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

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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.

Every event 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 arrhythmogenic events, in particular ventricular tachycardia and sudden cardiac arrest in middle-aged men. The ECG shows a peculiar downsloping elevation of the ST segment in the right precordial ECG leads with inversion of T-waves.2 The ECG shows a ST-segment elevation only in BrS 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 SCNS5A mutations and 7 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 Nav1.8-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+1,8 with the Na+1,5 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 studies13 performed using mouse cardiac tissue only revealed significant amounts of Na+1,5 and Na+1,4 peptides and none from Na+1,8. These observations by Behr et al. suggest that, while these rare Na+1,8 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 SCNS5A 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 on the genetic background of BrS.


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definition of the minor allele frequency (MAF) < 0.1% in an ethnically matched control population] was only observed for SCN10A, but not for SCN10A. These results are in line with the one of the current study of Behr et al. in this issue of Cardiovascular Research. Importantly, these authors discuss that if Hu et al. 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. and Le Scouarnec et al. 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 study4 to sort through the role of SCN10A in BrS and other genetic cardiac arrhythmias.

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