Letter by Olesen et al Regarding Article, “MOG1: A New Susceptibility Gene for Brugada Syndrome”

To the Editor:

In the June issue of Circulation: Cardiovascular Genetics, Kattygnarath and coworkers reported MOG1 as a new susceptibility gene for Brugada syndrome (BrS). A missense mutation p.E83D was identified in a female patient with aborted sudden cardiac death but not in 281 control subjects. This very interesting finding adds to our understanding of BrS and the (patho-) physiological role of macromolecular complexes underlying the sodium current INa in the heart. Yet, we would like to raise some concerns about this new player in the genetics of BrS.

Very recently, we have screened MOG1 in cohorts of BrS and early-onset lone atrial fibrillation. In 4 of 209 lone atrial fibrillation cases, we identified a nonsense variation c.181G>T (p. E61X), resulting in premature stop codon that truncates the protein upstream of the sequence region that has been shown to interact with NaV1.5. However, the variant was also identified in 2 of 488 healthy individuals, that is, it was present in 1.8% of patients and 0.4% of control subjects. Of note, Kattygnarath and colleagues have also reported this variant identified in an asymptomatic male patient with a type-1 BrS ECG pattern in earlier proceedings from the American Heart Association Scientific Sessions.

We studied the variant E61X, using patch-clamp recordings from transfected CHO-K1 cells and found that it completely eliminated the sodium current-increasing effect of MOG1 and thereby caused loss of function in the sodium current. We also performed electrophysiological studies mimicking heterozygosity by coexpression of Nav1.5 with wild-type MOG1 and p.E61X-MOG, yet did not see a decrease comparable to that observed for p.E83D described by Kattygnarath et al. We concluded that a person may have complete loss of 1 MOG1 allele without having any signs of disease. Our conclusion is based on the notion that a dominant-negative mutant will affect wild-type proteins to suppress their function. Kattygnarath et al11 ascribed a dominant-negative effect to the mutation p.E83D. Although the mutation led to a complete loss of the MOG1-increasing effect, we would favor a more cautious notion because, based on the strong endogenous expression in HEK293 cells as elegantly shown in siRNA knock-down experiments resulting in a ca. 50% reduction of INa current densities, we anticipate a true dominant-negative mutant to suppress NaV1.5 current densities below wild-type levels.

Kattygnarath and coworkers noted that they could not unequivocally confirm the BrS phenotype. In line with this, we find that the ECG shown in Figure 1C of their report displays a wide array of pronounced changes typical for a postresuscitation ECG and rather may be indicative of ischemia than of BrS. The ECG presented in Figure 1D could be mildly indicative but not diagnostic of BrS.

As noted recently, one must be extremely cautious when associating mutations and thereby genes with an arrhythmia syndrome. Limitations to linking the mutation to the disease in this study are mainly the lack of family history. Furthermore, because the p.E61X polymorphism shows that haploinsufficiency of MOG1 can be tolerated without overt signs of disease, we would like to state that MOG1 is not a likely candidate for causing BrS except in very rare instances. Although the studies by Kattygnarath et al and us2 certainly add MOG1 to the list of genes to be considered in the pathophysiology of cardiac arrhythmia, it will be intriguing to screen larger cohorts and to identify and analyze other MOG1 variants to increase our knowledge about the role of MOG1 in cardiac function.

Disclosures

None.

References


Morten S. Olesen, MSc, PhD
Anders G. Holst, MD
Department of Cardiology
Laboratory for Molecular Cardiology
Copenhagen University Hospital
Rigshospitalet, Denmark

Danish National Research Foundation Centre for Cardiac Arrhythmia
Copenhagen N, Denmark

Nicole Schmitt, PhD
Danish National Research Foundation Centre for Cardiac Arrhythmia
Copenhagen N, Denmark

Department of Biomedical Sciences
Faculty of Health Sciences
University of Copenhagen
Copenhagen, Denmark

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Morten S. Olesen, Anders G. Holst and Nicole Schmitt

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