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1 **Genome-wide association meta-analysis identifies novel Brugada syndrome susceptibility loci and**
2 **highlights a new mechanism of sodium channel regulation in disease susceptibility**

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47 **Brugada syndrome is a cardiac arrhythmia disorder associated with sudden death in**
48 **young adults. With the exception of *SCN5A*, encoding the cardiac sodium channel $Na_v1.5$,**
49 **susceptibility genes remain largely unknown. Here we performed a genome-wide**
50 **association meta-analysis comprising 2,820 unrelated cases with Brugada syndrome and**
51 **10,001 controls and identified 21 association signals at 12 loci (10 novel). SNP-heritability**
52 **estimates indicate a strong polygenic influence. Polygenic risk score analyses based on the**
53 **21 susceptibility variants demonstrate varying cumulative contribution of common risk**
54 **alleles among different patient sub-groups, as well as genetic associations with cardiac**
55 **electrical traits and disorders in the general population. The predominance of cardiac**
56 **transcription factor loci indicates that transcriptional regulation is a key feature of**
57 **Brugada syndrome pathogenesis. Furthermore, functional studies conducted on *MAPRE2*,**
58 **encoding the microtubule plus-end-binding protein EB2, point to microtubule-related**
59 **trafficking effects on $Na_v1.5$ expression as a novel underlying molecular mechanism.**
60 **Taken together, these findings broaden our understanding of the genetic architecture of**
61 **Brugada syndrome and provide new insights into its molecular underpinnings.**

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63

64 Brugada syndrome (BrS) is a cardiac disorder characterized by hallmark ST-segment
65 elevation in the right precordial leads of the electrocardiogram (ECG) and increased risk of
66 sudden death in young adults^{1,2}. Rare coding variants in *SCN5A*, encoding the cardiac
67 sodium channel $Na_v1.5$ which underlies the sodium current (I_{Na}), are reported in
68 approximately 20% of cases^{3,4}. Other susceptibility genes contributing to the disorder
69 remain largely unknown. In a genome-wide association study (GWAS) conducted in 312
70 patients with BrS, we previously identified 3 common susceptibility variants and provided
71 evidence for a complex genetic architecture⁵. Here we extended this original association
72 scan to a large meta-analysis comprising 2,820 unrelated cases and 10,001 controls of
73 European ancestry (**Supplementary Table 1, Supplementary Table 2**), testing 6,990,521
74 variants with a minor allele frequency (MAF) ≥ 0.01 (**Figure 1, Supplementary Fig. 1,**
75 **Supplementary Fig. 2**). A total of 12 loci (10 novel) reached the genome-wide statistical
76 significance threshold of $P < 5 \times 10^{-8}$ (**Table 1; Supplementary Fig. 3, panels a-l**). Conditional
77 analysis uncovered 7 additional association signals at genome-wide significance at the
78 chromosome 3 locus, and an additional signal at the chromosome 6 and the chromosome 7
79 loci (**Table 1; Supplementary Fig. 3, panels m-u**). Analysis of SNP-based heritability (h^2_{SNP})
80 demonstrated that a substantial portion of susceptibility to BrS is attributable to common
81 genetic variation. h^2_{SNP} estimates ranged from 0.17 (standard error, SE, 0.035) using LDSC⁶
82 to 0.34 (SE 0.02) using GREML⁷, assuming a disease prevalence of 0.05%⁸, with 24% of the
83 total SNP-based heritability being explained by the 12 loci reaching genome-wide
84 significance (**Supplementary Table 4**).

85

86 Seven association signals (defined by the lead SNP and SNPs with $r^2 \geq 0.6$) at the
87 chromosome 3 locus overlapped *SCN5A* and one overlapped the neighboring *SCN10A* gene
88 encoding the sodium channel isoform $Na_v1.8$ (**Supplementary Fig. 4, panels a-h**). While
89 previous work⁹ proposed that the latter signal may act through regulation of *SCN5A*
90 expression, a possible involvement of *SCN10A* itself is suggested by a significant eQTL in left
91 ventricular tissue ($P = 5.29 \times 10^{-6}$, colocalization posterior probability (CLPP) = 0.16)
92 (**Supplementary Fig. 4, panel h, Supplementary Table 3**), whereas no eQTL was detected
93 for *SCN5A* ($P = 0.27$). Notably, 6 association signals overlapped genes encoding cardiac

94 developmental transcription factors (*HEY2*, *TBX20*, *ZFPM2*, *GATA4*, *WT1*, *TBX5*) and 4 were
95 <300kb from such genes (*TBX20*, *IRX3/IRX5*, *HEY2*)¹⁰. In support for the involvement of
96 transcription factor genes, an enrichment in genes encoding DNA binding proteins was
97 found at BrS GWAS loci by permutation testing (one-tailed permutation $P = 1 \times 10^{-4}$;
98 **Supplementary Fig. 5**). The transcription factors HEY2, TBX20, GATA4, TBX5 and IRX3/IRX5
99 are established regulators of ion channel expression in the adult heart, including that of
100 $Na_v1.5$ ¹¹⁻¹⁵, suggesting that modulation of ion channel expression is an important
101 mechanism in BrS. Potential regulatory effects of the transcription factors WT1 and ZFPM2
102 on ion channel expression have not yet been investigated. One association signal
103 overlapped *PRKCA* (supported by a co-localizing eQTL ($P = 4.63 \times 10^{-28}$, CLPP = 0.99);
104 **Supplementary Fig. 4, panel s, Supplementary Table 3**), which encodes protein kinase C
105 alpha involved in contractility and calcium handling in cardiomyocytes¹⁶. Lastly, two
106 association signals overlapped genes encoding microtubule or myofiber associated proteins,
107 namely *MAPRE2*¹⁷ and *MYO18B*¹⁸. A full annotation of the association signals (see Online
108 Methods) is presented in **Supplementary Table 3 and Supplementary Fig. 4**.
109

110 We performed a transcriptome-wide analysis (TWAS)¹⁹ based on predicted gene expression
111 in cardiac tissues²⁰ and identified 24 associations corresponding to 20 unique genes at the
112 Bonferroni-corrected threshold of $P < 5.2 \times 10^{-6}$ (**Supplementary Table 5**). Eighteen of these
113 genes are within ≈ 0.5 Mb of GWAS signals while two point to additional loci
114 (**Supplementary Table 5**). MAGMA gene property analysis for tissue specificity²¹ as well as
115 enrichment analysis using LDSC-SEQ²² and GARFIELD²³ identified left ventricle, right
116 ventricle and fetal heart, respectively, as significantly associated with BrS (**Supplementary**
117 **Fig. 6 and 7, Supplementary Tables 6 and 7**). MAGMA gene-set analysis²¹ identified,
118 amongst others, gene sets related to heart development and regulation of heart growth
119 (**Supplementary Table 8**), which may point to a broader role of transcriptional dysregulation
120 in the pathogenesis of BrS, beyond regulation of ion channel expression.
121

122 *MAPRE2* overlaps the association signal tagged by rs476348 and its causal role is supported
123 by chromatin interaction between its promoter region and the association signal and by a
124 significant eQTL ($P = 2.9 \times 10^{-5}$, CLPP = 0.10) **Supplementary Fig. 4, panel t, Supplementary**
125 **Table 3**), where the BrS risk allele is associated with lower *MAPRE2* expression in left
126 ventricular tissue compared to the non-risk allele. *MAPRE2* encodes the microtubule plus-
127 end binding protein EB2, a regulator of microtubule organization¹⁷. While effects on
128 transcription factor expression and ion-channel patterning are established molecular
129 mechanisms associated with BrS susceptibility^{5,13}, mechanisms involving microtubule
130 function and ion channel trafficking, as suggested by the association signal near *MAPRE2*,
131 have not yet been explored. We therefore generated loss-of-function mutants (KO) using
132 CRISPR/Cas9 in both zebrafish (**Supplementary Fig. 8**) and human induced pluripotent stem
133 cell derived cardiomyocytes (hiPSC-CMs) (**Supplementary Fig. 9**) to study the role of
134 *MAPRE2* in cardiac electrophysiology. Using optical mapping, we observed a significantly
135 lower conduction velocity and action potential upstroke velocity (V_{max}) in zebrafish hearts
136 isolated from *mapre2* KO compared to control (CTRL) larvae (**Fig. 2a,b**). Similarly, V_{max}
137 observed in single *MAPRE2* KO hiPSC-CMs was lower than isogenic control hiPSC-CMs
138 measured using manual patch clamp (**Fig. 2d,e**). The lower V_{max} observed in both mutant
139 zebrafish and hiPSC-CMs suggested lower I_{Na} . This was confirmed by automated patch-
140 clamp measurements which demonstrated $\approx 50\%$ less I_{Na} density in *MAPRE2* KO compared to

141 control hiPSC-CMs (**Fig. 2f**, left panel). Additionally, a small positive shift in voltage
142 dependency of activation was observed, while voltage dependency of inactivation and
143 recovery from inactivation were not different between control and KO cells (**Supplementary**
144 **Fig. 10a,b,c**). Whereas no repolarization abnormalities were observed in intact *mapre2* KO
145 zebrafish hearts (**Fig. 2c**), significant action potential duration (APD) prolongation was
146 observed in single *MAPRE2* KO hiPSC-CMs (**Fig. 2d and e**). This APD prolongation may be
147 explained by the significantly lower repolarizing outward current ($I_{outward}$) amplitude in the
148 KO hiPSC-CMs (**Fig. 2f**, right panel), although the voltage-dependency of activation was
149 unchanged (**Supplementary Fig. 10d,e**). Together with the multiple levels of evidence that
150 implicate conduction slowing and decreased I_{Na} in the pathogenesis of BrS, and previous
151 work linking end-binding proteins to ion channel targeting to the plasma membrane²⁴, our
152 data suggest that modulation of microtubule function and subsequent alterations in ion
153 channel trafficking may be a novel molecular mechanism contributing to BrS. Future work is
154 needed to address the underlying molecular mechanisms and provide insight into the ion
155 channels that underlie the observed abnormalities in repolarization, although a role for
156 prolonged repolarization is not reconcilable with current hypotheses on BrS pathogenesis²⁵.

157

158 To further explore the genetic architecture of BrS in specific patient subgroups as well as the
159 association of common variants in aggregate with disease severity, we calculated a
160 polygenic risk score (PRS_{BrS}) per individual based on the 21 risk alleles and their
161 corresponding effect sizes. Of the 2,469 study participants tested, 454 (18.4%) carried a rare
162 pathogenic or likely pathogenic variant in *SCN5A* (*SCN5A*⁺). *SCN5A*⁺ cases had a lower mean
163 PRS_{BrS} compared to cases without such variants (*SCN5A*⁻) (8.8±1.1 vs. 9.3±1.0; $P=2.1\times 10^{-17}$;
164 **Fig. 3a**), suggesting a higher burden of BrS-associated common variants in *SCN5A*⁻ patients,
165 as similarly shown in other heritable diseases^{26,27}. Using LDSC, we observed a strong
166 genome-wide correlation between the genetic contributors in *SCN5A*⁺ and *SCN5A*⁻ patient
167 subgroups ($r_g=0.82$; SE=0.2), suggesting the involvement of the same risk alleles. Out of
168 2,367 BrS cases with complete data, 228 had a life-threatening arrhythmic event (LAE) at
169 diagnosis or during follow-up (median age at last follow-up was 50.0 years, interquartile
170 range 39.5 - 60.7). Although *SCN5A*⁺ cases had a higher risk for LAE compared to *SCN5A*⁻
171 cases (HR 1.87; 95% CI 1.37-2.55; $P=8.1\times 10^{-5}$; **Supplementary Table 9**), PRS_{BrS} was not
172 significantly associated with LAE in BrS cases ($P=0.30$, **Supplementary Fig. 11**). On the other
173 hand, PRS_{BrS} was significantly higher in BrS cases that presented with a spontaneous type 1
174 BrS ECG compared to those with a type 1 BrS ECG after sodium channel blocker challenge
175 (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
176 subgroup of *SCN5A*⁻ cases (9.2±1.0 vs. 9.5±1.1; $P=3.5\times 10^{-8}$; **Supplementary Fig. 12**). These
177 data support the concept that disease susceptibility in different individuals relies upon
178 varying contributions of multiple factors including both rare and common genetic variations
179 and exposure to sodium channel blockade.

180

181 To explore the genetic relationship of BrS with other traits, we performed a phenome-wide
182 association study (PheWAS) in the UK Biobank using PRS_{BrS}, applying Bonferroni correction
183 ($P<7\times 10^{-4}$) to define statistical significance (**Supplementary Tables 10-12 and Fig. 4A**). PRS_{BrS}
184 was associated with greater risk for atrioventricular conduction disorders ($P=1.5\times 10^{-9}$;
185 OR=1.16 [1.10-1.21] per SD increase), as well as longer ECG activation/conduction times
186 reflected in the P-wave duration ($P=5.3\times 10^{-9}$; $\beta=0.76$ ms, SE=0.13), PQ interval duration
187 ($P=1.9\times 10^{-45}$; $\beta=2.70$ ms, SE=0.19), and QRS duration ($P=4.2\times 10^{-55}$; $\beta=1.23$ ms, SE=0.08). This

188 underscores the important role of conduction slowing in the pathogenesis of BrS, and is
189 further supported by a significant positive genome-wide correlation between BrS and QRS
190 duration²⁸ ($r_g=0.44$, $P=1\times 10^{-8}$; **Supplementary Table 13**). In contrast, PRS_{BrS} was negatively
191 associated with the QT interval duration ($P=4.8\times 10^{-16}$; $\beta=-1.56$ ms, SE=0.19), consistent with
192 suggestions of higher cardiomyocyte phase 1 repolarizing drive in BrS^{13,25}. PRS_{BrS} was also
193 negatively associated with the occurrence of atrial fibrillation (AF) or flutter ($P=6.2\times 10^{-13}$;
194 OR=0.94 [0.92-0.95]). The effects of each of the 21 BrS risk alleles in previously published
195 GWAS of PQ²⁹, QRS²⁸, QT³⁰ and AF³¹ are generally concordant with the aggregate effect of
196 those alleles (PRS_{BrS}) in the PheWAS (**Fig. 4B, Supplementary Table 14-17, Supplementary**
197 **Fig. 13**). One exception is the BrS risk allele near *MYO18B* (rs133902-T) which was also
198 associated with greater risk for AF ($P=9\times 10^{-10}$ in Nielsen et al³², and $P=1\times 10^{-7}$ in Roselli et al³¹;
199 **Supplementary Fig. 13**). This suggests that although changes in conduction velocity through
200 sodium channel expression effects modulate risk for AF and BrS in opposite directions, some
201 disease mechanisms such as those involving structural proteins (e.g. MYO18B) may be
202 shared in both arrhythmias, with concordant effects. We also observed novel associations of
203 PRS_{BrS} with non-electrical phenotypes namely body mass index (log-transformed; $P=6.2\times 10^{-6}$;
204 $\beta= 0.0012$, SE=0.0003) and systolic blood pressure ($P=4.3\times 10^{-5}$; $\beta=0.12$ mmHg, SE=0.03;
205 **Supplementary Table 12**). Of note, a recent study identified a modulatory effect of
206 hypertension in cardiac sodium channel disease³³. Lastly, a lookup of loci previously
207 associated with ECG traits and AF identified 9 additional novel loci associated with BrS at a
208 Bonferroni-corrected $P<1.9\times 10^{-4}$ (**Supplementary Table 18**).

209

210 In conclusion, several important findings emerge from this work: (1) We identified a total of
211 12 loci, of which 10 novel, associated with BrS, a rare disease and a significant cause of
212 sudden cardiac death in young adults. Of these loci, 3 harbour multiple association signals.
213 (2) The 8 independent association signals at the *SCN5A-SCN10A* locus highlight the primacy
214 of reduced sodium channel function in BrS susceptibility, whereas the 8 loci harboring
215 cardiac transcription factor genes point to transcriptional regulation as a key feature of BrS
216 pathogenesis. (3) Functional studies of *MAPRE2* support a novel mechanism of Na_v1.5
217 modulation via the microtubule network in BrS pathogenesis. (4) Analyses using the UK
218 Biobank highlight a genetic overlap between the BrS and cardiac electrical traits and
219 common disorders in the general population. (5) Polygenic risk score analyses support the
220 concept that disease threshold in different individuals with BrS is reached by varying
221 contributions of rare *SCN5A* variants, common risk alleles and sodium channel blockade.
222 Taken together, these findings broaden our understanding of the genetic architecture of BrS
223 and provide new insights into its molecular underpinnings.

224

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226

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538 **Disclosures**

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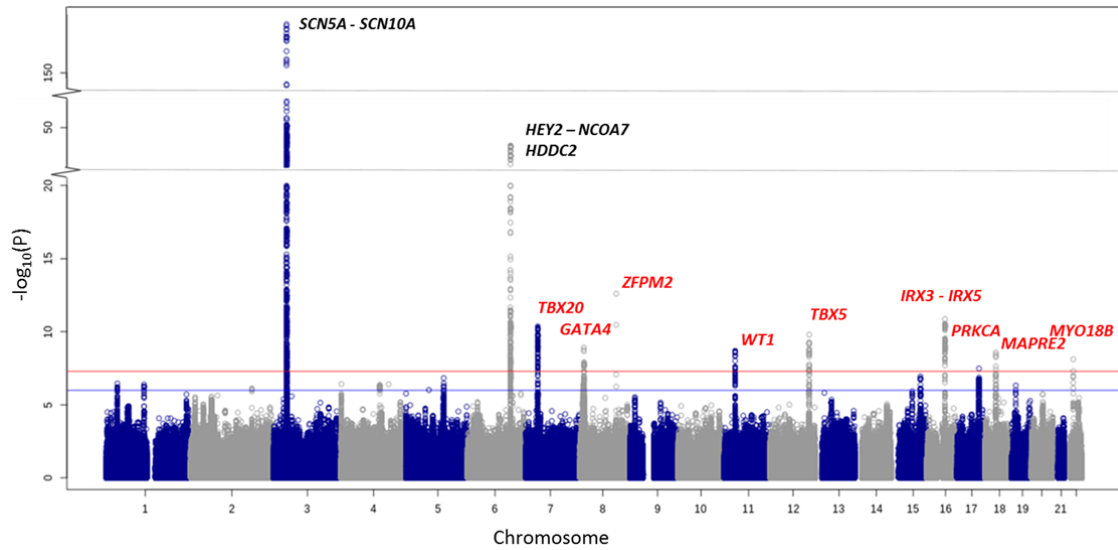
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547

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

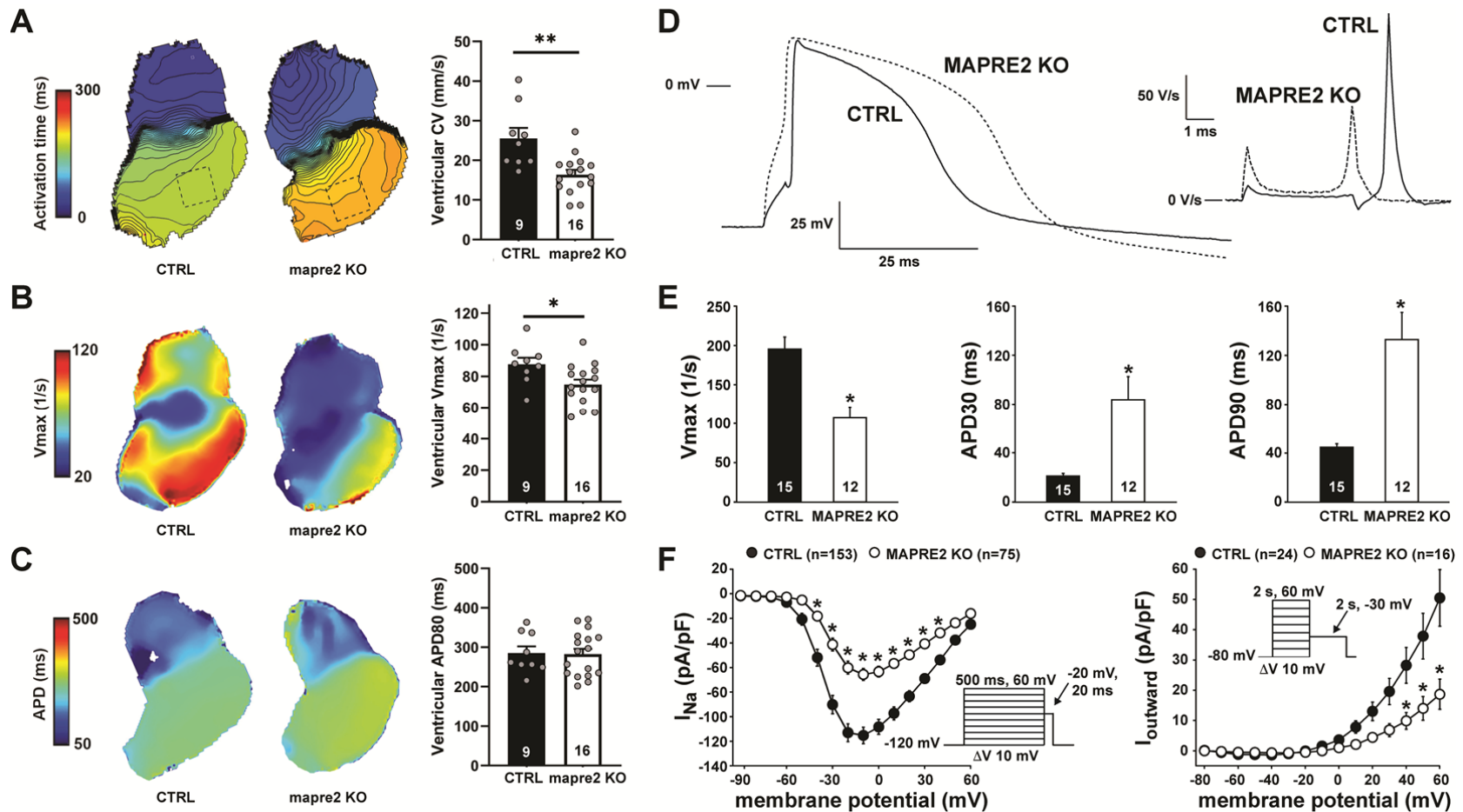
Locus	Lead SNP	Genomic position (hg19)	Risk allele	Other allele	Risk allele frequency in cases	Risk allele frequency in controls	OR [95% CI]	P value	Nearest gene
1	rs7638909*	3:38594973	G	T	0.32	0.24	1.28 [1.17 - 1.40]	2.79E-08	SCN5A
	rs62241190*	3:38607468	G	A	0.06	0.03	1.96[1.63 - 2.32]	8.56E-14	SCN5A
	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	1.2 [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

549 *Variants associated with BrS in conditional analyses. **Abbreviations:** 95% CI, 95% confidence interval; OR, odds ratio referring to each unit increase in the risk
550 allele. Confidence intervals are given for a nominal p-value of 0.05 in order to allow comparability with other studies and reports.



551 **Fig 1: Manhattan plot of genome-wide association meta-analysis comprising 2820**
 552 **unrelated Brugada Syndrome cases and 10001 controls.** The association P values were
 553 derived from a meta-analysis of the 10 GWAS strata using a fixed effects model with an
 554 inverse-variance weighted approach. The y-axis has breaks to emphasize the novel loci. The
 555 red and blue lines indicate the genome-wide significance ($P < 5 \times 10^{-8}$) and suggestive
 556 significance ($P < 1 \times 10^{-6}$) thresholds, respectively. Genes at novel loci are depicted in red.

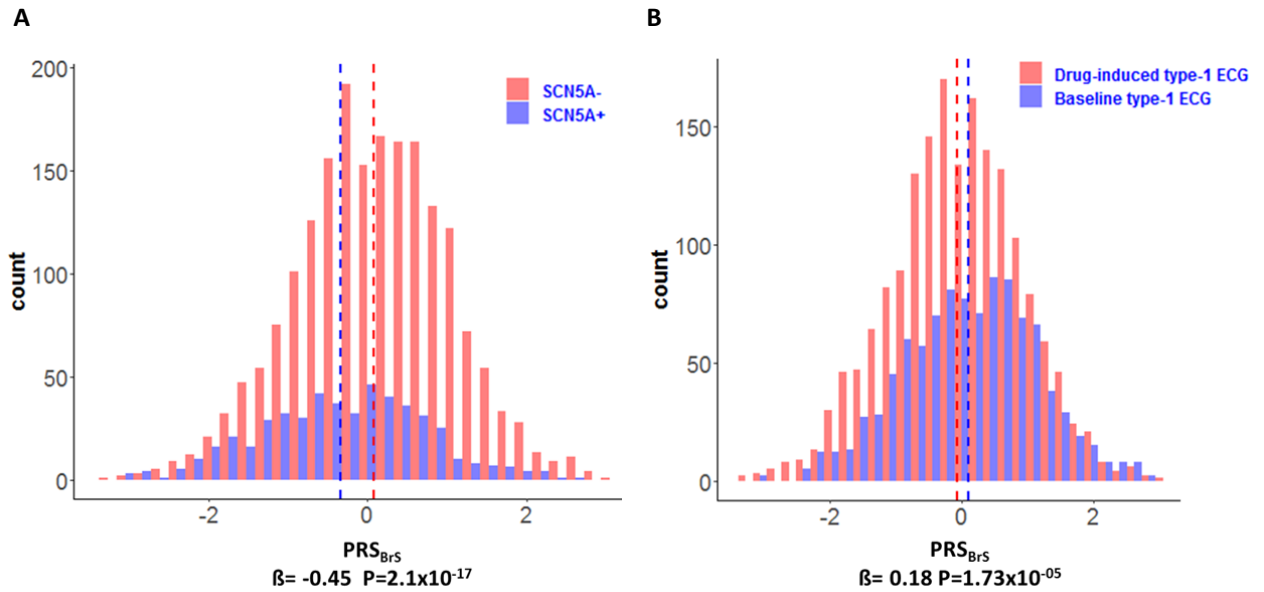
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578 **Fig 2: Loss of *MAPRE2* leads to lower conduction velocity, action potential upstroke velocity and sodium current.** (a) Left panel.
 579 Representative isochrone maps of hearts isolated from 5 day post-fertilization zebrafish larvae injected with tracrRNA/Cas9 and multiple
 580 gRNAs targeting *mapre2* (*mapre2* KO) or tracrRNA/Cas9 without gRNA (CTRL). The dotted squares reflect the main ventricular area in the
 581 hearts from which the various parameters are measured. **Right panel.** Average ventricular conduction velocity (CV) in CTRL and *mapre2* KO
 582 hearts. **(b) Left panel.** Representative maximum action potential (AP) upstroke velocity (V_{max}) maps from zebrafish hearts. **Right panel.**

583 Average V_{\max} in CTRL and *mapre2* KO hearts. **(c) Left panel.** Representative maps of AP duration at 80% repolarization (APD80) in isolated
584 hearts paced at 100 bpm. **Right panel.** Average APD80 in CTRL and *mapre2* KO hearts. **(d)** Representative APs at 1 Hz pacing from single
585 human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) with CRISPR/Cas9-mediated *MAPRE2* knockout and isogenic control
586 (CTRL) hiPSC-CMs. A constant ohmic current was injected to set the membrane potential just before the APs at approximately -80 mV to
587 overcome the depolarized state of the hiPSC-CMs (see Online Methods). **Inset.** First derivative of the AP upstroke velocity (V_{\max}). **(e)** Average
588 V_{\max} and APD at 30 and 90% repolarization (APD₃₀ and APD₉₀, respectively) in CTRL and MAPRE2 KO hiPSC-CMs. Maximal diastolic potential
589 and AP amplitude did not differ significantly between CTRL and MAPRE2 KO hiPSC-CMs (data not shown) **(f) Left panel.** Average current-
590 voltage relationships of the sodium current (I_{Na}). **Right panel.** Average repolarizing outward current (I_{outward}) in CTRL and MAPRE2 KO hiPSC-
591 CMs. **Insets.** Voltage protocol used. Results are expressed as mean \pm s.e.m. Numbers in the bar graph refer to the number of hearts or cells
592 studied. * $P < 0.05$, ** $P < 0.01$ vs. CTRL.

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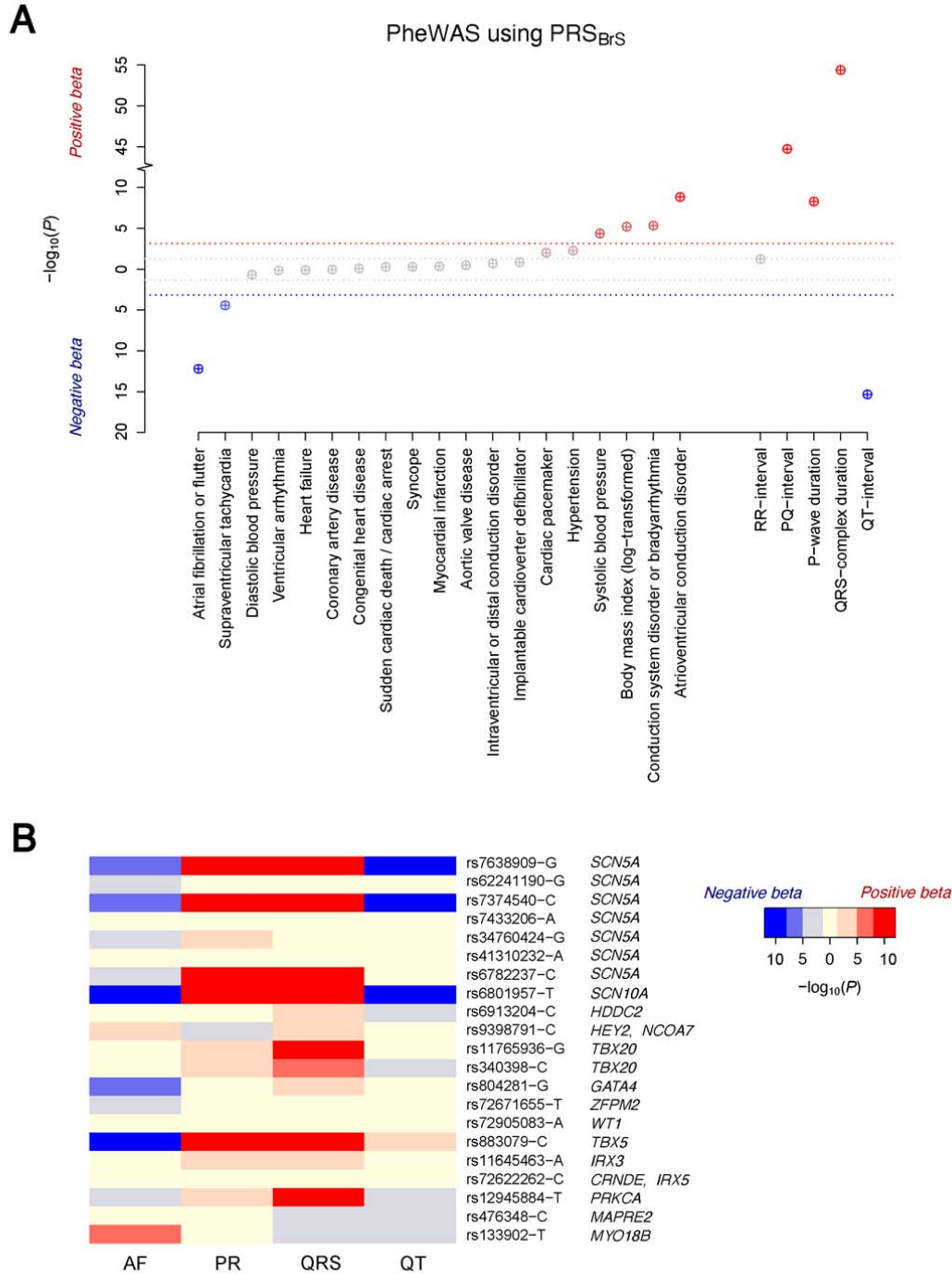


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598 **Fig 3: Distribution of PRS_{BrS} in specific patient sub-groups.** (A) Histograms displaying PRS_{BrS}
599 distribution in BrS cases carrying a rare pathogenic or likely-pathogenic variant in *SCN5A*
600 (*SCN5A*⁺; blue) compared to BrS cases without such variants (*SCN5A*⁻; red). (B) Histograms
601 displaying PRS_{BrS} distribution in BrS cases presenting with a spontaneous type 1 BrS ECG
602 (blue) compared with those presenting with a type 1 BrS ECG only after sodium channel
603 blocker challenge (drug-induced; red). PRS_{BrS} was calculated per individual based on the 21
604 BrS risk alleles and their corresponding effect sizes. Reported *P* values refer to the
605 difference in PRS_{BrS} units between two groups. Dashed lines showing the mean PRS_{BrS} for
606 each group.

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 610 **Fig 4. Associations between polygenic susceptibility to Brugada syndrome and common**
 611 **cardiovascular diseases and traits.** Panel A shows the results of the phenome-wide association
 612 analysis (PheWAS) for the Brugada syndrome (BrS) polygenic risk score (PRS_{BrS}) among individuals of
 613 European ancestry from the UK Biobank. Phenotypes significantly associated with PRS_{BrS} and
 614 phenotypes relevant to the heart are shown on the x-axis (5 electrocardiographic traits are depicted
 615 on the right of the plot); the P values from multiple regression are depicted on the y-axis. Red circles
 616 indicate that polygenic predisposition to BrS is associated with a positive beta (e.g. increased risk of
 617 the condition or higher value for continuous traits), whereas blue circles indicate that polygenic
 618 predisposition to BrS is associated with a negative beta (e.g. decreased risk of the condition or lower

619 value). We set the significance threshold to $P < 0.0007$ after Bonferroni correction ($P < 0.05/70$),
620 shown as dotted colored lines. The grey dotted lines indicate the nominal significance threshold ($P <$
621 0.05). The complete PheWAS results are shown in **Supplementary Tables 11 and 12** for dichotomous
622 and continuous traits, respectively. **Panel B** depicts a heat-map of associations between BrS risk
623 alleles and atrial fibrillation/flutter (AF), PR-interval (PR), QRS-complex duration (QRS) and QT
624 interval duration (QT) from previously published GWAS²⁸⁻³¹. Each row represents an independent
625 BrS risk allele, while each column represents a phenotype. Red indicates that the BrS risk allele (or a
626 proxy with $R^2 > 0.8$) is associated with higher risk of AF or prolongation of the electrocardiographic
627 interval; blue indicates that the BrS risk increasing allele is associated with lower risk of AF or
628 shortening of the interval. The darkest red and blue colors represent conventional genome-wide
629 significance in the published GWAS ($P < 5 \times 10^{-8}$).
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