MOG1
A New Susceptibility Gene for Brugada Syndrome

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Background—Brugada syndrome (BrS) is caused mainly by mutations in the SCN5A gene, which encodes the α-subunit of the cardiac sodium channel Na\textsubscript{1.5}. However, ~20% of probands have SCN5A mutations, suggesting the implication of other genes. MOG1 recently was described as a new partner of Na\textsubscript{1.5}, playing a potential role in the regulation of its expression and trafficking. We investigated whether mutations in MOG1 could cause BrS.

Methods and Results—MOG1 was screened by direct sequencing in patients with BrS and idiopathic ventricular fibrillation. A missense mutation p.Glu83Asp (E83D) was detected in a symptomatic female patient with a type-1 BrS ECG but not in 281 controls. Wild type (WT)- and mutant E83D-MOG1 were expressed in HEK Na\textsubscript{1.5} stable cells and studied using patch-clamp assays. Overexpression of WT-MOG1 alone doubled sodium current (I\textsubscript{Na}) density compared to control conditions (P<0.01). In contrast, overexpression of mutant E83D alone or E83D+WT failed to increase I\textsubscript{Na} (P<0.05), demonstrating the dominant-negative effect of the mutant. Microscopy revealed that Na\textsubscript{1.5} channels failed to properly traffic to the cell membrane in the presence of the mutant. Silencing endogenous MOG1 demonstrated a 54% decrease in I\textsubscript{Na} density.

Conclusions—Our results support the hypothesis that dominant-negative mutations in MOG1 can impair the trafficking of Na\textsubscript{1.5} to the membrane, leading to I\textsubscript{Na} reduction and clinical manifestation of BrS. Moreover, silencing MOG1 reduced I\textsubscript{Na}, demonstrating that MOG1 is likely to be important in the surface expression of Na\textsubscript{1.5} channels. All together, our data support MOG1 as a new susceptibility gene for BrS. (Circ Cardiovasc Genet. 2011;4:261-268.)

Key Words: Brugada syndrome ■ sudden cardiac death ■ arrhythmia ■ MOG1 protein ■ SCN5A protein ■ sodium channels ■ protein trafficking

Brugada syndrome (BrS) is a rare, autosomal-dominant clinical entity (OMIM [Online Mendelian Inheritance in Man] 601144) characterized by ST-segment elevation in right precordial leads1–3 but without structural heart disease. Patients may develop syncope, ventricular arrhythmia, and sudden cardiac death (SCD) resulting from episodes of ventricular fibrillation. In 1998, Chen et al4 reported the first BrS mutations in SCN5A, the gene encoding the α-subunit of the cardiac sodium channel Na\textsubscript{1.5}. However, these mutations occur in only ~20% of affected individuals,3,5 suggesting involvement of other genes. The Na\textsubscript{1.5} α-subunit interacts with several proteins, such as the β1 sodium channel subunit, ankyrin G, caveolin 3, or syntrophin,6 which all are implicated in channel function and localization. Mutations of some of these partners already have been linked to BrS. One recent example has been reported by Watanabe and coworkers,7 who described mutations in the SCN1B gene encoding the β1-subunit that affect the trafficking of Na\textsubscript{1.5} to the cell surface and cosegregate with BrS and atrioventricular conduction abnormalities.

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Human MOG1 (multicopy suppressor of Gsp1\textsuperscript{8}) is a small, ubiquitous 28-kDa protein encoded by the MOG1 gene.9 In yeast, MOG1 is characterized as a nuclear protein that regulates nuclear import and export by binding to the
RanGTP complex and stimulating GTP release, thereby mediating the RanGTP gradient from cytoplasm to nucleus. Recently, MOG1 was described as a new partner of Na\textsubscript{1.5}. MOG1 interacts with Na\textsubscript{1.5} through its intracellular loop between domains II and III and colocalizes with the channel at intercalated disks in mouse ventricular myocytes. Moreover, SCN5A and MOG1 coexpression results in an increase in the sodium current (I\textsubscript{Na}) without changes in biophysical properties of the channel, suggesting that MOG1 regulates the surface expression of Na\textsubscript{1.5}.\textsuperscript{1,2}

In this study, we tested whether MOG1 could be a relevant candidate gene within a BrS SCN5A-negative cohort, and we report that a missense mutation is associated with a proarrhythmic phenotype in a symptomatic patient with BrS. Furthermore, we investigated whether this missense mutation could affect Na\textsubscript{1.5} activity and provide molecular and clinical evidence that the MOG1 loss-of-function mutation is linked to BrS physiopathology.

**Methods**

**Patients**

Patients received a diagnosis of BrS or idiopathic ventricular fibrillation on the basis of established criteria. Diagnosis was based on 12-lead ECG analysis, personal history of syncope or resuscitated SCD, and family history of SCD or arrhythmic events. Patients with BrS (n=246) presented with a type-1 ECG pattern (ST-segment elevation ≥2 mm in ≥1 right precordial lead) either spontaneously or after a sodium blocker challenge test (ajmaline). Patients with no clearly established BrS phenotype but showing ventricular fibrillation with or without documented resuscitated SCD were categorized as having idiopathic ventricular fibrillation (n=24). Structural heart disease was excluded by echocardiography. Related family members were known to be affected in 11% of the cases, suggestive of familial disease. All patients gave informed consent for genetic testing and had negative test results for SCN5A and SCN1B mutations.

**MOG1 Mutational Analysis**

DNA was extracted from peripheral blood leukocytes according to standard procedures. Screening for mutations in the MOG1 gene was performed by genomic DNA amplification of all exons and splice junctions (Primers and polymerase chain reaction conditions are available on request). Polymerase chain reaction products were directly sequenced with the Big Dye Terminator version 3.1 kit (Applied Biosystems). Sequencing was performed on the ABI PRISM 3730 automatic DNA sequencer (Applied Biosystems). Variants and mutations were identified by visual inspection of the sequence with Sequencher software (Applied Biosystems). We also genotyped MOG1 in 281 healthy white subjects as a control population and 48 patients with BrS harboring SCN5A mutations.

**MOG1 Cloning and Mutagenesis**

The pcDNA3.1C-MOG1 plasmid was provided by Q. Wang from the Cleveland Clinic Foundation.\textsuperscript{1,2} MOG1-enhanced green fluorescent protein (EGFP) fusion constructs (in the pEGFP-C3 vector) (BD Biosciences Clontech) were designed to trace the trafficking of MOG1 in cardiomyocytes by microscopy. Constructs with the pRES bicistronic vector and EGFP (pRES2-EGFP) (BD Biosciences Clontech) were generated for patch-clamp assays. The mutant construct E83D-MOG1 was prepared using the QuikChange II XL Site-Directed Mutagenesis Kit (Stratagene) according to the manufacturer’s instructions. Inserts were subsequently sequenced to ensure that there were no other mutations.

**Cell Preparation and Transfection of HEK293 Na\textsubscript{1.5} Stable Cell Line**

The human embryonic kidney HEK293 cell line stably expressing human Na\textsubscript{1.5} was cultured in Dulbecco modified eagle medium (Gibco; Invitrogen) supplemented with 10% fetal bovine serum, 100 IU/mL penicillin, 100 μg/mL streptomycin, and 25 μg/mL Zeocin (Invitrogen) at 37°C in a 5% CO\textsubscript{2} incubator. For overexpression assays, cells were transiently transfected at 80% confluence using a liposomal approach (Lipofectamine 2000; Invitrogen). The amounts of each construct used for transfection of a 6-well plate well were 1 μg of wild type (WT)-MOG1, 1 μg of mutant E83D, or 1 μg of empty vector pRES-EGFP as a negative control. To simulate allelic heterozygosity, cells were transfected with an equimolar mix of 0.5 μg WT and 0.5 μg mutant E83D. For silencing assays, cells also were cotransfected at 80% confluence with either 12 nmol/L scrambled siRNA (siSCR) Cy3 tagged as negative control or a mix of 10-nmol/L antihuman MOG1 siRNA (siMOG1) and 2 nmol/L of Cy3-tagged siSCR, both purchased from Ambion/Applied Biosystems (siMOG1 sequence reference ID# s195167). Western blotting confirmed the efficacy of silencing.

**Electrophysiological Measurements**

Forty-eight to 72 hours after transfection, cells displaying GFP for expression assays, or red fluorescence (Cy3) for silencing experiments were selected for electrophysiological measurements. Cells were bathed in an extracellular Tyrode solution containing 135 mmol/L NaCl, 4 mmol/L KCl, 1 mmol/L NaH\textsubscript{2}PO\textsubscript{4}, 1 mmol/L CaCl\textsubscript{2}, 2 mmol/L MgCl\textsubscript{2}, 10 mmol/L HEPES, and 20 mmol/L glucose (pH 7.4, adjusted with NaOH). Patch pipettes were filled with an internal solution containing 5 mmol/L NaCl, 130 mmol/L CsF, 4 mmol/L MgATP, 2 mmol/L MgCl\textsubscript{2}, 15 mmol/L EGTA, and 10 mmol/L HEPES (pH 7.4, adjusted with CsOH). During patch-clamp recordings, cells were perfused with an external solution with reduced sodium concentration containing 80 mmol/L NaCl, 50 mmol/L CsCl, 2 mmol/L CaCl\textsubscript{2}, 2.5 mmol/L MgCl\textsubscript{2}, 10 mmol/L HEPES, and 10 mmol/L 10 glucose (pH 7.4, adjusted with CsOH). I\textsubscript{Na} was recorded at room temperature (20°C) in the whole-cell configuration with a patch-clamp amplifier (Axopatch 200B; Molecular Devices). Patch pipettes (Corning Kvarov Sealing code 7052; WPI) had resistances of 1 to 2 MΩ. Currents were low-pass filtered at 10 kHz (−3 db) and digitized with DigiData 1200 (Molecular Devices). Data were acquired and analyzed with Acquis-1 software (G. Sadoc, CNRS, Gif-sur-Yvette, France). Patch-clamp recordings for peak I\textsubscript{Na} amplitude, activation, and steady-state inactivation were assessed with standard protocols, as described previously.\textsuperscript{13} The current amplitudes were normalized by cell capacitances (current densities, picocamperes per picofarad [pA/pF]). All activation potential and steady-state inactivation curves were fitted with a single Boltzmann function as follows:

\[
y = 1/(1 + e^{-[(V_m - V_{1/2})/k]})
\]

where V\textsubscript{1/2} is the half activation potential or half inactivation potential (ie, half availability); V\textsubscript{m} test voltage; and k, slope factor.

**Adult Rat Cardiomyocyte Isolation and Transfection**

Adult rat cardiomyocytes (ARCs) were isolated from the atrium of adult Wistar rats as previously described.\textsuperscript{14} After dissociation, cardiomyocytes were cultured overnight in a 1% CO\textsubscript{2} incubator before transfection with a 1-μg GFP-fused construct of WT- or mutant E83D-MOG1 using a liposomal approach (Lipofectamine 2000; Invitrogen). Three days after transfection, cardiomyocytes were fixed for immunocytochemistry.

**Immunocytochemistry**

Indirect immunofluorescence was performed on ARC primary culture fixed with 4% paraformaldehyde solution for 10 minutes at room temperature. Cells were then incubated for 1 hour at room temperature with permeabilizing/blocking buffer (0.1% Triton X-100 in PBS, 1% BSA, 10% normal goat serum, and 10% chicken serum) and double labeled overnight by incubation at 4°C with a mixture of primary
antibodies diluted in blocking buffer (PBS containing 1% BSA, 3% normal goat serum, and 3% chicken serum) as follows: mouse-anti-GFP (1:300; Roche) to detect MOG1-GFP and rabbit anti-Nav1.5 (1:50; ASC005; Alomone). Detection was performed the next day by a 1-hour incubation with secondary antibodies as follows: chicken antimouse Alexa Fluor 488, goat antirabbit Alexa Fluor 594 (1:500; Molecular Probes), and the nuclear dye DAPI (1:500; Sigma) also diluted in the blocking buffer. Control experiments were performed by omitting the primary antibodies.

**Imaging and Quantitative Fluorescence**

Labeled cardiomyocytes were observed with an Olympus epifluorescent microscope (60×/H11003). Images were acquired with a CoolSnap camera (Ropper Scientific) and analyzed with Metamorph software (Molecular Devices) equipped with a 3D deconvolution module. For each sample, a series of consecutive plans (stack of images) were acquired (sectioning step, 0.2 μm). To quantify the proportion of Nav1.5 at the membrane, 5 random regions of similar length were delineated at the membrane cell periphery, and fluorescence for Nav1.5 antibody was quantified in each of these regions with ImageJ software. For each cell, a mean fluorescent signal was normalized to the length to generate a value in arbitrary units (AU). For each transfection condition, 21 cells from 3 different cultures (7 cells/culture per condition) were quantified.

**Statistical Analysis**

Data are expressed as mean±SEM. Statistical significance was estimated with a Student t test or a Mann-Whitney rank sum test, as appropriate. P<0.05 was considered significant. Statistical analyses were performed with SigmaPlot software.

**Results**

**Identification of a MOG1 Mutation in a Patient With a BrS ECG Pattern**

Mutational analysis of the MOG1 gene revealed a novel mutation, potentially causing BrS, in 1 (0.3%) of 270 white subjects with BrS or idiopathic ventricular fibrillation phenotypes. DNA sequencing revealed a c.249G>C transversion in exon 3 (Figure 1A, arrow), predicting a glutamic-to-aspartic acid substitution at amino acid 83 (p.Glu83Asp, E83D). This missense mutation was absent in 281 ethnically matched unrelated controls and in 48 patients with BrS with SCN5A mutation. Alignment of the MOG1 amino acid sequence demonstrated that the glutamic acid in position 83 is conserved in several species, suggesting its importance at this position (Figure 1B). The patient was a symptomatic, 41-year-old woman with a medical history of syncope who experienced a cardiac arrest. She required defibrillation followed by adrenaline injection to recover a sinus rhythm. The ECG recorded after the Rescue maneuver showed a sinus tachycardia with an ST-segment elevation in precordial leads (V1, V2), an atypical right bundle branch block, and a prolonged PR interval, evoking a type-1 BrS pattern (Figure 1C). Blood tests showed metabolic acidosis and hyperlactemia but no traces of cocaine or other drugs of abuse. Because of the abnormal ECG pattern, echocardiography and coronary angiography were performed and showed an absence of structural cardiac abnormalities, healthy coronary arteries, and normal left ventricular function. Twenty-four hours later, the ST elevation had regressed, but the atypical right bundle branch block persisted, suggestive but not diagnostic of BrS (Figure 1D). An electroencephalogram showed postanoxic encephalopathy, and the patient died 4 days later from sepsis while in a comatose state. None of her family members have been available for clinical or genetic testing.

**WT-MOG1 Increases I_{Na} Density but Not Mutant E83D-MOG1**

We next tested whether the E83D-MOG1 mutant had a proarrhythmic cellular phenotype. To characterize the functional consequences on I_{Na}, we performed whole-cell patch-
MOG1 Silencing Reduces \( I_{\text{Na}} \) Density

To further characterize the consequences of the loss of MOG1 on \( I_{\text{Na}} \), we studied the effects of endogenous MOG1 silencing using siRNA in HEK293 cells stably expressing Na\(_{1.5}\), transfected with siMOG1 or siSCR. First, we confirmed that siMOG1 suppressed endogenous MOG1 by Western blot as shown in Figure 3A. Second, whole-cell patch-clamp recordings in cells transfected with siMOG1 showed that the \( I_{\text{Na}} \) density was reduced by 54\% compared to cells transfected with siSCR (siMOG1, \(-51.6 \pm 6.7\) pA/pF at \(-20\) mV, \( n=12 \); siSCR, \(-114.6 \pm 12.5\) pA/pF at \(-20\) mV, \( n=12 \); \( P<0.001 \)) (Figure 3B and 3C). The decrease in peak current by siMOG1 was not associated with changes in current biophysical properties (Table).

### E83D-MOG1 Mutation Causes a Defect in Na\(_{1.5}\) Intracellular Trafficking to the Membrane in Isolated ARCs

Subsequently, we studied cellular localization of MOG1 and Na\(_{1.5}\) in isolated atrial ARCs transfected with GFP-tagged MOG1 constructs (WT and mutant E83D) using 3D micros-
copy. Figure 3 shows 3D deconvolution images of cardiomyocytes double stained with anti-GFP and anti-Na\textsubscript{v}1.5 antibodies. MOG1 was widely distributed throughout the cardiomyocytes except in the nucleus. WT- and mutant E83D-MOG1 displayed a similar subcellular distribution. In contrast, Na\textsubscript{v}1.5 channel distribution was clearly different. In cells transfected with WT-MOG1 (Figure 4A), channels were mostly localized at the cell membrane (yellow arrows) and around the nuclei (white arrows). In contrast, Na\textsubscript{v}1.5 accumulated in the perinuclear regions in cardiomyocytes transfected with mutant E83D, whereas a low fluorescent signal was detected at the cell periphery (Figure 4B). This observation was confirmed by quantification of the fluorescence intensity in random regions delineated at the cell membrane periphery (Figure 4C). The fluorescent signal for the sodium channel Na\textsubscript{v}1.5 was drastically reduced by 58% in mutant E83D-transfected myocytes compared with WT-MOG1 (normalized membrane fluorescence intensity with anti-Na\textsubscript{v}1.5 antibody for WT-MOG1-GFP transfected, 1224±160 AU; for E83D-MOG1-GFP transfected, 507±17 AU; P<0.001).

**Discussion**

The first mutations to be identified in patients with BrS were in SCN5A, resulting in a loss of channel function.\textsuperscript{4-15} They reduce I\textsubscript{Na} by altering Na\textsubscript{v}1.5 cell surface expression and modifying its gating properties, and they are the major cause of this disorder.\textsuperscript{3,16,17} However SCN5A mutations account for only \textasciitilde20% of cases,\textsuperscript{3} and the frequency of mutations in other implicated genes (GDP1L,\textsuperscript{18} CACNA1C,\textsuperscript{19} CACNB2b,\textsuperscript{19} SCN1B,\textsuperscript{7} SCN3B,\textsuperscript{20} and KCNE3\textsuperscript{21}) appears to be rare.\textsuperscript{15} Thus, almost 75% of BrS cases remain without a genetic cause. In the heart, sodium channels are composed not only of pore-forming \alpha-subunits encoded not only by SCN5A, but also by multiple interacting partners to form macromolecular complexes (the “channelosome”). Some of them have already been implicated in the pathogenesis of arrhythmias and SCD.\textsuperscript{6}

In the present study, we provide for the first time to our knowledge molecular and clinical evidence implicating a novel partner of Na\textsubscript{v}1.5, MOG1, in BrS, by reporting a patient in which the observed disease phenotype may result from a mutation in the MOG1 gene. Genetic screening identified the MOG1 missense mutation E83D in 1 (0.3%) symptomatic patient presenting a type-1 BrS ECG of 270 affected individuals, which was absent in 562 healthy ethnically matched control alleles. Using targeted mutagenesis, heterologous expression in an HEK Na\textsubscript{v}1.5 stable cell line, and a functional approach by patch-clamp assay, we demonstrated that the E83D mutation failed to increase I\textsubscript{Na} density in contrast to WT-MOG1 in homozygous and heterozygous conditions. Thus, we assumed that the mutant exerted a dominant-negative effect on WT-MOG1. Therefore, the presence of a mutation in 1 affected individual, its absence in a healthy control population, and the clear effect of the mutation on I\textsubscript{Na} support E83D-MOG1 as a BrS susceptibility mutation rather than as a polymorphism.

Mechanisms underlying the effects of MOG1 on Na\textsubscript{v}1.5 remain unclear. A recently published study reported MOG1 as a new partner of Na\textsubscript{v}1.5.\textsuperscript{12} The 2 proteins colocalize at the level of the intercalated disks in mouse ventricular myocytes, and moreover, MOG1 increased I\textsubscript{Na} when coexpressed with Na\textsubscript{v}1.5 in a heterologous system and in neonatal cardiomyocytes.\textsuperscript{12} In the present study, we provide further evidence for the role of MOG1 as a partner of Na\textsubscript{v}1.5 channels by demonstrating that the missense E83D mutant had no effect on I\textsubscript{Na} and that silencing endogenous MOG1 dramatically reduced I\textsubscript{Na} in a heterologous expression system. Because MOG1 shows no effect on the biophysical and gating properties of the I\textsubscript{Na}, this partner could regulate the surface expression of channels rather than their

**Figure 3.** Effect of silencing endogenous MOG1. A, Western blot of total protein lysates of HEK293 cells stably expressing Na\textsubscript{v}1.5 alone or transiently transfected with siSCR or siMOG1. B, Representative traces of I\textsubscript{Na} in MOG1-silenced HEK cells. C, Dot plot of I\textsubscript{Na} densities at −20 mV in HEK 293 cells stably expressing Na\textsubscript{v}1.5 transiently transfected with siRNA. Each dot represents the current density for 1 cell; lines represent the means (siSCR I\textsubscript{Na}, −114.6±12.5 pA/pF, n=12; siMOG1 I\textsubscript{Na}, −51.6±6.7 pA/pF, n=12). Data are presented as mean±SEM. siMOG1 indicates antihuman MOG1 siRNA; siSCR, scrambled siRNA. Other abbreviations as in Figure 2. **P<0.001.
intrinsic properties. This also is supported by the observation that in cardiomyocytes transfected with mutant E83D, Nav1.5 channels remained trapped in the perinuclear region, whereas their localization at the membrane periphery was reduced, suggesting a defect in channel trafficking. Several mutations in SCN5A that affect trafficking already have been described as causing a BrS phenotype.\textsuperscript{16,22–25} Indeed, a reduced channel density at the membrane has been observed for the GDP1L mutation associated with a BrS family\textsuperscript{18} as well as for an SCN3B mutation in 1 individual with BrS.\textsuperscript{20} Therefore, in accordance with these previous studies, the E83D-MOG1 mutation may cause BrS by reducing Na\textsubscript{1.5} channel trafficking to the cell surface. This observation also is consistent with the role of MOG1 in other cell types, which is to regulate protein trafficking by mediating the RanGTP gradient from nucleus to cytoplasm.\textsuperscript{26}

Other Na\textsubscript{1.5} partners are known to regulate membrane expression of the channel. For instance, ankyrin G associates with the cardiac sodium channel at intercalated disks and T tubules, and silencing of ankyrin G reduces both the surface expression of Na\textsubscript{1.5} and the I\textsubscript{Na} density.\textsuperscript{27,28} Interestingly, MOG1 and ankyrin G\textsuperscript{27} colocalize with Na\textsubscript{1.5} at the level of the intercalated disks, and both partners interact with the

![Figure 4. MOG1 and Na\textsubscript{1.5} localization in isolated adult rat atrial cardiomyocytes. Three-dimensional deconvolution images of MOG1-GFP (green) and Na\textsubscript{1.5} (red) in myocytes transfected with WT-MOG1-GFP construct (A) or with mutant E83D-MOG1-GFP construct (B). Note the localization of Na\textsubscript{1.5} around the nucleus (white arrows) and at the cell membrane (yellow arrows) in WT-MOG1-transfected myocytes and the lack of Na\textsubscript{1.5} at the cell membrane in mutant E83D-MOG1-transfected myocytes (scale bar, 10 \textmu m). C, Dot plot of normalized membrane fluorescence intensities with anti-Na\textsubscript{1.5} antibody in cells transfected with WT-MOG1 or mutant E83D-MOG1. Each dot represents the normalized membrane fluorescence intensity for 1 cell; lines represent the means for each condition (WT-MOG1, 1224\(\pm\)160 AU, n=21; mutant E83D-MOG1, 507\(\pm\)17 AU, n=21). Data are presented as mean\(\pm\)SEM. AU indicates arbitrary unit; GFP, green fluorescent protein; WT, wild type. **P<0.001.](http://circgenetics.ahajournals.org/figure/4)
in the intracellular loop between domains II and III of the channel, suggesting that this loop is involved in the surface expression of the Na\(_{\text{a}1.5}\) channel. In the present study, silencing endogenous MOG1 resulted in a reduction of \(I_{\text{Na}}\), as also was observed after ankyrin G silencing. Taken together, these observations suggest that MOG1 and ankyrin G may belong to the same protein complex that regulates the expression of sodium channels to the plasma membrane of cardiac myocytes.

Phenotypic penetrance varies in patients with BrS with SCN5A haploinsufficiency mutations, even between individuals carrying the same mutation.\(^{29}\) In fact, a mouse model with a heterozygous targeted disruption of Scn5a\(^{-/-}\) shows a similar pattern of phenotypic heterogeneity. Ultimately, phenotypic severity was correlated with levels of WT Na\(_{\text{a}1.5}\) protein expression.\(^{30}\) Considering that MOG1 regulates the sodium channel expression at the membrane, it is clear that MOG1 also could be a potential BrS modifier gene and could explain some of the variable penetrance of the disease.

**Limitations**

The genotype-phenotype correlation between the MOG1 mutation and the BrS phenotype is hampered by the absence of a sodium channel blockade test to confirm the diagnosis of BrS. However, the presence of a type-I BrS ECG a few hours after resuscitated SCD and the persistence of atypical right bundle branch block for 24 hours in a patient with a personal history of syncope are in favor of a true BrS diagnosis. Linkage analysis was also impossible because genetic material from other family members was not available. Thus, we could not provide cosegregation data to determine whether this mutation is familial or sporadic. In such patients with an incomplete clinical and genetic exploration, it is difficult to prove whether the observed phenotype is only due to the presence of the MOG1 mutation. Genetic screening of other BrS populations would indeed confirm the role of MOG1.

Another limitation is the difficulty in extrapolating data obtained in a heterologous system to cardiac electrophysiology. We cannot eliminate the possibility that in situ, some other mechanisms could compensate for the MOG1 loss of function. However, there is no other example of a mutation causing a >50% decrease in \(I_{\text{Na}}\) without it affecting cardiac function. For instance, an extensive review of SCN5A mutations showed that every mutation associated with BrS and a conduction defect invariably lead to a reduced peak of \(I_{\text{Na}}\) in heterologous systems.\(^{31}\) In addition, mutations in known partners such as GDP1L\(^{18}\); SCN1B\(^{7}\); and, recently, SCN3B\(^{20}\) that showed drastic decreases of \(I_{\text{Na}}\) in vitro also were found in patients with BrS and conduction defects. Thus, we can speculate that the in vitro cellular characteristics of the E83D-MOG1 mutation is in accordance with the BrS phenotype observed in the present patient and that in combination with our genetic data, provide evidence of a relationship between the mutation and the disease.

**Conclusions**

We propose that MOG1 is a novel susceptibility gene for BrS. Moreover, we have established that MOG1 is likely to be an important partner for the normal surface expression of Na\(_{\text{a}1.5}\) channels. Our findings are relevant not only for BrS, but also for other channelopathies because they underline the presence of a multiprotein machinery specialized in sodium channel membrane targeting. Thus, the dynamics of cardiac channel surface expression has become even more essential. Beyond revealing precise explanations of the physiopathology of acquired and inherited channelopathies, the findings may provide new clues in improving clinical management by generating new targets for antiarrhythmic drugs.

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**Disclosures**

None.

**References**


Brugada syndrome (BrS) is a rare, autosomal-dominant arrhythmia that arises from heritable defects affecting cardiac ion channel function. Since the first discovery of cardiac sodium channel mutations as a pathogenic basis of BrS, the condition has been considered a cardiac channelopathy. However, it appears that this disorder can result from a diverse set of genetic mutations. The list of genes includes not only expected ion channels and their critical subunits, but also partners implicated in their trafficking and correct targeting to the plasma membrane. In the present investigation, we studied MOG1, a recently identified gene that inherited arrhythmia syndromes, such as BrS, may originate from defects in partner proteins rather than the channel itself, opens the field to an entire class of candidate genes implicated for the unexplained BrS or idiopathic ventricular fibrillation.
MOGI: A New Susceptibility Gene for Brugada Syndrome
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