Response to the Letter by Kattygnarath et al

We want to answer the letter Olesen et al addressed to Circulation: Cardiovascular Genetics after the publication of our report on MOG1 as a new susceptibility gene for Brugada syndrome (BrS).

Olesen et al screened MOG1 in 23 patients with BrS and in 197 patients with early-onset lone atrial fibrillation, and they identified the nonsense variation c.181G>T (p.E61X) in 4 patients with atrial fibrillation, resulting in a premature stop codon that truncates the protein upstream of the region that interacts with Na\textsubscript{1.5}. They also identified this variant in 2 of 488 healthy individuals (ie, in 0.4% of control subjects vs 1.8% of patients). As indicated by Olesen et al, we reported this nonsense variant at the American Heart Association 2009 scientific sessions,\textsuperscript{2} in an asymptomatic male patient with a type 1 BrS ECG. This variant was thought to be relevant because it had not been found in 100 control individuals. We later found it in 3 other BrS probands, positive or negative for the SCN5A mutation, and in some family members; in addition, we found it in 2 (0.7%) of 281 controls. We, thus, assumed that this variant was a polymorphism and focused our study on the nonsense p.E61D. The frequency for the nonsense variant tended to be higher in our BrS patient cohort (4 [1.26%] of 318) compared with the control population (2 [0.7%] of 281).

By using patch-clamp analysis in a heterologous expression system, Olesen and coworkers\textsuperscript{1} showed that coexpression of wild-type MOG1 and p.E61X-MOG1, to mimic the heterozygous condition, does not cause loss of function of the sodium current, showing that a complete loss of 1 MOG1 allele is not pathogenic by itself. We agree with this conclusion, reinforced by the fact that 2 of our BrS patients, father and son, were both carriers of a nonsense mutation in SCN5A (p.W193X) and of the MOG1 nonsense variant (p.E61X). The proband was diagnosed at the age of 33 years after being referred for chest pain. The results of coronarography were normal, but the ECG showed type 2 BrS. An ajmaline test revealed a type 1 BrS pattern, and a polymorphic ventricular tachycardia (VT) was induced at electrophysiological stimulation. His 70-year-old father was asymptomatic and had a normal ECG result. The Ajmaline test was refused by the patient.

The question raised by Olesen and colleagues\textsuperscript{1} directly concerns the role of MOG1 as a physiological modulator of the sodium current. In vitro experiments strongly suggested that MOG1 modulates Na\textsubscript{1.5} activity. To summarize, 3 different groups repeatedly demonstrated the ability of MOG1 to increase the sodium current in a heterologous system, after cotransfection with Na\textsubscript{1.5} or in cells overexpressing Na\textsubscript{1.5}.\textsuperscript{3,4} This observation was confirmed in neonatal rat cardiomyocytes.\textsuperscript{5} Then, our study demonstrated that the p.E83D-MOG1 mutant abolishes the effect of MOG1 on the sodium current in Na\textsubscript{1.5}-stable human embryonic kidney (HEK) cells and has a dominant-negative effect on wild-type MOG1. Our silencing experiments confirmed the role of MOG1 on the cardiac sodium channel because we observed a decrease of 54% of endogenous sodium current. This effect has also been shown by Chakrabati et al in neonatal rat cardiomyocytes, in which silencing MOG1 almost completely abolished the sodium current.\textsuperscript{6} Altogether, these findings support the hypothesis that only a dominant-negative mutation in MOG1 might be implicated in BrS pathogenesis.

However, further studies are certainly needed to fully elucidate the role of MOG1 in BrS and in normal heart physiological features. The first point concerns the lack of genetic linkage between MOG1 variants and the pathological features. We agree with Olesen et al\textsuperscript{1} that MOG1 should be tested in larger cohorts of patients to find other variants cosegregating with the disease, which would allow for clear incrimination of MOG1 as a putative gene for BrS. The second point concerns the unconfirmed/unclear phenotype of our patient. No ajmaline test could be performed after her resuscitated sudden death. Nevertheless, she had experienced several syncopes earlier and had no cardiac morphological abnormalities. These findings were suggestive of a canalopathy, and the ECG abnormalities were compatible with BrS.

The last point is that most of our knowledge about MOG1 function originates from in vitro studies in heterologous expression systems. The effects of MOG1 on cardiac sodium channel function may differ after overexpression in cell lines and human or murine cardiomyocytes. This problem could be partially resolved by the phenotype analysis of an MOG1 knockout mouse model: Will it show a reduction of sodium current? Will it present with ECG changes and a higher risk of arrhythmia? Because mouse models have their own limits, it would be of interest to screen consanguineous populations, patients with arrhythmias, and controls to identify whether homozygous p.E61X MOG1 carriers could occur. This would help determine the physiological role that MOG1 plays in humans. Another informative approach could be the study of cardiomyocytes derived from induced pluripotent stem cells of patients with dominant-negative MOG1 missense mutants or homozygous nonsense variants.

Disclosures

None.

References


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