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ARTICLE

Brugada syndrome risk loci seem protective against atrial fibrillation

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Several studies have shown an overlap between genes involved in the pathophysiological mechanisms of atrial fibrillation (AF) and Brugada Syndrome (BrS). We investigated whether three single-nucleotide polymorphisms (SNPs) (rs11708996; G>C located intronic to *SCN5A*, rs10428132; T>G located in *SCN10A*, and rs9388451; T>C located downstream to *HEY2*) at loci associated with BrS in a recent genome-wide association study (GWAS) also were associated with AF. A total of 657 patients diagnosed with AF and a control group comprising 741 individuals free of AF were included. The three SNPs were genotyped using TaqMan assays. The frequencies of risk alleles in the AF population and the control population were compared in two-by-two models. One variant, rs10428132 at *SCN10A*, was associated with a statistically significant decreased risk of AF (odds ratio (OR) = 0.77, $P = 0.001$). A meta-analysis was performed by enriching the control population with allele frequencies from controls in the recently published BrS GWAS (2230 alleles). In this meta-analysis, both rs10428132 at *SCN10A* (OR = 0.73, $P = 5.7 \times 10^{-6}$) and rs11708996 at *SCN5A* (OR = 0.80, $P = 0.02$) showed a statistically significant decreased risk of AF. When assessing the additive effect of the three loci, we found that the risk of AF decreased in a dose-responsive manner with increasing numbers of risk alleles (OR = 0.50, $P = 0.001$ for individuals carrying ≥ 4 risk alleles *vs* ≤ 1 allele). In conclusion, the prevalence of three risk alleles previously associated with BrS was lower in AF patients than in patients free of AF, suggesting a protective role of these loci in developing AF.
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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia that requires treatment and is associated with increased morbidity and mortality.[1] The prevalence of AF increases with age, and affects 1–2% of the general population, a proportion that is likely to increase in the next 50 years.[2,3] Cardiac risk factors such as hypertension and ischemic or other structural heart disease are known as risk factors for AF.[1,4,5] However, a subgroup of patients diagnosed with AF is younger than 60 years of age and lacks these well-established risk factors. This condition is called 'lone' AF and accounts for 10–20% of the total number of patients with AF.[6,7]

Brugada Syndrome (BrS) is characterized by ST-segment elevations in the right precordial leads and an increased risk of ventricular arrhythmias and sudden cardiac death.[8]

There is a significant overlap between genes associated with AF and BrS.[8,9] Accordingly, several rare variants in genes encoding cardiac sodium and potassium channels have been found both in patients with AF and in patients with BrS. This is the case for the variants in *SCN5A* (c. 647C>T (p.(Ser216Leu)), rs201002736,[10,11] c. 1127G>A (p.(Arg376His)), rs199473101,[10,12] c. 3157G>A (p.(Glu1053Lys)), rs137854617,[10,13] and c. 6010T>C (p.(Phe2004Leu)), rs41311117[14,15]), *SCN1Bb* (c. 641G>A (p.(Arg214Gln)), rs66876876[16,17]), *SCN3B* (c. 29T>C (p.(Leu10Pro)), rs121918282[18,19]), *MOG1* (c. 181G>T (p.(Glu61Xaa[20,21])), rs140704891, and *KCNJ8* (c. 1265C>T (p.(Ser422Leu)), rs72554071[22,23]). Furthermore, several studies have showed that the common AF-associated variant c. 1673A>G (p.(His558Arg)), rs1805124, in *SCN5A* may have a protective role against BrS in patients with other Brugada-associated *SCN5A* variants.[11,24–26] Since some mutations can result in different phenotypes,[18,19] the presence of additional single-nucleotide polymorphisms (SNPs) might have a disease-modifying effect. Of note, a recent genome-wide association study (GWAS) identified three loci (rs9388451; T>C, rs10428132; T>G, and rs11708996; G>C), to be associated with BrS. Patients carrying more than four risk alleles had an odds ratio (OR) of 21.5 for BrS, compared with patients carrying less than two risk alleles.[27] All three GWAS-identified loci are presumed to affect the sodium current.

Since ~20% of Brugada patients also develop supraventricular arrhythmias including AF,[28] we hypothesized that SNPs previously associated with BrS in GWAS[27] may also modify the risk of AF.

MATERIALS AND METHODS

Study population

A total of 358 patients with lone AF (ie, the absence of clinical or echocardiographic findings indicating other cardiovascular diseases, metabolic, or pulmonary diseases) and onset of disease before the age of 50 (ranging from

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16 to 49 years of age) were included from Copenhagen, Denmark and from Oslo and Vestre Viken, Norway, as described previously.[29] In addition, 299 'non-lone' AF patients were included.

An ethnically matched control population was recruited from the same geographic area as the cases. This control population comprised (1) 208 healthy blood donors <48 years of age and free of cardiac diseases[19] and (2) 533 men and women aged 55–75 years without history of AF or other cardiovascular diseases or stroke, despite a high prevalence of risk factors for AF[30] (control group I). The latter control group was considered as highly relevant, because of their high AF resistance. To add power to our data, we added summarized data from the recently published BrS GWAS[27] (control group II).

Written informed consent was obtained from all participants. The study conforms to the principles outlined in the Declaration of Helsinki, and was approved by the Scientific Ethics Committee of Copenhagen and Frederiksberg (Protocol reference number: H-KF-01313322) and the Regional Ethics Committee in Norway (Protocol reference number: 2009/2224-5).

SNP genotyping

Genotyping was performed as previously described.[31] In brief, the DNA was extracted from whole blood that had been stored at −20 °C using the QIAamp DNA Blood Mini and Maxi kits (Qiagen, Hilden, Germany). SNP genotypes for rs9388451, rs10428132, and rs11708996 were determined using fluorescence-based real-time PCR (ABI PRISM 7900 Sequence Detection System; Applied Biosystems, Foster City, CA, USA) and pre-developed TaqMan assays (Applied Biosystems). An allelic discrimination run was performed allowing for discrimination between the allele compositions of each sample.

SNP genotypes for rs9388451, rs10428132, and rs11708996 have been submitted to ResearchGate, URL: https://www.researchgate.net/publication/259990810_Brugada_syndrome_risk_loci_seem_protective_against_atrial_fibrillation?ev=prf_pub.

Table 1 Clinical data of patient and control populations

	Controls	*Lone AF*	*Non-lone AF*
N	741	358	299
Median age, years (IQR)	60 (55–70)	35 (28–39)	61 (51–69)
Male gender, %	52.3	81.9	69.5
Hypertension, %[a]	26.2	0	36.5

Abbreviations: AF, atrial fibrillation; IQR, interquartile range.
[a]Hypertension defined as diastolic blood pressure >90 mm Hg or systolic blood pressure >140 mm Hg at clinical examination.

Statistical analyses

The proportion of risk alleles (risk allele frequencies) was compared between AF cases and controls in two-by-two tables. Analyses were performed separately for the three investigated SNPs using either (1) in-house controls (control group I) or (2) both the in-house controls and summarized data on controls from the recently published BrS GWAS[27] (control group I and control group II). The latter meta-analysis was done to add power to our analysis.

To assess the additive effect of the three SNPs, logistic regression models were performed including AF patients and control group I. Individuals were categorized into having 0–1, 2–3, or 4–6 risk alleles. The additive effect of carrying multiple BrS-risk alleles was assessed in four different models including (1) all three alleles, (2) the two loci that were statistically significant associated with AF, (3) all three alleles but without the non-lone AF patients, and finally (4) only the two statistically significant loci and without the non-lone AF patients. A two-tailed *P*-value of <0.05 was considered as statistically significant. Analyses were performed with the Stata 11.0 software package (StataCorp LP, College Station, TX, USA).

RESULTS

Clinical characteristics of the two AF groups and the control group are shown in Table 1. The lone and non-lone AF groups are combined in one case group throughout all analyses, unless otherwise stated.

The results of the genotyping are summarized in Tables 2 and 3. One of three variants, rs10428132 in *SCN10A*, showed a statistically significant decreased risk of AF (OR = 0.77, $P = 0.001$) when comparing AF cases with control group I. Combining control groups I and II, both rs10428132 in *SCN10A* and rs11708996 intronic to *SCN5A* showed a statistically significant decreased risk of AF (rs10428132: OR = 0.73, $P = 5.7 \times 10^{-6}$, rs11708996: OR = 0.80, $P = 0.02$) (Table 3).

In a pooled analysis of all three SNPs, we found that the risk of AF decreased consistently with increasing numbers of BrS-risk alleles (Figure 1a). Carrying four or more risk alleles was associated with an OR of 0.50 (95% CI: 0.33–0.76, $P = 0.001$) for AF compared with individuals carrying less than two risk alleles. A subgroup analysis of the lone AF patient group showed a similar association (OR = 0.41, 95% CI: 0.23–0.74, $P = 0.003$) (Figure 1b). Similar pooled analyses were carried out for the two variants shown to be significantly associated with a decreased risk of AF. Again, AF risk decreased consistently with increasing numbers of BrS-risk alleles that an individual carried (Figure 1c and d). The distribution of risk alleles

Table 2 Effect size of BrS-risk alleles in AF population *vs* control I

Nearest gene	*SNP*	*Chr*	*Bp substitution*	*Risk allele*[27]	*RAF cases*	*RAF control I*	*OR (95% CI)*	P-*value*
HEY2	rs9388451	6	C>T	C	0.49	0.51	0.94 (0.81–1.09)	0.42
SCN10A	rs10428132	3	G>T	T	0.33	0.39	0.77 (0.66–0.90)	0.001
SCN5A	rs11708996	3	C>G	C	0.13	0.15	0.82 (0.65–1.02)	0.07

Abbreviations: bp, basepair; Chr, chromosome; CI, confidence interval; OR, odds ratio; RAF, risk allele frequency; SNP, single-nucleotide polymorphism.
Control I: in-house controls. Cases: combined lone AF and non-lone AF patient group. *P*-value defined as two-sided.

Table 3 Effect size of BrS-risk alleles in AF population *vs* controls I + II

Nearest gene	*SNP*	*Chr*	*Bp substitution*	*Risk allele*[27]	*RAF cases*	*RAF control I*	*RAF control II*[27]	*RAF controls I + II*	*OR (95%CI) controls I + II*	P-*value controls I + II*
HEY2	rs9388451	6	C>T	C	0.49	0.51	0.50	0.51	0.97 (0.85–1.10)	0.64
SCN10A	rs10428132	3	G>T	T	0.33	0.39	0.41	0.40	0.73 (0.64–0.84)	5.7×10^{-6}
SCN5A	rs11708996	3	C>G	C	0.13	0.15	0.15	0.15	0.80 (0.66–0.98)	0.02

Abbreviations: bp, basepair; Chr, chromosome; CI, confidence interval; OR, odds ratio; RAF, risk allele frequency; SNP, single-nucleotide polymorphism.
Control II: GWAS[27] controls, controls I + II: in-house + GWAS[27] controls. Cases: combined lone AF and non-lone AF patient group. *P*-value defined as two-sided.

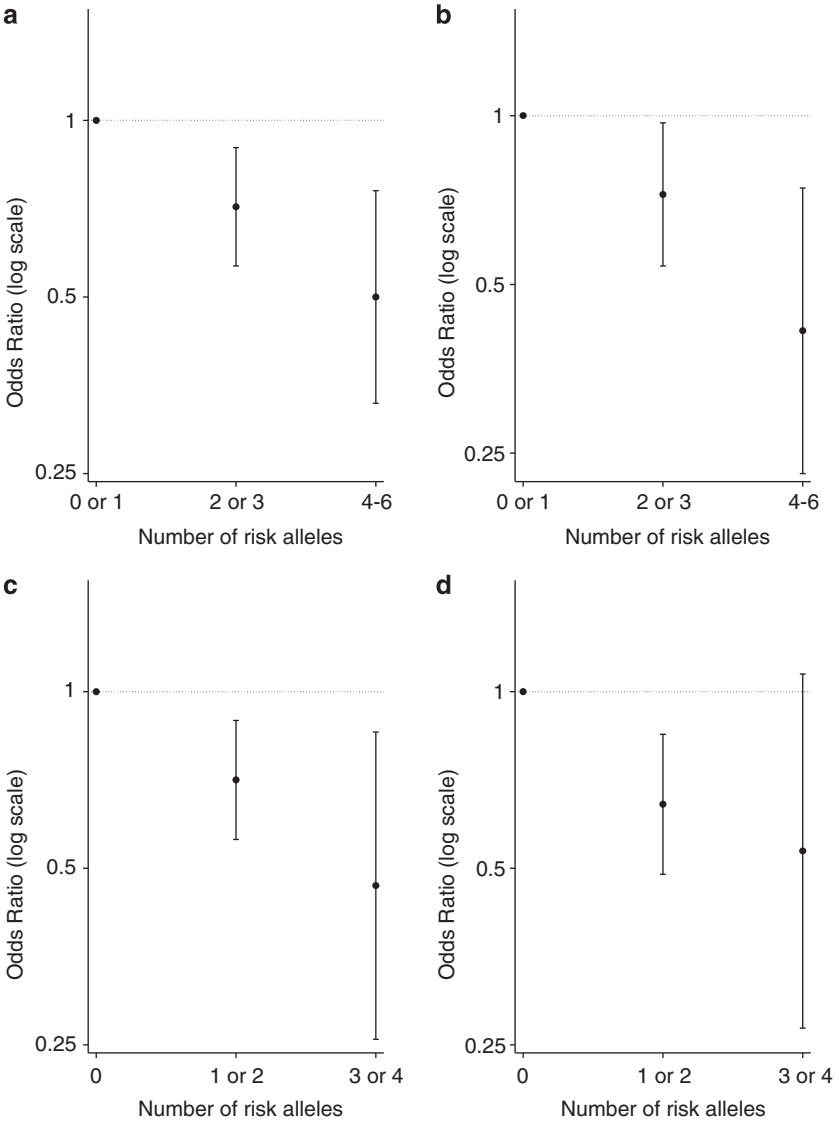

Figure 1 ORs calculated according to the number of risk alleles in the in-house controls. Each dot represents the log(OR) value and each bar the 95% confidence interval (vertical). (**a**) Pooled analysis of all three loci in the lone AF and the non-lone AF patients *vs* the in-house controls. (**b**) Pooled analysis of all three loci in the lone AF patients *vs* the in-house controls. (**c**) Pooled analysis of the two loci significantly associated with AF (rs10428132 in *SCN10A* and rs11708996 intronic to *SCN5A*) in the lone AF and the non-lone AF patients *vs* the in-house controls. (**d**) Pooled analysis of the two loci significantly associated with AF in the lone AF population *vs* the in-house controls.

in patients and controls (control group I) is shown in Figure 2. The risk of AF decreases consistently with increasing numbers of BrS-risk alleles, indicated by the right-shifted patient population.

DISCUSSION

We investigated the prevalence of three SNPs recently shown to be associated with BrS, in a group of AF patients and in controls, and found that the additive effect of the three loci decreased the risk of AF in a dose-response manner (OR = 0.50, 95% CI: 0.33–0.76, $P = 0.001$ in the presence of ≥ 4 risk alleles *vs* ≤ 1).

The finding that the same group of SNPs known to be associated with BrS, with ORs of >20, at the same time possess a protective effect against AF is fascinating. The reported SNPs are either within or close to genes underlying or regulating the cardiac sodium current (I_{Na}). rs10428132 resides in the gene *SCN10A* encoding $Na_V1.8$, rs11708996 is intronic to *SCN5A* encoding $Na_V1.5$, and rs9388451 resides near the *HEY2* locus. The loci at *SCN10A* and *SCN5A* are also associated with both PR interval and QRS duration.[32,33]

From an evolutionary perspective, our results may suggest that these common variants known to increase the risk of a rare, but potentially lethal syndrome such as BrS seem to have a dualistic effect, protecting against a much more common disease such as AF.

Noteworthy, the *SCN10A* SNP, rs10428132, is in high linkage (0.98 r^2) with rs6795970, also located in *SCN10A*. rs6795970 has, in a recent GWAS,[34] been shown to protect against AF and atrial flutter (OR = 0.85, $P = 8.45 \times 10^{-4}$), along with arterial embolism and thrombosis (OR = 0.69, $P = 3.20 \times 10^{-3}$). This SNP leads to the substitution of valine to alanine at amino-acid position 1073 (c. 3218T>C (p.(Val1073Ala))) in the sodium channel isoform Nav1.8, resulting in this channel displaying both increased peak and late sodium current in functional studies.[35] The $Na_V1.8$ channel protein seems to be expressed in working myocardium and the cardiac

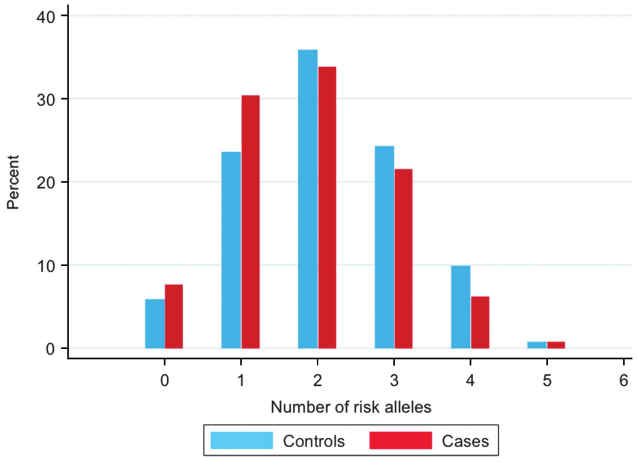

Figure 2 Distribution of risk alleles among individuals with AF (red bars) and among the in-house controls (blue bars).

conduction system,[36] although it has also been found in intracardiac neurons.[37] Its contribution to the total cardiac sodium current in the atria remains elusive. In addition, rs10428132 is in complete linkage with the PR-prolonging allele of rs6800541 which Pfeufer *et al*[32] also noted to have a protective effect on AF risk. Finally, rs10428132 is in almost complete linkage with rs6801957 ($r^2 = 0.97$), which has been reported to affect the binding of the *TBX3* transcription factor and thereby the regulation of *SCN5A*/*SCN10A* expression.[38]

The majority of the cardiac sodium current is conducted by $Na_V1.5$, and several studies including knock-out mouse models suggest a central role of *SCN5A*/$Na_V1.5$ in the pathogenesis of AF. Heterozygote knock-out mice display compromised conduction velocity, impaired AV conduction, and QRS prolongation.[39] An altered *SCN5A*/*SCN10A* expression could affect the conduction velocity and thereby the risk for BrS. Of note, both the *SCN5A* SNP rs11708996 and the *SCN10A* SNP rs10428132 have previously been associated with PR interval duration in a GWAS,[32] supporting a protective role in AF. Pazoki *et al*[40] replicated the association between the *SCN5A* SNP and PR duration, showing a trend for association between the rs11708996 C allele and a PR interval of ≥ 200 ms (OR = 2.39, $P = 0.004$).

rs9388451 is located in close proximity to the *HEY2* gene, encoding a transcriptional repressor important in the development of the cardiovascular system.[41–44] Bezzina *et al*[27] found homozygous *HEY2* knock-out embryos to have increased $Na_V1.5$ expression and a flattened transmural expression gradient of the channel in the cardiac ventricles. In *HEY2* +/− knock-out mice, the conduction velocity was increased in the right ventricle outflow tract (RVOT), and the action potential upstroke velocity was increased, indicating an increase in sodium channel peak current. This is in line with the characteristic ST-segment elevation in the right precordial leads of BrS ECGs, and proposes the RVOT as an origin of ventricular arrhythmias in BrS. Assuming that the variant also gives rise to an increased conduction velocity in the atria it may protect against other genetic variants, or age- and sport-induced decreases in conduction velocity caused by fibrosis, and thereby protect against AF. Furthermore, *HEY2*-deficient embryos displayed a change in the expression patterns of *GJA5*, *NPPA*, and *TBX5*.[43,45,46] These genes have all previously been associated with AF.[47–50]

Thus, several studies support our finding that BrS-associated genetic variants protect against AF. Further mechanistic studies might help decipher how cellular electrophysiological changes induced by each of these variants (separately and additively) result in protection against AF. The elucidation of the mechanism(s) might provide keys to a more detailed understanding of the pathophysiology of AF and BrS. From a clinical point of view, our result highlights the complexity of personalized medicine as the AF patients with BrS-risk alleles, known to increase the sodium peak current, on one hand might benefit from a sodium peak current blocker such as flecainide, but on the other hand, flecainide treatment might increase the risk of sudden cardiac death in these patients, since they are predisposed for BrS by the same BrS-risk alleles.

Study limitations

Our study population was highly selected and relatively small. As a consequence, the power to detect associations was reduced. The study only included cases of Scandinavian ancestry, and the generalizability of the results to other ethnicities might be limited.

CONCLUSIONS

We found the risk of AF to decrease consistently with increasing numbers of BrS-risk alleles carried, suggesting that these variants have a protective role against developing AF.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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