IRX3 variant as a modifier of Brugada syndrome with frequent ventricular fibrillation

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Introduction

Brugada syndrome (BrS) is characterized by coved-type ST-segment elevation in the right precordial leads of electrocardiogram (ECG) and the development of ventricular fibrillation (VF) leading to sudden cardiac death.1-3 Inheritance of BrS occurs via an autosomal-dominant mode of transmission. The first gene linked to BrS is SCN5A, the gene that encodes the alpha subunit of the cardiac sodium channel.1 SCN5A mutations, mainly loss-of-function, have been identified in 10%–28% of BrS probands in 9 international centers around the world.4 Over 300 mutations in SCN5A have been linked to BrS.5

SCN5A mutations are associated with both BrS and familial atrial fibrillation, progressive cardiac conduction defect, sick sinus syndrome, early repolarization syndrome, dilated cardiomyopathy, and sudden infant death syndrome.6 Furthermore, BrS has been linked to mutations in 18 other genes, but they are rarer. Thus, BrS is often genetically undetermined and the genotype-phenotype correlations are not completely matched, even in SCN5A mutation–positive BrS families.7,8

Recently, we have identified IRX3 mutation as a genetic risk factor of idiopathic VF, including BrS without SCN5A mutation.9 Here we present the first case report demonstrating that both the SCN5A mutation and the IRX3 variant accentuated the Brugada phenotype, inducing repetitive VF.

Case report

Patient

A 35-year-old man was admitted to our hospital after successful resuscitation of cardiac arrest caused by VF in 1989. His past history was noncontributory, with no familial history involving sudden cardiac death. He was initially diagnosed with idiopathic VF, and there had been no episodes in 15 years following treatment with disopyramide. He was subsequently diagnosed with BrS on the basis of spontaneous type 1 Brugada ECG, which was more pronounced in the third intercostal space (Figure 1A), and received an implantable cardioverter-defibrillator in 1998. When he was 50 years old, he underwent 4 successful implantable cardioverter-defibrillator interventions for VF (Figure 1B). Denopamine was added and effectively reduced premature ventricular complexes, especially at nighttime. VF episodes then decreased to 0–2 times per year. At the age of 60, however, he experienced multiple VF episodes, including a VF storm, despite the combination therapy with disopyramide (450 mg/day), denopamine (15 mg/day), and cilostazol (200 mg/day). Quinidine was considered but not used, because disopyramide, which has a similar effect of suppressing the transient outward potassium (Ito) current, may have already been ineffective.

Genetic study

We examined the sequence of exons in 13 proposed BrS-related genes in humans (SCN5A, GPD1-L, CACNA1C, CACNB2, KCNE3, SCN1B, SCN3B, KCNJ8, MOG1, HCN4, KCND3, KCNE5, and SLCAP) and found 1 SCN5A mutation, 2205C>T (A735V), in the patient (proband) and...
his father and son. The SCN5A-A735V has already been reported as causing BrS, a sudden unexplained nocturnal death syndrome.\textsuperscript{10}

Even though the proband’s father and son have the same SCN5A mutation, their ECGs did not show BrS and they had no symptoms or ventricular arrhythmias (his father had atrial fibrillation) (Figure 1C). Therefore, we further examined the IRX3 gene, which we had reported as a risk factor of idiopathic VF\textsuperscript{9} in this family. The proband carried the IRX3 2207G>T (Q479H) variant in addition to the SCN5A A735V mutation. (A735V). The patient’s father and son, who had the same SCN5A-A735V mutation, did not have the IRX3 Q479H variant. In contrast, his mother and daughter, who did not have the SCN5A mutation, had the IRX3 2207G>T (Q479H) variant (Figure 2A). None of these 4 family members had the Brugada ECG or episodes of syncope, ventricular tachyarrhythmias, or sudden cardiac death. Thus, the IRX3 2207G>T (Q479H) variant appears to act as a modifier in BrS.

Discussion

Inheritance of BrS occurs via an autosomal-dominant mode of transmission, and more than 13 responsible genes have been associated with BrS. Genetic abnormalities are only found in one-third of BrS patients. Even SCN5A, the first and most well-documented gene, accounts for less than 30% of clinically diagnosed BrS patients.\textsuperscript{4} The penetrance of BrS is thus considered to be low. SCN5A mutation carriers had, on average, longer PR and QRS intervals than noncarriers, demonstrating that these mutations exerted functional effects.\textsuperscript{3} A recent genome-wide association study revealed the 3 genes, SCN10A, SCN5A, and HEY2, as risk factors of the Brugada phenotype.\textsuperscript{11} Therefore, SCN5A mutations probably act as major modulating factors in revealing BrS. BrS is likely an oligogenic disease, and is not considered a monogenic Mendelian disease.\textsuperscript{12}

A previous Xenopus oocytes patch clamp study demonstrated that SCN5A A735V mutant expressed current with steady-state activation voltage shifted to more positive potentials and that slower recovery from inactivation resulted in reduced sodium channel current.\textsuperscript{10} These findings are consistent with the QRS interval prolongation in the proband and family members with SCN5A A735V (Figure 1A), although only the proband suffered lethal arrhythmias due to BrS. Irx3/IRX3 encodes a transcription factor specifically for the heart and is expressed in the atria and ventricles. It is involved in the development of the heart and the regulation of gene expression during embryonic development. In this family, the proband carried the IRX3 2207G>T (Q479H) variant, which may act as a modifier of Brugada syndrome (BrS) and ventricular fibrillation (VF) storm.

KEY TEACHING POINTS

- IRX3 gene, even if it is not a mutation but also a variant, may act as a modifier of Brugada syndrome (BrS) and ventricular fibrillation (VF) storm.
- SCN5A mutations probably act as a major modulating factor in revealing the BrS phenotype.
- BrS and its VF episodes are likely due to multiple mechanisms.
expressed in the His-Purkinje system in the heart. Genetic deletion of Irx3 in a mouse model shows ventricular fast conduction disturbance without anatomical or contraction abnormalities. We recently reported the link between the perturbed His-Purkinje system and idiopathic VF in Irx3-null mice, and Irx3 mutations are associated with idiopathic VF patients, including BrS without SCN5A or other Brugada-related mutations. It remains unclear how Irx3 variants contribute to the manifestation of BrS and the risk of VF or sudden cardiac death.

To show the functional differences of mRNA expression in SCN5A by IRX3 variants, we performed transfection of wild-type (WT) or Q485H (human Q479H, Figure 2B) Irx3 in pcDNA3.1 vector into HL-1 cells as shown previously. The transfection of WT Irx3 increased the expression of SCN5A mRNA; however, Q485H variant did not increase the SCN5A mRNA expression as much as the WT (Figure 2C). Thus, a common variant, Irx3 Q479H, might be one of the modifiers for BrS as a cause of relative downregulation of mRNA expression in SCN5A.

The 2207G>T (Q479H) is a common variant in a chaperone binding domain of IRX3 that was identified as “benign” by PolyPhen-2, found in 16.8% in the 1000 genome project and 22%–23% in Europeans but 2.1% in East Asians by ExAC. In the Japanese population, the frequency of the 2207 G>T variant was 3.1% (4/130) in idiopathic VF cases but 0.4% (1/250) in control subjects. Although the precise explanation for 2207G>T remains unknown, it may be due to ethnic differences. In this family, the only proband has both SCN5A mutation and IRX3 variant, which is likely why he has the Brugada ECG with repetitive VF episodes. These findings suggest that the IRX3 gene, even if it is also a variant and not a mutation, may act as a modifier of the BrS and VF storm. However, it might be specified to the group of the Japanese population but not a large population.

This study did not completely exclude all other possible modifiers; additional (or unknown) factors such as SCN10A or HEY2 genes could be involved as well in the clinical presentation of the patient. However, the role of rare variants in SCN10A and HEY2 on the BrS phenotype remain controversial. The proband had suffered a VF storm when elderly. Age-dependent conduction abnormalities due to the patient’s genetic background are strongly associated with the development of VF storm. Further genetic studies are necessary to investigate the role of the IRX3 gene and other candidate genes in the risk of VF storm in BrS.

In conclusion, IRX3 variant Q479H may play a critical role as a modifier for BrS-related frequent VF events in SCN5A mutation–positive subjects.

**Acknowledgments**
The authors thank Naotaka Ohta, Toshiko Shibata, Hiromi Fujiyama, Miyuki Hozan, and Akihiro Fujiwara for their excellent technical assistance.

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