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EDITORIAL

Genetic background of Brugada syndrome is more complex than what we would like it to be!

Hugues Abriel*

Department of Clinical Research, Ion Channel Research Group, University of Bern, Murtenstrasse 35, Bern 3010, Switzerland

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This editorial refers to 'Role of common and rare variants in *SCN10A*: results from the Brugada syndrome QRS locus gene discovery collaborative study' by E.R. Behr *et al.*, pp. 520–529.

> Everything must be taken into account. If the fact will not fit the theory—let the theory go.
>
> —Agatha Christie, The Mysterious Affair at Styles

Brugada syndrome (BrS) has been named after the description of the disease made by the Brugada brothers in 1992.[1] BrS is clinically characterized by arrhythmic events, in particular ventricular fibrillation, resulting in syncope and sudden cardiac arrest mainly in middle-aged men. The ECG shows a peculiar down-sloping elevation of the ST segment in the right pre-cordial ECG leads with inversion of T-waves.[2] Since 1998, a genetic component to BrS has been demonstrated.[3] Over the past years, at least 20 genes have been proposed either to cause BrS or to be BrS-susceptibility genes.[4]

For several years, *SCN5A*, which encodes the 'cardiac sodium channel' $Na_v1.5$, was presented as a gene 'causing' BrS in ~20% of the patients; however, this concept had to be revised due to recent findings. First, in some families where the probands were found to carry *SCN5A* rare variants, other family members diagnosed with BrS did not carry the supposedly pathogenic variant.[5,6] Second, a recent genome-wide association study (GWAS) led to the concept that BrS could no longer be considered a monogenic disease and it suggested a key role for the three genes: *SCN10A*, *SCN5A*, and *HEY2*.[7] Patients who accumulated more than four of the risk alleles in these genes had an odds ratio of >20 to have BrS. The two genes *SCN5A* and *SCN10A*, which encode two different voltage-gated sodium channels, were also implicated in other GWAS studies[8] in physiological cardiac conduction, assessed as ECG parameters. These findings motivated several groups to investigate the, thus far, unknown role of the *SCN10A* gene product, the sodium channel $Na_v1.8$, in cardiac electrical activity as this channel was only thought to be important in the sensory nervous system.

As it sometimes happens in science, this has led to controversial results. The first unresolved question is the location of expression of $Na_v1.8$ in cardiac tissues. Two hypotheses are currently debated. On the one hand, expression of $Na_v1.8$ is proposed by one research group to be specific to intracardiac neurons,[9] while on the other hand, expression in cardiac myocytes of the myocardium and of the conduction pathway was suggested by another group.[10] The second point of disagreement is the role of genetic variants that were found in the gene *SCN10A* in patients with cardiac arrhythmias, in particular BrS. Upon investigation of a population of 150 BrS probands and family members, a recent study by Hu *et al.*[11] came to the conclusion that *SCN10A* genetic variants may cause BrS in 16.7% of these probands, thus putting *SCN10A* as a major susceptibility gene of BrS.

In the current issue of *Cardiovascular Research*, Dr E.R. Behr presents a multi-centre collaborative study,[12] involving 156 *SCN5A* mutation negative BrS probands where 7 candidate genes, including *SCN10A*, were sequenced. Contrary to the previous study by Hu *et al.*,[11] while most of the rare genetic variants were found in *SCN10A*, no statistical association with these *SCN10A* variants and BrS was observed. However, many of these variants showed functional alterations, such as reduction in $Na_v1.8$-mediated sodium current when studied by patch clamping. Behr *et al.*[12] did not investigate the functional consequences of the co-expression of the $Na_v1.8$ with the $Na_v1.5$ channel in the same cells as done by Hu *et al.*[11] Their rationale not to study it is based on the evidence that these two channels are not co-expressed in cardiomyocytes.[9] This question of co-expression still remains unsolved, but one can nevertheless note that proteomic studies[13] performed using mouse cardiac tissue only revealed significant amounts of $Na_v1.5$ and $Na_v1.4$ peptides and none from $Na_v1.8$. These observations by Behr *et al.* suggest that, while these rare $Na_v1.8$ variants and their functional effects are consistent with the observed role of this channel in cardiac conduction, they are not directly involved in the pathogenesis of BrS.

The authors of the present study thus concluded that 'rare variation in *SCN10*, particularly in *SCN5A* mutation negative cases, is unlikely to cause BrS'. Behr *et al.* discuss the possible origins of this discrepancy and propose that their studied BrS population is more focused (enriched), and that a more stringent 'mutation' definition had been used. They also mention that by looking at larger control variant databases, only 2% of the *SCN10A* variants reported by Hu *et al.*[11] should be classified as 'rare'. Here, one should also mention the recent study by Le Scouarnec *et al.*[4] from the Institut du Thorax in Nantes, where the burden of rare coding variants in 20 BrS genes was estimated. Using a 'burden test' for the exonic sequences of these genes from 167 BrS probands, a significant enrichment in rare variants [with a

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* Corresponding author. Tel: +41 31 6320928; fax: +41 31 6320946, Email: hugues.abriel@dkf.unibe.ch

definition of the minor allele frequency (MAF) <0.1% in an ethnically matched control population] was only observed for *SCN5A*, but not for *SCN10A*. These results are in line with the ones of the current study of Behr *et al.* in this issue of *Cardiovascular Research*. Importantly, these authors discuss that if Hu *et al.*[11] would also have used such a stringent rare variant definition of MAF <0.1% (instead of <0.5%), the proportion of *SCN10A* carriers in BrS patients would have fallen to 7.3% instead of 16.7%. Thus, these two studies by Behr *et al.*[12] and Le Scouarnec *et al.*[4] do not support the concept that *SCN10A* is a major susceptibility gene in BrS and propose plausible methodological explanations for the discrepant results.

There is no doubt that controversies are intrinsic to the scientific process; this is most likely a positive thing! However, in this case one has to be extremely careful, since these findings may have important consequences, as they may be used for guiding the work-up of patients with BrS and their family members. It is therefore important to replicate similar studies in larger populations (and similarly sized control populations) as well as from other ethnic backgrounds, and use a cautious definition of 'rare variant' as proposed in study[4] to sort through the role of *SCN10A* in BrS and other genetic cardiac arrhythmias.

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