is an important mechanism in BrS. Potential regulatory effects of the transcription factors WT1 and ZFPM2 on ion channel expression have not yet been investigated. One association signal overlapped *PRKCA* (supported by a co-localizing eQTL; $P = 4.63 \times 10^{-28}$, CLPP = 0.99) (**Supplementary Fig. 4s** and **Supplementary Table 3**), which encodes protein kinase C alpha involved in contractility and calcium handling in cardiomyocytes¹⁶. Lastly, two association signals overlapped genes encoding microtubule or myofiber associated proteins, namely *MAPRE2*¹⁷ and *MYO18B*¹⁸. A full annotation of the association signals (see Online Methods) is presented in **Supplementary Table 3** and **Supplementary Fig. 4**.

We performed a transcriptome-wide analysis (TWAS)¹⁹ based on predicted gene expression in cardiac tissues²⁰ and identified 24 associations corresponding to 20 unique genes at the Bonferroni-corrected threshold of $P < 5.2 \times 10^{-6}$ (**Supplementary Table 5**). Eighteen of these genes are within ~0.5 Mb of GWAS signals while two point to additional loci (**Supplementary Table 5**). MAGMA gene property analysis for tissue specificity²¹ as well as enrichment analysis using LDSC-SEQ²² and GARFIELD²³ identified left ventricle, right ventricle and fetal heart, respectively, as significantly associated with BrS (**Supplementary Figs. 5 and 6** and **Supplementary Tables 6 and 7**). MAGMA gene-set analysis²¹ identified, amongst others, gene sets related to heart development and regulation of heart growth (**Supplementary Table 8**), which may point to a broader role of transcriptional dysregulation in the pathogenesis of BrS, beyond regulation of ion channel expression.

MAPRE2 overlaps the association signal tagged by rs476348 and its causal role is supported by chromatin interaction between its promoter region and the association signal and by a significant eQTL ($P = 2.9 \times 10^{-5}$, CLPP = 0.10) (**Extended Data Fig. 2** and **Supplementary Table 3**), where the BrS risk allele is associated with lower *MAPRE2* expression in left ventricular tissue compared to the non-risk allele. *MAPRE2* encodes the microtubule plus-end binding protein EB2, a regulator of microtubule organization¹⁷. While effects on transcription factor expression and ion-channel patterning are established molecular mechanisms associated with BrS susceptibility^{5,13}, mechanisms involving microtubule function and ion channel trafficking, as suggested by the association signal near *MAPRE2*, have not yet been explored. We therefore generated loss-of-function mutants (KO) using CRISPR/Cas9 in both zebrafish (**Supplementary Fig. 7**) and human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) (**Supplementary Fig. 8**) to study the role of *MAPRE2* in cardiac electrophysiology. Using optical mapping, we observed a significantly lower conduction velocity and action potential upstroke velocity (V_{max}) in zebrafish hearts isolated from *mapre2* KO compared to control (CTRL) larvae (**Fig. 2a,b**). Similarly, V_{max} observed in single *MAPRE2* KO hiPSC-CMs was lower than isogenic control hiPSC-CMs measured using manual patch clamp (**Fig. 2d,e**). The lower V_{max} observed in both mutant zebrafish and hiPSC-CMs suggested lower I_{Na} . This was confirmed by automated patch-clamp measurements, which demonstrated ~50% less I_{Na} density in *MAPRE2* KO compared to control hiPSC-CMs (**Fig. 2f**, left panel). Additionally, a small positive shift in voltage dependency of activation was observed, while voltage dependency of inactivation and recovery from inactivation were not different between control and KO cells (**Extended**

Data Fig. 3a-c). Whereas no repolarization abnormalities were observed in intact *mapre2* KO zebrafish hearts (**Fig. 2c**), significant action potential duration (APD) prolongation was observed in single *MAPRE2* KO hiPSC-CMs (**Fig. 2d,e**). This APD prolongation may be explained by the significantly lower repolarizing outward current ($I_{outward}$) amplitude in the KO hiPSC-CMs (**Fig. 2f**, right panel), although the voltage-dependency of activation was unchanged (**Extended Data Fig. 3d,e**). Together with the multiple levels of evidence that implicate conduction slowing and decreased I_{Na} in the pathogenesis of BrS, and previous work linking end-binding proteins to ion channel targeting to the plasma membrane²⁴, our data suggest that modulation of microtubule function and subsequent alterations in ion channel trafficking may be a novel molecular mechanism contributing to BrS. Future work is needed to address the underlying molecular mechanisms and provide insight into the ion channels that underlie the observed abnormalities in repolarization, although a role for prolonged repolarization is not reconcilable with current hypotheses on BrS pathogenesis²⁵.

To further explore the genetic architecture of BrS in specific patient subgroups as well as the association of common variants in aggregate with disease severity, we calculated a polygenic risk score (PRS_{BrS}) per individual based on the 21 risk alleles and their corresponding effect sizes. Of the 2,469 study participants tested, 454 (18.4%) carried a rare pathogenic or likely pathogenic variant in *SCN5A* (*SCN5A*⁺). *SCN5A*⁺ cases had a lower mean PRS_{BrS} compared to cases without such variants (*SCN5A*⁻) (8.8 ± 1.1 vs. 9.3 ± 1.0 ; $P = 2.1 \times 10^{-17}$; **Fig. 3a**), suggesting a higher burden of BrS-associated common variants in *SCN5A*⁻ patients, as similarly shown in other heritable diseases^{26,27}. Using LDSC, we observed a strong genome-wide correlation between the genetic contributors in *SCN5A*⁺ and *SCN5A*⁻ patient subgroups ($r_g = 0.82$; s.e. = 0.2), suggesting the involvement of the same risk alleles. Out of 2,367 BrS cases with complete data, 228 had a life-threatening arrhythmic event (LAE) at diagnosis or during follow-up (median age at last follow-up was 50.0 years, interquartile range 39.5-60.7). Although *SCN5A*⁺ cases had a higher risk for LAE compared to *SCN5A*⁻ cases (HR 1.87; 95% CI 1.37-2.55; $P = 8.1 \times 10^{-5}$; **Supplementary Table 9**), PRS_{BrS} was not significantly associated with LAE in BrS cases ($P = 0.30$, **Supplementary Fig. 9**). On the other hand, PRS_{BrS} was significantly higher in BrS cases that presented with a spontaneous type 1 BrS ECG compared to those with a type 1 BrS ECG after sodium channel blocker challenge (9.3 ± 1.1 vs. 9.1 ± 1.1 ; $P = 1.7 \times 10^{-5}$; **Fig. 3b**), an effect that seemed more pronounced in the subgroup of *SCN5A*⁻ cases (9.2 ± 1.0 vs. 9.5 ± 1.1 ; $P = 3.5 \times 10^{-8}$; **Extended Data Fig. 4**). These data support the concept that disease susceptibility in different individuals relies upon varying contributions of multiple factors, including both rare and common genetic variations and exposure to sodium channel blockade.

To explore the genetic relationship of BrS with other traits, we performed a phenome-wide association study (PheWAS) in the UK Biobank using PRS_{BrS}, applying Bonferroni correction ($P < 7 \times 10^{-4}$) to define statistical significance (**Fig. 4a** and **Supplementary Tables 10-12**). PRS_{BrS} was associated with greater risk for atrioventricular conduction disorders ($P = 1.5 \times 10^{-9}$; OR = 1.16 (1.10-1.21) per s.d. increase), as well as longer ECG activation/conduction times reflected in the P-wave duration ($P = 5.3 \times 10^{-9}$; $\beta = 0.76$ ms, s.e. = 0.13), PQ interval duration ($P = 1.9 \times 10^{-45}$; $\beta = 2.70$ ms, s.e. = 0.19), and QRS duration ($P = 4.2 \times 10^{-55}$; $\beta = 1.23$ ms, s.e. = 0.08). This underscores the important role of conduction slowing in the pathogenesis of BrS, and is further supported by a significant positive genome-wide correlation between BrS and QRS duration²⁸ ($r_g = 0.44$, $P = 1 \times 10^{-8}$; **Supplementary Table 13**). In contrast, PRS_{BrS} was negatively associated with the QT interval duration ($P = 4.8 \times 10^{-16}$; $\beta = -1.56$ ms, s.e. = 0.19), consistent with suggestions of higher

cardiomyocyte phase 1 repolarizing drive in BrS^{13,25}. PRS_{BrS} was also negatively associated with the occurrence of atrial fibrillation (AF) or flutter ($P = 6.2 \times 10^{-13}$; OR = 0.94 (0.92-0.95)). The effects of each of the 21 BrS risk alleles in previously published GWAS of PQ²⁹, QRS²⁸, QT³⁰ and AF³¹ are generally concordant with the aggregate effect of those alleles (PRS_{BrS}) in the PheWAS (**Fig. 4b, Extended Data Fig. 5 and Supplementary Tables 14-17**). One exception is the BrS risk allele near *MYO18B* (rs133902-T), which was also associated with greater risk for AF ($P = 9 \times 10^{-10}$ in Nielsen et al.³², and $P = 1 \times 10^{-7}$ in Roselli et al.³¹; **Extended Data Fig. 5**). This suggests that, although changes in conduction velocity through sodium channel expression effects modulate risk for AF and BrS in opposite directions, some disease mechanisms such as those involving structural proteins (e.g. MYO18B) may be shared in both arrhythmias, with concordant effects. We also observed novel associations of PRS_{BrS} with non-electrical phenotypes, namely body mass index (log-transformed; $P = 6.2 \times 10^{-6}$; $\beta = 0.0012$, s.e. = 0.0003) and systolic blood pressure ($P = 4.3 \times 10^{-5}$; $\beta = 0.12$ mmHg, s.e. = 0.03; **Supplementary Table 12**). Of note, a recent study identified a modulatory effect of hypertension in cardiac sodium channel disease³³. Lastly, a lookup of loci previously associated with ECG traits and AF identified 9 additional novel loci associated with BrS at a Bonferroni-corrected $P < 1.9 \times 10^{-4}$ (**Supplementary Table 18**).

In conclusion, several important findings emerge from this work. First, we identified a total of 12 loci (10 novel) associated with BrS, a rare disease and a significant cause of sudden cardiac death in young adults. Three of these loci harbor multiple association signals. Second, the eight independent association signals at the *SCN5A-SCN10A* locus highlight the primacy of reduced sodium channel function in BrS susceptibility, whereas the eight loci harboring cardiac transcription factor genes point to transcriptional regulation as a key feature of BrS pathogenesis. Third, functional studies of *MAPRE2* support a novel mechanism of Na_v1.5 modulation via the microtubule network in BrS pathogenesis. Fourth, analyses using the UK Biobank highlight a genetic overlap between the BrS and cardiac electrical traits and common disorders in the general population. Finally, polygenic risk score analyses support the concept that disease threshold in different individuals with BrS is reached by varying contributions of rare *SCN5A* variants, common risk alleles and sodium channel blockade. Taken together, these findings broaden our understanding of the genetic architecture of BrS and provide new insights into its molecular underpinnings.

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Nantes Referral Center for inherited cardiac arrhythmia

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Author Contributions

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Competing Interests Statement

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Figure legends

Fig. 1 | Manhattan plot of genome-wide association meta-analysis comprising 2,820 unrelated Brugada syndrome cases and 10,001 controls. The association P values were derived from a meta-analysis of the 10 GWAS strata using a fixed effects model with an inverse-variance weighted approach. We performed logistic regression on the disease status under additive model of SNP's genotype. P -values are two-sided and not adjusted for multiple testing. The y -axis has breaks to emphasize the novel loci. The red and blue lines indicate the genome-wide significance ($P < 5 \times 10^{-8}$) and suggestive significance ($P < 1 \times 10^{-6}$) thresholds, respectively. Genes at novel loci are depicted in red.

Fig. 2 | Loss of *MAPRE2* leads to lower conduction velocity, action potential upstroke velocity and sodium current. **a**, Left panel shows representative isochrone maps of hearts isolated from 5 day post-fertilization zebrafish larvae injected with tracrRNA/Cas9 and multiple gRNAs targeting *mapre2* (*mapre2* KO) or tracrRNA/Cas9 without gRNA (CTRL). The dotted squares reflect the main ventricular area in the hearts from which the various

parameters are measured. Right panel shows average ventricular conduction velocity (CV) in CTRL and *mapre2* KO hearts. **b**, Left panel shows representative maximum action potential (AP) upstroke velocity (V_{max}) maps from zebrafish hearts. Right panel shows average V_{max} in CTRL and *mapre2* KO hearts. **c**, Left panel shows representative maps of AP duration at 80% repolarization (APD80) in isolated hearts paced at 100 bpm. Right panel shows average APD80 in CTRL and *mapre2* KO hearts. **d**, Representative APs at 1 Hz pacing from single human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) with CRISPR/Cas9-mediated *MAPRE2* knockout and isogenic control (CTRL) hiPSC-CMs. A constant ohmic current was injected to set the membrane potential just before the APs at approximately -80 mV to overcome the depolarized state of the hiPSC-CMs (see Online Methods). Inset shows first derivative of the AP upstroke velocity (V_{max}). **e**, Average V_{max} and APD at 30 and 90% repolarization (APD₃₀ and APD₉₀, respectively) in CTRL and MAPRE2 KO hiPSC-CMs. V_{max} ($P = 8.1 \times 10^{-6}$), APD₃₀ ($P = 4.8 \times 10^{-6}$), and APD₉₀ ($P = 6.0 \times 10^{-7}$) differed significantly between CTRL and MAPRE2 KO hiPSC-CM (** $P < 0.01$; unpaired two-tailed Student's *t*-test). Maximal diastolic potential (-56.4 ± 1.5 mV (CTRL) vs. -55.6 ± 1.6 mV (MAPRE2 KO)) and AP amplitude (114.8 ± 6.7 mV (CTRL) vs. 121.8 ± 4.2 mV (MAPRE2 KO)) did not differ significantly between CTRL ($n = 15$) and MAPRE2 KO ($n = 12$) hiPSC-CMs (unpaired two-tailed Student's *t*-test). **f**, Left panel shows average current-voltage relationships of the sodium current (I_{Na}). Right panel shows average repolarizing outward current ($I_{outward}$) in CTRL and MAPRE2 KO hiPSC-CMs. Insets show voltage protocol used. * $P < 0.05$, ** $P < 0.01$ vs. CTRL (two-way ANOVA). Results are expressed as mean \pm s.e.m. Numbers in the bar graph refer to the number of hearts or cells studied.

Fig. 3 | Distribution of PRS_{BrS} in specific patient sub-groups. **a**, Histograms displaying PRS_{BrS} distribution in BrS cases carrying a rare pathogenic or likely-pathogenic variant in *SCN5A* (*SCN5A*⁺; blue) compared to BrS cases without such variants (*SCN5A*⁻; red). **b**, Histograms displaying PRS_{BrS} distribution in BrS cases presenting with a spontaneous type 1 BrS ECG (blue) compared with those presenting with a type 1 BrS ECG only after sodium channel blocker challenge (drug-induced; red). PRS_{BrS} was calculated per individual based on the 21 BrS risk alleles and their corresponding effect sizes. Results were obtained after logistic regression, two sided p-value not corrected for multiple testing. Reported *P* values refer to the difference in PRS_{BrS} units between two groups. Dashed lines showing the mean PRS_{BrS} for each group.

Fig. 4 | Associations between polygenic susceptibility to Brugada syndrome and common cardiovascular diseases and traits. **a**, Results of the phenome-wide association analysis (PheWAS) for the Brugada syndrome (BrS) polygenic risk score (PRS_{BrS}) among individuals of European ancestry from the UK Biobank. Phenotypes significantly associated with PRS_{BrS} and phenotypes relevant to the heart are shown on the x-axis (five electrocardiographic traits are depicted on the right of the plot); the *P* values from multiple regression are depicted on the y-axis. Red circles indicate that polygenic predisposition to BrS is associated with a positive beta (e.g. increased risk of the condition or higher value for continuous traits), whereas blue circles indicate that polygenic predisposition to BrS is associated with a negative beta (e.g. decreased risk of the condition or lower value). We set the significance threshold to $P < 0.0007$ after Bonferroni correction ($P < 0.05/70$), shown as dotted colored lines. The grey dotted lines indicate the nominal significance threshold ($P < 0.05$). The complete PheWAS results are shown in **Supplementary Tables 11** and **12** for dichotomous

and continuous traits, respectively. **b**, Heat-map of associations between BrS risk alleles and atrial fibrillation/flutter (AF), PR-interval (PR), QRS-complex duration (QRS) and QT interval duration (QT) from previously published GWAS²⁸⁻³¹. The complete PheWAS results are shown in **Supplementary Tables 14-17**. Each row represents an independent BrS risk allele, while each column represents a phenotype. Red indicates that the BrS risk allele (or a proxy with $r^2 > 0.8$) is associated with higher risk of AF or prolongation of the electrocardiographic interval; blue indicates that the BrS risk increasing allele is associated with lower risk of AF or shortening of the interval. The darkest red and blue colors represent conventional genome-wide significance in the published GWAS ($P < 5 \times 10^{-8}$).

Table 1 | Lead SNPs and effect estimates for genome-wide significant association signals ($P < 5 \times 10^{-8}$) in the BrS GWAS meta-analysis

Locus	Lead SNP	Genomic position (hg19)	Risk allele	Other allele	Risk allele frequency in cases	Risk allele frequency in controls	OR [95% CI]	P value	Nearest gene
1	rs7638909*	3:38594973	G	T	0.32	0.24	1.28 [1.17 - 1.40]	2.79E-08	SCN5A
	rs62241190*	3:38607468	G	A	0.06	0.03	1.96[1.63 - 2.32]	8.56E-14	SCN5A
	rs7374540*	3:38634142	C	A	0.51	0.39	1.72 [1.61 - 1.81]	3.56E-57	SCN5A
	rs7433206*	3:38657708	A	T	0.45	0.42	1.48 [1.37 - 1.60]	9.52E-24	SCN5A
	rs34760424*	3:38683018	G	T	0.98	0.94	2.32 [1.96 - 2.70]	3.03E-23	SCN5A
	rs41310232*	3:38689242	A	G	0.16	0.09	1.56 [1.40 - 1.74]	1.19E-15	SCN5A
	rs6782237*	3:38696553	C	G	0.78	0.68	1.74 [1.61 - 1.87]	1.05E-47	SCN5A
	rs6801957	3:38767315	T	C	0.65	0.42	2.49 [2.34 - 2.65]	1.30E-180	SCN10A
2	rs6913204*	6:125664540	C	T	0.51	0.47	1.22 [1.13 - 1.29]	1.30E-08	HDDC2
	rs9398791	6:126115821	C	T	0.61	0.51	1.53 [1.44 - 1.63]	1.49E-39	HEY2, NCOA7
3	rs11765936	7:35349146	G	T	0.18	0.15	1.37 [1.25 - 1.49]	4.30E-11	TBX20
	rs340398*	7:35413788	C	T	0.42	0.38	1.22 [1.15 - 1.30]	1.76E-09	TBX20
4	rs804281	8:11611865	G	A	0.63	0.58	1.22 [1.15 - 1.30]	1.22E-09	GATA4
5	rs72671655	8:106347897	T	A	0.97	0.95	1.85 [1.59 - 2.22]	2.51E-13	ZFPM2
6	rs72905083	11:32474374	A	G	0.1	0.08	1.43 [1.27 - 1.60]	2.09E-09	WT1
7	rs883079	12:114793240	C	T	0.34	0.28	1.25 [1.16 - 1.33]	1.59E-10	TBX5
8	rs11645463	16:54456353	A	G	0.59	0.54	1.22 [1.15 - 1.30]	1.27E-09	IRX3
9	rs72622262	16:54662944	C	G	0.87	0.83	1.36 [1.25 - 1.49]	1.37E-11	CRNDE, IRX5
10	rs12945884	17:64300281	T	C	0.58	0.53	1.20 [1.12 - 1.28]	3.31E-08	PRKCA
11	rs476348	18:32670021	C	T	0.73	0.69	1.25 [1.16 - 1.33]	2.64E-09	MAPRE2
12	rs133902	22:26164079	T	C	0.48	0.43	1.21 [1.13 - 1.29]	7.73E-09	MYO18B

*Variants associated with BrS in conditional analyses. Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio referring to each unit increase in the risk allele. We performed logistic regression on the disease status under additive model of SNP's genotype. P-values are two-sided and not adjusted for multiple testing. Confidence intervals are given for a nominal P-value of 0.05 in order to allow comparability with other studies and reports.

Online Methods

Case inclusion and study design. We established an international consortium allowing the inclusion of 2,820 unrelated individuals with Brugada syndrome (BrS) from 39 BrS reference centers in 12 countries (**Supplementary Table 1**). All human participants provided written informed consent, and all studies had received approval from the appropriate ethical review boards (see Reporting Summary). The diagnosis of BrS was made according to the 2013 Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA) and Asia Pacific Heart Rhythm Society (APHRS) expert consensus statement³⁷, the 2015 European Society of Cardiology guidelines², and the 2017 American Heart Association guidelines³⁸. Specifically, cases were included if they had a type 1 BrS ECG, that is, a coved type ST elevation at baseline (spontaneous) or after a drug challenge test, in one or more leads in the right precordial leads V1 and/or V2 in the standard position (4th intercostal space) or in high positions (2nd or 3rd intercostal spaces). Diagnostic ECGs were centrally assessed by a cardiac electrophysiologist with expertise in BrS (J.B.G., Y.M. or R.T.) to ensure the diagnostic ECG criteria were reached. Clinical data collection was performed at each site, including age at diagnosis, presence of a variant in *SCN5A*, presence of a spontaneous type 1 BrS ECG or a type 1 BrS ECG observed after drug challenge, implantable cardioverter-defibrillator implantation, time of occurrence of life-threatening arrhythmic events (LAEs), and family history of sudden cardiac death. LAEs were defined as out-of-hospital cardiac arrest or hemodynamically unstable ventricular tachycardia/ventricular fibrillation.

Assessment of the pathogenicity of reported *SCN5A* variants. The *SCN5A* gene had been screened for rare variants in 87.6% of individuals. Pathogenicity of rare variants in *SCN5A* identified in included BrS cases was centrally assessed using the American College of Medical Genetics and Genomics and Association of Molecular Pathology (ACMG/AMP) guidelines³⁹, using an adapted version of CardioClassifier⁴⁰ incorporating a quantitative approach based on case-control analyses, as performed previously in hypertrophic cardiomyopathy genes³, as well as a curated compendium of functional data⁴. Specifically, the following ACMG/AMP rules were applied:

- PM2/BS1: The PM2 or BS1 rules were activated depending on whether the gnomAD exomes filtering allele frequency was below or above the calculated maximum tolerated allele frequency for BrS. The threshold applied was 2.5×10^{-5} , calculated with <https://www.cardiodb.org/allelefrequencyapp/> using a disease prevalence of 1 in 2,000, allelic heterogeneity of 0.01 and penetrance of 0.10.
- BA1: Filtering allele frequency in gnomAD exomes > 0.001.
- PVS1: Truncating variants in *SCN5A*, i.e. frameshift, nonsense, splice donor and splice acceptor variants.
- PS4: Variant is enriched in case cohorts (based on published BrS *SCN5A* compendium⁴¹) compared to ExAC population controls (Fisher's exact test, $P < 1.79 \times 10^{-6}$ after multiple testing correction), as applied by CardioClassifier.
- PP3/BP4: Multiple lines of computation evidence support or refute a deleterious effect, as applied by CardioClassifier.

- PM4: A protein length change as a result of an in-frame deletion or insertion in a non-repeat region.
- BP3: In-frame insertion or deletion that falls within a region annotated by repeat masker.
- PS1: Same amino acid change as a previously established pathogenic variant (multiple ClinVar submissions with no conflicting evidence).
- PM5: Novel missense change at an amino acid residue where a different missense change has previously been established as pathogenic (multiple ClinVar submissions with no conflicting evidence).
- PS1_moderate/PM5_supporting: Known disease-causing variant affecting the same residue in a paralogous protein⁴², either with the same or a different amino acid substitution, respectively.
- PS3/BS3: Functional evidence showing a deleterious effect (or no deleterious effect) of the variant based on published cellular electrophysiology studies curated by Denham et al.⁴³.
- PM1: This rule was applied based on pre-computed etiological fraction (EF) values for rare, non-truncating variants as described by Walsh et al.⁴⁴. This approach defines the prior probability, as calculated through case-control cohort analysis, that a variant in a particular gene/protein region is pathogenic. The rules applied are PM1_strong ($EF \geq 0.95$), PM1_moderate ($0.9 \leq EF < 0.95$) or PM1_supporting ($0.8 \leq EF < 0.9$). For SCN5A variants, this analysis was performed using case data from this study and population data from gnomAD exomes. Protein domains were defined according to the Uniprot (version 207) entry Q14524 with the four transmembrane regions and three interlinker domain regions assessed together as functionally equivalent domains. The PM1_strong rule was applied to the transmembrane regions (amino acid residues 132-410, 718-938, 1207-1466, 1530-1771) and the PM1_supporting rule was applied to the N-terminus region (residues 1-131).

Rules based on co-segregation of variants with disease in family pedigrees (PP1/BS4) or de novo inheritance with/without confirmed paternity and maternity (PS2/PM6) were not applied.

GWAS analysis design, description of the strata and quality control. Quality control (QC) and case-control association analysis were performed in 10 strata (see **Supplementary Note** for a full description of the 10 different strata; **Supplementary Table 2**) followed by meta-analysis, as described in the following sections. Samples were grouped into strata on the basis of common ancestry (as determined by principal component analysis of genotypic data; **Supplementary Fig. 1**), same genotyping platform and time of genotyping. To ensure that none of the BrS cases were included in multiple strata, a genotypic relatedness analysis based on identity by state was performed using a linkage-disequilibrium (LD) pruned set of single nucleotide polymorphisms (SNP) that were overlapping between all strata.

Imputation and association analyses. Genome-wide imputation was performed per stratum using Eagle2 phasing, Minimac3 and the Haplotype Reference Consortium (HRCr1.1) panel implemented on the Michigan Imputation Server v.1.0.2⁴⁵. After imputation, only SNPs with MAF > 0.01 and a Minimac $R^2 > 0.5$ were taken forward in the association analysis.

The association of alternate allele dosage with BrS was performed for each of the 10 strata using a frequentist test in an additive model implemented in SNPTEST (v2.5.2), correcting for the first six genotypic principal components. The summary results of the 10 strata were then combined using an inverse variance weighted fixed-effect meta-analysis, performing meta-analysis heterogeneity analysis, implemented in METAL (version released on 2011-03-25). SNPs that were missing in $\geq 4/10$ strata, as well as those with a heterogeneity test $P < 10^{-7}$ were excluded.

We sought to uncover additional association signals at BrS loci using conditional analysis. Specifically, for each locus reaching the genome-wide statistical significance threshold ($P < 5 \times 10^{-8}$), a frequentist test implemented in SNPTEST (v2.5.2) was performed correcting for the first six genotypic principal components and conditioning on the lead SNP at the locus, for each of the 10 strata, followed by meta-analysis. If another independent signal reaching genome-wide significance was identified at the locus in the meta-analysis, a second analysis conditioning on the two independent lead SNPs at the locus was then performed. This was repeated until no independent signal reached genome-wide statistical significance.

The results of the case-control meta-analysis are shown in **Fig. 1, Table 1** and **Supplementary Table 3**. Principal component analyses plots of cases and controls in each of the 10 GWAS strata are shown in **Supplementary Fig. 1**. QQ plots of each stratum are reported in **Supplementary Fig. 2** and forest plots for all loci reaching $P < 5 \times 10^{-8}$ are shown per stratum and overall (summary) in **Supplementary Fig. 3**. Stratum-specific odds ratios, 95% confidence intervals, and P values are based on logistic regression assuming an additive genetic model. Summary odds ratios and 95% confidence intervals are from fixed effects meta-analysis. Forest plots were generated using the rmeta library implemented in the R project (R foresplot).

Analysis of heritability attributable to common variants. We used the generalized restricted maximum likelihood (GREML) approach of GCTA (version 1.92.4 beta)^{46,47} to estimate how much of the variance in BrS susceptibility could be attributed to common genetic variants (SNP-based heritability, h^2_{SNP}). The analysis was performed by stratum, followed by a fixed-effects meta-analysis using the meta package in R version 3.6.0. The GSA_TUR stratum was excluded given its small sample size ($n = 300$) where GREML failed. Prior to heritability analyses, we performed additional stringent post-imputation QC as suggested⁴⁸, using hard call genotypes (genotype probability, GP > 0.9) and excluding SNPs with missing rate > 0.01, MAF < 0.05, Hardy-Weinberg test $P < 0.05$ and phenotype biased missingness $P < 0.05$, as well as samples with missing rate > 0.01. Less stringent QC was used for the GSA_IT stratum to allow for sufficient SNPs to remain for GREML. For each stratum, we generated a genetic relationship matrix (GRM) and excluded distantly related individuals (proportion IBD > 0.05). We estimated h^2_{SNP} on the liability scale assuming a prevalence ranging from 0.005 to 0.0005^{8,49} with the first 20 genotypic principal components and sex as covariates. We also estimated h^2_{SNP} attributable to the 12 loci associated with BrS at

genome-wide statistical significance. Loci were defined as +/- 500 kb from the lead SNP(s) in primary or conditional analyses. The proportion of heritability explained by the 12 loci was calculated by dividing their h^2_{SNP} by the genome-wide h^2_{SNP} . As an alternative to GREML, we also used LDSC (1.0.0) to calculate SNP heritability using the meta-analysis summary statistics, restricted to the ~1.2 million HapMap SNPs, using the 1000 Genomes European population as a reference. The results of h^2_{SNP} estimation are shown in **Supplementary Table 4**.

Locus annotation. Association signals from the meta-analysis were annotated by presence of: (i) (proxy) coding variants; (ii) cis-expression quantitative trait loci (eQTL); (iii) cis-splice quantitative trait loci (sQTL); and (iv) contact with promoters of nearby genes.

(Proxy) coding variants. We performed a lookup to assess whether the lead SNP or variants in LD with the lead SNP alter the protein-coding region of a gene. An $r^2 \geq 0.6$ was applied, defined using the European subset of the 1000 Genomes Project in LDlink⁵⁰. Protein-altering coding variants were defined as missense, splice site (within 2 nucleotides of the exon-intron boundary), in-frame deletions/insertions, frameshift, and stopgain. Coding variants defined in this way are listed in **Supplementary Table 3**.

cis-eQTL. For each association signal, we used the left ventricular tissue dataset from the Genotype-Tissue Expression project (GTEx, accessed December 2019)²⁰ to identify cis-eQTLs. Significance of a variant-gene association was defined using a Bonferroni-corrected P -value threshold, correcting for the number of genes within 1 Mb of the association signal. As such, the P -value thresholds ranged from 5.56×10^{-3} to 1.85×10^{-3} . Significant eQTLs are listed in **Supplementary Table 3** and displayed in **Supplementary Fig. 4**. Significant eQTLs were assessed for colocalization using eCAVIAR⁵¹ to determine colocalization with the GWAS hit. Heart - Left Ventricle eQTLs from GTEx v.7 were used; eCAVIAR used SNP, eQTL z -scores and LD correlation values to calculate a colocalization posterior probability of a trait GWAS locus and an eQTL. We calculated LD of SNPs 1Mb on both sides of the SNPs, using European ancestry HRS samples (dbGaP accession code phs000428.v2.p2) as a reference. We used the default assumption of two causal SNPs. Colocalization posterior probability (CLPP) for eQTL hits are displayed in **Supplementary Table 3**.

cis-sQTL. We assessed whether the lead SNP at each locus displayed a cis-sQTL effect by performing a lookup in the left ventricular tissue dataset of GTEx (accessed March 2020)²⁰. Only variants with a significant variant-gene association are reported.

Hi-C. Interaction between associated loci and target regions was assessed using the tissue specific 3D chromatin interaction (Hi-C) mapping function, incorporated in FUMA⁵². Hi-C data from human left ventricle³⁶ was explored and interactions with an $\text{FDR} \leq 10^{-6}$ are reported in **Supplementary Fig. 4** and listed in **Supplementary Table 3**. Target regions including the transcription start site are displayed in bold.

Analysis for enrichment in genes encoding DNA binding proteins. We used SNPsnap⁵³ to generate 10,000 sets of 12 SNPs that had characteristics matching the lead SNPs at the non-chromosome 3 BrS loci. We took 12 SNPs since the two lead SNPs at the *TBX20* locus were located close to each other and only one of these was therefore considered. SNPs were matched based on minor allele frequency, number of SNPs in LD, distance to nearest gene

and number of nearby genes (gene density). Genes listed in GO term ‘sequence-specific DNA binding’ (GO:0043565) were used as a broad list of genes encoding DNA binding proteins. Enrichment was assessed by permutation testing across the 10,000 SNP sets to determine the neutral expectation for the number of DNA binding proteins overlapping or in vicinity to SNPs with characteristics similar to ours, yielding a *P* value for a one-tailed test. A SNP was considered near a gene encoding a DNA binding protein if it was within a radius of 300 kb upstream or downstream of any gene on the GO term list.

Genome-wide visualization and annotation. The BrS GWAS summary statistics were uploaded to FUMA (Functional Mapping and Annotation of GWAS)⁵² for visualization and genome-wide analyses. Gene-set and tissue expression analyses were performed using MAGMA⁵⁴ implemented in FUMA. Gene Ontology (GO) gene sets from the Molecular Signatures Database (MSigDB, v6.2)⁵⁵ were used for the gene-set analysis, and the Genotype-Tissue Expression project (GTEx, version 8) was used for tissue specificity analysis²⁰. The results of MAGMA gene-set analyses are shown in **Supplementary Table 8** and the results of MAGMA tissue specificity analyses are shown in **Supplementary Fig. 5**.

We used GARFIELD²³ to correlate the GWAS findings with regulatory or functional annotations and find features relevant to a phenotype of interest. Since our GWAS included only European individuals, we used the original files describing the allele frequencies and linkage disequilibrium from the UK10K data provided in the GARFIELD distribution. We also used the annotation and distance to TSS files provided with the GARFIELD release. The annotations included 1,005 features extracted from ENCODE, GENCODE and Roadmap Epigenomics projects, including genic annotations, chromatin states, histone modifications, DNaseI hypersensitive sites and transcription factor binding sites, among others, in a number of publicly available cell lines. Enrichment *P*-value is determined empirically through a permutation procedure accounting for associated regions structures based on the number of SNPs and mean LD. Because the chromosome 3p region presents a complex structure with a set of SNPs both physically close and highly associated, we also ran the enrichment analysis without this region. Results of GARFIELD functional enrichment analyses are shown in **Supplementary Table 7** and **Supplementary Fig. 6**.

Alternatively, we used stratified LDscore regression⁵⁶ to estimate the contribution to heritability for cell type or tissue-specific elements. In this extended model, the expected SNP association statistic (c^2) is modelled by LDscore as previously and by a binary variable *C* (for category) which takes value 1 if the SNP falls into the functional category (and 0 otherwise). Multiple-regression is applied. We label regions as putatively functional or not for each annotation (function/tissue) using the functional map estimated by the method FUN-v-LDA⁵⁷ for the Roadmap-Epigenomic project. Results from this LDSC enrichment test are shown in **Supplementary Table 6**.

Transcriptome-wide association study (TWAS). TWAS was performed using FUSION¹⁹ and eQTL data in cardiac tissues (left ventricle and atrial appendage) from GTEx²⁰. Gene expression weights were calculated using prediction models implemented in FUSION. This includes top1 (i.e., the single most significant eQTL-SNP as the predictor), LASSO regression, enet (elastic net regression) and BLUP (best linear unbiased predictor). SNP data located 500 kb on both sides of the probes were used to obtain expression weights. There were 4,490

and 5,225 genes with significant cis-heritability ($h^2 > 0.05$) for left ventricle and atrial appendage cardiac tissues, respectively, to calculate expression weights. Expression weights were then combined with summary-level results from the meta-analysis to estimate association statistics between gene expression and BrS. Genome-wide significant TWAS genes were considered at $P_{\text{TWAS}} < 5.2 \times 10^{-6}$ (Bonferroni = $0.05/4,490+5,225$). Significant genes identified by TWAS are listed in **Supplementary Table 5**.

Brugada syndrome polygenic score (PRS_{BrS}). A BrS polygenic risk score (PRS_{BrS}) was derived from the BrS case-control GWAS. All independent lead SNPs reaching the genome-wide significance threshold ($P < 5 \times 10^{-8}$) in either the primary or conditional analyses were included (total of 21 SNPs, **Table 1**). The score for each individual was calculated by taking the sum of risk allele dosage weighted by the beta coefficient estimated in the GWAS over these SNPs. To assess whether the burden of BrS-associated common variants differs between distinct BrS subgroups, we tested the association between certain subgroups and PRS_{BrS} using linear regression. We performed a total of seven predefined analyses involving PRS_{BrS}: (i) comparison of PRS_{BrS} in *SCN5A*⁺ vs. *SCN5A*⁻ ($n = 1$); (ii) association of PRS_{BrS} with life-threatening arrhythmic events (LAE) in all BrS, *SCN5A*⁻ BrS and *SCN5A*⁺ BrS ($n = 3$); and (iii) Association of PRS_{BrS} with the occurrence of type 1 ECG at baseline vs. drug-induced in all BrS, *SCN5A*⁻ BrS, and *SCN5A*⁺ BrS ($n = 3$). The Bonferroni-corrected threshold for significance was set to $P < 0.007$ ($0.05/7$). The five first principal components were used as covariates in a sensitivity analysis, and results were similar to the analysis without covariates. These data are presented in **Fig. 3** and **Extended Data Fig. 4**.

Survival analyses. Time to life-threatening arrhythmic events (LAE defined as out-of-hospital cardiac arrest or hemodynamically unstable ventricular tachycardia/ventricular fibrillation) survival analyses were performed in the BrS cases. Follow-up started at birth and ended at the date of an event, the last visit or the 70st birthday, whichever came first. Cox proportional hazards regression models were first used to assess the association of clinical risk factors with LAE in univariable followed by multivariable models. The adjusted Cox regression multivariable model included sex, *SCN5A*⁺ and spontaneous type 1 ECG. The proportional hazard assumptions were verified through examination of Schoenfeld residuals plots. For all analyses, a P -value < 0.05 was considered statistically significant. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc, NC, USA), and R version 3.4. Kaplan Meier curves were created to illustrate the event free survival within PRS_{BrS} quartiles, and single SNP genotypes and log rank tests were used to compare the survival curves. The effect of the PRS_{BrS} (continuous) and single SNP genotypes was estimated using Cox proportional hazards regression with adjustment for sex, genotypic PC1-PC6, the presence of a pathogenic or likely pathogenic variant in *SCN5A* and spontaneous type 1 BrS ECG. All SNP- or PRS_{BrS}-based statistical analysis were performed in three strata separately based on genotypic platform (Affymetrix CEU, PMRA and Illumina GSA) followed by meta-analysis using an inverse variance weighted fixed effect model, implemented in METAL (version 2011-03-25)⁵⁸. Results from these survival analyses are shown in **Supplementary Table 9** and **Supplementary Fig. 9**.

Pairwise genetic correlation. We performed pairwise genetic correlation between BrS and published GWAS studies of ECG traits (PR²⁹, QRS²⁸ and QT³⁰) and atrial fibrillation^{31,32}, using LDSC (Version 1.0.1)^{38,39}. For each GWAS, we first reformatted summary statistics using the “munge_sumstats.py” command, filtering for the HapMap3 SNPs with corresponding alleles using the “--merge-alleles w_hm3.snplist” flag, as recommended. The HapMap3 SNPs were downloaded from “https://data.broadinstitute.org/alkesgroup/LDSCORE/w_hm3.snplist.bz2”. We then assessed genetic correlation using the “ldsc.py -rg” command and pre-computed LD scores from the European 1000 Genomes Project dataset which were downloaded from “https://data.broadinstitute.org/alkesgroup/LDSCORE/eur_w_ld_chr.tar.bz2”. In the primary analysis, we did not constrain the single-trait and cross-trait LD score regression intercepts. The results of the genetic correlation analyses are shown in **Supplementary Table 13**.

Phenome-wide association study (PheWAS) of PRS_{BrS} in the UK Biobank. The UK Biobank is a large prospective cohort study from the United Kingdom with deep phenotypic and genotypic data on ~500,000 individuals enrolled aged 40-69^{59,60}. Phenotypic data was ascertained from anthropometric measurements, surveys, medical history reviews and electronic health records. Individuals were genotyped using one of two similar custom arrays (UK BiLEVE Axiom Array or UK Biobank Axiom Array) with over 800,000 genome-wide markers⁶⁰. Quality-control and imputation using the UK10K panel and the 1000 Genomes reference panels were performed centrally. For the present analysis, we excluded individuals with outliers for heterozygosity or genotype missingness, individuals with discordance between self-reported and genetically inferred sex, individuals with putative sex chromosome aneuploidy, and individuals who decided to withdraw consent. Additionally, we restricted ourselves to white-British individuals as determined by previous principal component analysis⁶¹ and kept only unrelated individuals (those with 3rd degree or closer relationships were removed) while maximizing the final sample size⁶². The final cohort consisted of 359,017 individuals (54% females; median baseline age 59; median follow-up 7 years) of which 15,208 had a high-quality 12-lead resting ECG. Genetic dosages of imputed variants (version 3) were used to calculate PRS_{BrS} using PLINK2⁶³. Scores were standardized so that the population mean was 0 and the standard deviation was 1.

A PheWAS with an emphasis on cardiovascular traits was performed in this cohort using a list of 65 curated (disease) phenotypes (**Supplementary Table 10**). Associations between PRS_{BrS} and continuous phenotypes were tested using multivariable linear regression models in R version 3.5.0. Models were adjusted for age at baseline, sex, genotyping array and the first 10 principal components of ancestry. Binary phenotypes were included if there were at least 500 cases and were assessed using multivariable logistic regression adjusted for the same covariates (**Supplementary Table 11**).

For associations between the PRS_{BrS} and ECG-traits we further excluded: (i) individuals with heart rates over 120 bpm; (ii) individuals with previous myocardial infarction, Wolff-Parkinson-White syndrome or heart failure; (iii) individuals with pacemakers; (iv) individuals taking class 1 or class 3 antiarrhythmic or QT-prolonging medication (including digoxin); and (v) individuals with atrial fibrillation/flutter, atrioventricular block or any fascicular block on automated ECG. Trait-specific exclusions

were also applied (**Supplementary Table 12**). Exclusions were based on previously published GWAS^{28–30} as well manual inspection of trait distributions. Associations were assessed using multivariable linear regression adjusted for age at ECG, sex, genotyping array, the first 10 principal components of ancestry and optionally the RR-interval. Alpha for the entire PheWAS was determined at $0.05 / 70 = 7.00 \times 10^{-4}$ (Bonferroni correction).

Zebrafish model of MAPRE2 knockout. *Zebrafish maintenance.* Zebrafish (*Danio rerio*) were maintained in a dedicated fish facility at 28.5 °C with a stable circulating system that continuously filters, treats (with UV light), and aerates the water. All experiments using zebrafish followed animal protocols approved by the Harvard Medical School Institutional Animal Care and Use Committee and complied with ethical guidelines. For all zebrafish studies, wild-type embryos were injected at 1-cell stage (as described under “Genome editing”) and used for experiments at 5 days post-fertilization. Sex in zebrafish is not determined until adulthood around 2–3 months of age.

Genome editing. Wild-type (WT) AB/Tuebingen (AB/Tu) zebrafish were crossed and resultant embryos from the same clutches were divided into two different groups injected with a solution containing either three gRNAs targeting *mapre2* at three independent loci (exon 1: TGCTCGCCAGGGTCTGGAGGGGG, exon 3: TTCTTAAGACTGATACAGCCGGG, exon 4: GACAGAGCTTGGGTCGGACCGGG), Alt-R[®] tracrRNA (#1072533), and Alt-R[®] S.p. HiFi Cas9 Nuclease V3 (#1081060), or tracrRNA and Cas9 alone (all from Integrated DNA Technologies, Inc., Iowa, USA), according to the manufacturer’s instructions (**Supplementary Fig. 7a**). All larvae injected with gRNAs and used for optical mapping were sequenced using three primer pairs corresponding to the target sites of the three gRNAs: exon 1 (CTGTGAGTGGAAAGacacattc, CGCACTGTGTTCTTTCTGTAGG), exon 3 (TCATCTCTGTGCATTGTTTTCC, CTGCACATGTCTAAAGCAAAGG), and exon 4 (CAACCTTGACTTCATTCAGTGG, acagaatttccatctttgggtg). All larvae had evidence of editing at two loci or more by Sanger sequencing.

Optical mapping of isolated zebrafish hearts. Optical mapping and signal processing were performed as previously described⁶⁴. Briefly, isolated hearts were incubated with a voltage-sensitive fluorescent dye in the FluoVolt™ Membrane Potential Kit (Invitrogen, USA) for 20 min at room temperature (RT). Subsequently, the hearts were transferred into a perfusion chamber (RC-49MFS; Warner Instruments) with Tyrode’s solution (RT) containing: 136 mM NaCl, 5.4 mM KCl, 1.8 mM CaCl₂, 1.0 mM MgCl₂, 0.3 mM Na₂HPO₄, 5.0 mM glucose, 10 mM HEPES; pH 7.4 (NaOH). Cytochalasin D (1 mM; Sigma, USA) was added to uncouple electrical impulses from contractions. The chamber was then mounted onto the stage of an inverted microscope (TW-2000; Nikon) with electrical wires connected to the built-in platinum wires in the chamber for pacing. The heart was excited with a 470-nm light-emitting diode, and the emission was collected by a high-speed 80 by 80 pixel CCD camera (RedShirtImaging, USA) with 14-bit resolution. Using a 20× objective and 0.5× C-mount adapter, the final magnification was 10× with a pixel-to-pixel distance of 2.4 μm. For signal processing and quantification, the images were analyzed by customized scripts in MATLAB (MathWorks, USA)⁶⁴. Optical mapping data are shown in **Fig. 2a-c**.

Quantitative real-time PCR on whole zebrafish larvae. Total RNA was extracted from whole 5 dpf larvae using RNeasy Plus Mini Kit (Qiagen, USA) and reversed transcribed using iScript™ Reverse Transcription Supermix for RT-qPCR (Bio-Rad, USA), according to the

manufacturers' instructions. cDNA libraries were used for quantitative real-time PCR using iTaq Universal SYBR Green Supermix (Bio-Rad, USA) on the CFX96 Touch Real-Time PCR Detection System (Bio-Rad, USA). Samples were run in technical triplicates and data were analyzed using the delta-delta Ct method, normalized to the level of *eef1a* (**Supplementary Fig. 7b,c** and **Supplementary Table 19**).

Statistics. Data are presented as mean \pm standard error of the mean (s.e.m.). Data were analyzed using Excel. Groups were compared with unpaired two-tailed Student's *t*-test and $P < 0.05$ defines statistical significance.

hiPSC-CM model of MAPRE2 knockout. *hiPSC maintenance.* The human induced pluripotent stem cell (hiPSC) line 19c3 was previously derived from peripheral blood mononuclear cells of a healthy male using Sendai virus (Invitrogen) and expressed an exogenous TNNT2 promoter-derived Zeocin resistance cassette⁶⁵. The hiPSCs were passaged at a ratio of ~1:15 every 4 days using 0.5 mM EDTA (for 6 min at RT), achieving ~75-80% confluence. The cells were routinely maintained in B8 mediumX2 on 1:800 diluted growth factor reduced Matrigel (Corning), except for the first 24 h after passage when B8 was supplemented with 2 μ M thiazovivin (LC Labs, T-9753), hereby referred to as B8T medium. All cultures (pluripotent and differentiation) were maintained in 2 ml medium per 9.6 cm² of surface area or equivalent.

Genome editing. To generate *MAPRE2* knockout gRNA expression vectors, two gRNAs targeting all four splicing variants of *MAPRE2* were designed using an online CRISPR design tool (IDT) with high predicted on-target score and minimal predicted off-target effect (**Supplementary Fig. 8**). DNA oligos (IDT) encoding each gRNA with BbsI ligation overhangs were annealed and inserted into the BbsI restriction site of a pSpCas9(BB)-2A-Puro (PX459, Addgene 62988) plasmid. The constructed gRNA expression plasmids were confirmed by Sanger sequencing (Eurofins) with the LKO1_5_primer (5'-GACTATCATATGCTTACCG-3'). CRISPR/Cas9-mediated knockout of *MAPRE2* was induced after cell passage by electroporation of 5×10^6 hiPSC with 5 μ g of each gRNA expression vector. Subsequently, cells were maintained for 48 h in B8T medium supplemented with 0.5 μ g/ml of puromycin (Gibco). Puromycin resistant individual colonies were picked and expanded ~10 days after electroporation. Clones with indels were identified by genomic sequencing with primers outside of the targeting region. Genomic DNA was extracted from the cell pellets using a Quick-DNA Miniprep Plus kit (Zymo).

hiPSC-CMs differentiation. Differentiation into hiPSC-CMs was performed according to previously described protocol with slight modifications^{66,67}. Briefly, at the start of differentiation (day 0), B8 medium was changed to R6C, consisting of RPMI 1640 (Corning, 10-040-CM), supplemented with 6 μ M of glycogen synthase kinase 3- β inhibitor CHIR99021 (LC Labs, C-6556). On day 1, medium was changed to RPMI, and on day 2 medium was changed to RBA-C59, consisting of RPMI supplemented with 2 mg/ml fatty acid-free bovine serum albumin (GenDEPOT, A0100), 200 μ g/ml L-ascorbic acid 2-phosphate (Wako, 321-44823) and 0.5 μ M Wnt-C59 (Biorbyt, orb181132). Medium was then changed on day 4 and then every other day with RBAI consisting of RPMI supplemented with 0.5 mg/ml fatty acid-free bovine serum albumin, 200 μ g/ml L-ascorbic acid 2-phosphate, and 1 μ g/ml *E. coli*-derived recombinant human insulin (Gibco, A11382IJ). Contracting cells were noted from day 7, differentiated cardiomyocytes were treated with 25 μ g/ml of Zeocin from day 10 to day 14. On day 20 of differentiation, cardiomyocytes were dissociated using DPBS for 20 min

at 37 °C followed by 1:200 Liberase TH (Roche, 5401151001) diluted in DPBS for 20 min at 37 °C, centrifuged at 300×g for 5 min, and filtered through a 100 µm cell strainer (Falcon). hiPSC-CMs were then plated on a Matrigel-coated 18-mm cover glass (Warner Instruments) for action potential (AP) measurements and into 30-mm culture dishes for membrane current recordings.

Cellular electrophysiology of hiPSC-CMs. APs and membrane currents were measured with manual and automated patch clamp, respectively. The experiments were not randomized and the investigators were blinded to allocation during experiments and outcome assessment. APs were recorded at 37 °C from spontaneously beating hiPSC-CMs using the amphotericin-B perforated patch-clamp technique with a Multiclamp 700B amplifier and Clampex 10.3 software (Molecular Devices, Sunnyvale, CA, USA). Pipettes (resistance 3-3.5 MΩ) were pulled from thin wall borosilicate glass capillaries (WPI, 1B120F-4) using a horizontal microelectrode puller (Sutter instrument, P-1000). Signals were low-pass-filtered with a cutoff of 10 kHz and digitized at 10 kHz. Bath solution contained: 140 mM NaCl, 4.0 mM KCl, 1.0 mM CaCl₂, 0.5 mM MgCl₂, 10 mM glucose, 10 mM HEPES; pH 7.4 (NaOH). Pipettes were filled with solution containing: 125 mM K-gluconate, 20 mM KCl, 5.0 mM NaCl, 0.26 mM amphotericin-B, 5.0 mM HEPES; pH 7.2 (KOH). To overcome the spontaneous activity and depolarized state of hiPSC-CMs⁶⁸, an ohmic current ~4 pA/pF was continuously injected to maintain a stable resting potential at approximately -80 mV, except where mentioned otherwise. The injected current did not differ significantly between the CTRL and MAPRE2 knockout hiPSC-CMs (4.0 ± 0.2 pA (CTRL, *n* = 15) vs. 4.3 ± 0.4 pA (MAPRE2 KO, *n* = 12). APs were evoked at 1 Hz by 4-ms, ~1.3× threshold current pulses through the patch pipette, and were characterized by maximum AP amplitude (APA), AP duration at 20 and 90% of repolarization (APD₂₀, APD₉₀, respectively), and maximal upstroke velocity (*V*_{max}). The maximal diastolic potential was analyzed during spontaneous activity. Potentials were corrected for the calculated liquid junction potential⁶⁹.

The sodium current (*I*_{Na}) and outward currents (*I*_{Outward}) were recorded at RT using a Syncropatch 768 PE automated patch clamp instrument (Nanion Technologies, München, Germany). Pulse generation and data collection were performed with PatchController384 V.1.3.0 and DataController384 V1.2.1 (Nanion Technologies). Whole-cell currents were filtered at 3 kHz and acquired at 10 kHz. The access resistance and apparent membrane capacitance were estimated using built-in protocols. Series resistance was compensated for 95% and leak and capacitance artifacts were subtracted using the P/4 method. The average seal resistance was 0.54 ± 0.05 GΩ (average ± s.e.m., *n* = 234), and cells were excluded from analysis if the maximum peak *I*_{Na} amplitude was less than 300 pA.

For the automated patch clamp recordings, hiPSC-CMs were plated into 30-mm culture dishes 5 days prior to the experiment. The day of the experiment, cells were washed once with DPBS⁻ for 20 min. Cells were then detached with 5 min treatment of TrypLE followed by 20-30 min treatment with RBAI media with 1:200 dilution of Liberase TH. Cells were then re-suspended in 15% RBAI media and 85% external solution at 180,000 cells/ml. Cells were allowed to recover for at least 30 min at 15 °C while shaking on a rotating platform. Following equilibration, 10 µl of cell suspension was added to each well of a 384-well, single-hole, low resistance (2 MΩ) for *I*_{Na} study and medium resistance (4 MΩ) for *I*_{Outward} study 'chip' (Nanion Technologies). The external solution contained: 140 mM NaCl, 4.0 mM KCl, 2.0 mM CaCl₂, 1.0 mM MgCl₂, 5.0 mM glucose, 10 mM HEPES; pH 7.4 (NaOH). The internal solution to study *I*_{Na} contained: 110 mM CsF, 10 mM CsCl, 10 mM NaCl, 10 mM

EGTA, 10 mM HEPES; pH 7.2 (CsOH). The internal solution to study I_{Outward} contained: 60 mM KF, 50 mM KCl, 10 mM NaCl, 10 EGTA, 10 mM HEPES; pH 7.2 (KOH).

I_{Na} was measured using a double pulse protocol (**Fig. 2f**, inset left panel) from a holding potential of -120 mV (cycle length of 5 seconds). I_{Na} was defined as the difference between peak and steady state current and current densities were calculated by dividing current amplitude by C_m . Recovery from inactivation was measured using a two pulse protocol, where a conditioning pulse -20 mV inactivated Na^+ channels, followed by a test pulse to -20 mV after a variable recovery interval ranging between 1 and 5,000 ms at -120 mV. Voltage dependence of activation and inactivation curves were fitted with Boltzmann function ($y = [1 + \exp\{(V - V_{1/2})/k\}]^{-1}$), where $V_{1/2}$ is the half-maximal voltage of (in)activation and k , the slope factor. I_{Outward} was acquired with a double pulse protocol (**Fig. 2f**, inset right panel) from a holding potential of -80 mV (cycle length of 10 seconds). I_{Outward} was measured at the end of the first pulse and densities were calculated by dividing current amplitude by C_m .

Quantitative real-time PCR. RNA was isolated using TRI reagent (Zymo) and Direct-zol RNA microprep kit (Zymo) including on-column DNase digestion to remove genomic DNA. cDNA was produced from 2 μg of total RNA using a High Capacity RNA-to-cDNA kit (Applied Biosystems). All PCR reactions were performed in triplicate in a 384-well plate format using TaqMan Gene Expression Master Mix in a QuantStudio 5 Real-Time PCR System (both Applied Biosystems) with following TaqMan Gene Expression Assays (Applied Biosystems): *18S* (Hs99999901_s1), *ACTB* (Hs01060665_g1), *GAPDH* (Hs02786624_g1), and *MAPRE2* (Hs00936741_m1). Relative quantification of gene expression was calculated using $2^{-\Delta\Delta\text{Ct}}$ method, normalized to the reference *18S*, *ACTB*, or *GAPDH* and untreated control samples as specified in **Supplementary Fig. 7**.

Statistics. Data were presented as mean \pm s.e.m.. Data were analyzed and graphed in GraphPad Prism 8. Comparisons were conducted via two-way ANOVA test and unpaired two-tailed Student's *t*-test. $P < 0.05$ defines statistical significance. The experiments were not randomized and the investigators were blinded to allocation during experiments and outcome assessment.

Data Availability

Data from the Genome Aggregation Database (gnomAD, v2.1) are available at <https://gnomad.broadinstitute.org>. Data from the UK Biobank participants can be requested from the UK Biobank Access Management System (<https://bbams.ndph.ox.ac.uk>). Data from the Genotype Tissue Expression (GTEx) consortium are available at the GTEx portal (<https://gtexportal.org>) accessed December 2019 & March 2020. Molecular Signatures Database (MSigDB, v6.2) is available at <http://www.gsea-msigdb.org/gsea/index.jsp>. Other datasets generated during and/or analyzed during the current study can be made available upon reasonable request to the corresponding authors. Individual-level data sharing is subject to restrictions imposed by patient consent and local ethics review boards. The Brugada syndrome GWAS summary statistics are available on Zenodo, at <https://doi.org/10.5281/zenodo.5095177> and on the GWAS catalog database (study ID accession: GCST90086158). The BrS polygenic score is available on the PGScatalog (PGS ID accession: PGS001779).

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