Sudden cardiac death (SCD) is a tragic event that can occur even among apparently healthy patients with no structural heart disease. SCD in the absence of an identifiable cause has been considered to be due to idiopathic ventricular fibrillation (IVF). However, by virtue of progress in molecular genetics, it is increasingly recognized that ion channel mutations may underlie many cases previously regarded as IVF. Brugada syndrome (BS) is 1 such channelopathies and has been identified as the same entity, previously called sudden unexpected nocturnal death syndrome, found in Southeast Asian countries, including Japan. BS is characterized by ST-segment elevation with a “coved” morphology in the right precordial leads (V1–3) and right bundle branch block, and is associated with SCD resulting from episodes of VF. Although the pathophysiological mechanisms underlying the BS phenotype are not completely understood, 2 hypotheses have been proposed to explain the ST segment alterations in BS patients: depolarization and repolarization theories. Both models, which are not mutually exclusive, point to right ventricular alterations involving either early repolarization or late activation. These electrophysiological alterations can be brought about by genetic disorders of cardiac ion channels.

BS was first described in 1992 by Brugada and Brugada. In 1998, Chen et al reported the first BS mutations in SCN5A, the gene encoding the α-subunit of the cardiac Na+ channel (Nav1.5). These mutations lead to loss-of-function phenotypes by altering Nav1.5 cell surface expression or modifying its gating properties, and are the major cause of BS. To date, almost 300 SCN5A mutations have been linked to BS. However, because SCN5A mutations account for only 11–28% of BS cases, extensive investigations for other responsible genes have been and are being carried out. So far, 12 more BS-susceptible genes have been identified, of which 2 are genes encoding the α-subunits of the sodium channel (Nav1.5 and Nav1.6) and 1 is the β3 subunit of the sodium channel (SCN3B). The SCN3B mutation V110I is found in 10% of BS patients and is associated with SCD. These mutations lead to impaired trafficking of the Nav1.5 channel, which reduces the sodium current (INa).

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.
coding the β-subunit of the Na⁺ channel (SCN1B and SCN3B), and 2 are genes encoding proteins that functionally or physically interact with the Na⁺ channel (GPD1L and MOG1). The other identified genes encode the cardiac L-type Ca²⁺ channel (CACNA1C, α-subunit; CACNB2B, β-subunit; CACNA2D1, α1β-subunit), the transient outward K⁺ channel (KCND3, α-subunit; KCNE3, β-subunit; KCNE5, β-subunit); the ATP-sensitive K⁺ channel (KCNJ8), and the Iₗ channel (HCN4) (Figure). Disease-causing mutations of these proteins either decrease depolarizing inward currents (Iₛ, I_Ca,L, and I_L) or increase repolarizing outward currents (I_KATP). Each of these 12 genes is responsible for less than 1% of BS cases.

In humans, five β-subunits (Navβ1, Navβ1b (a splice variant), Navβ2, Navβ3, and Navβ4, encoded by SCN1B to SCN4B) have been identified, which associate with the α-subunit of Na⁺ channels. With the exception of Navβ1b, they share a similar membrane topology, having a large extracellular N-terminal domain with an immunoglobulin loop, 1 transmembrane domain, and a small intracellular C-terminal domain. In addition to modulation of Na⁺ channel expression and function, β-subunits have been suggested to play other roles, including cell adhesion, signal transduction and recruitment of anchoring proteins. Obviously, β-subunits play an important role in cardiac excitability, because many genetic variants of β-subunits are found in various electrophysiological disorders of the heart.

In this issue of the Journal, Ishikawa et al report a novel SCN3B mutation in Japanese BS patients who were negative for SCN5A mutations. SCN3B encodes the Na⁺ channel Navβ3 subunit that modulates cell surface expression and function of the Nav1.5 channel. The mutation they identified was V110I, which caused a reduction of Iₛ through impairment of Nav1.5 trafficking to the plasma membrane. This is the second SCN3B mutation identified in BS patients. In 2009, Hu et al reported the first SCN3B mutation, L10P, in a Caucasian male with a type 1 BS ECG. The L10P mutation also impairs Nav1.5 trafficking to the plasma membrane, leading to reduced Iₛ current. The trafficking defect induced by these mutations was not related to disruption of the association of Nav1.5 and the Navβ3 subunit, which suggested abnormal retention of the Navβ3 mutants in the endoplasmic reticulum (ER). Thus, normal trafficking of the Na⁺ channel may be restored if the Navβ3 mutants abnormally retained in the ER are rescued by drugs etc.

When coexpressed with Nav1.5 in tsA-201 cells, Navβ3-L10P slowed recovery from inactivation of the Na⁺ channel, whereas the novel V110I mutation had little effect on the biophysical properties of the Na⁺ channel. However, the electrophysiological changes induced by Navβ3-L10P were not the same when Navβ1 was included together with Nav1.5: additional acceleration of inactivation and negative shift of steady-state inactivation curve were observed, which indicates that the phenotype induced by SCN3B mutations can be influenced by another β-subunit Navβ1. It is also known that heterologous expression of SCN3B yields discrepant results, which may be related to differences in other modifying proteins in different expression systems. Although the contribution of other modifying proteins may make it hard to fully understand BS caused by β-subunit mutations, the novel SCN3B mutation V110I is probably a relatively common cause in Japanese BS patients.

As stated before, loss-of-function mutations in the SCN5A-coded α-subunit represent the most common genetic disorders, accounting for 11–28% of all BS cases, whereas the prevalence of other BS-susceptible genes are reported to be very low. However, the SCN3B mutation V110I was found in approximately 10% familial cases and approximately 0.6% sporadic cases of SCN5A-negative BS patients. In 2011, 2 expert consensus statements were published on the use of genetic testing for channelopathies and cardiomyopathies: from the Heart Rhythm Society/the European Heart Rhythm Association, and from the Canadian Cardiovascular Society/Canadian Heart Rhythm Society. The former states that comprehensive or SCN5A-specific genetic testing can be useful for any BS patient. The latter states that genetic testing should be limited to analysis of SCN5A and considered for other BS-responsible genes only under special circumstances. The relatively high prevalence of the SCN3B mutation V110I reported by Ishikawa et al suggests the usefulness of SCN3B-targeted genetic testing especially for SCN5A-negative Japanese BS patients with familial history. Future study in a large cohort will help answer this question.

References

14. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm 2011;8:1308–1339.