It is acknowledged that mutations in the cardiac sodium channel gene, SCN5A, are associated with various arrhythmia syndromes such as long QT syndrome type 3 (LQT3), Brugada syndrome (BrS), conduction disease, sick sinus syndrome, atrial fibrillation, atrial standstill, and sudden infant death syndrome (SIDS). Mixed phenotypes can be frequently observed as “cardiac sodium channel overlap syndrome”. In 1999, Bezzina et al reported that a single Na+ channel mutation (SCN5A-1795insD) can lead to overlap syndrome with symptoms of LQT3 and BrS in combination. Grant et al reported another Na+ channel mutation (SCN5A-∆K1500) showing a mixed phenotype of LQT3 and BrS. In addition, Makita et al have recently reported that the E1784K mutation in SCN5A is associated with the phenotypic overlap of type LQT3 syndrome and BrS. Thus, several SCN5A mutations are reported to produce a mixed phenotype of LQT3 and BrS (Figure 1).

In this issue of the Journal, Kanters et al report that a novel mutation (L1786Q) in SCN5A is associated with a combined LQT3 and concealed BrS (Figure 1). Flecainide challenge unmasked coved ST elevation, a typical Brugada ECG pattern, in all the mutation carriers. Similar combination of LQT3 and concealed BrS, which was revealed by Na+ channel blockade with flecainide, pilsicainide or ajmaline, has been observed in patients with SCN5A-E1784K mutations. Provocation test with class Ic sodium channel blockers in LQT3 patients may be useful to unmask concealed BrS.

Kanters et al evaluated the functional changes in the mutated Na+ channel using patch-clamp techniques. They indicated a reduced peak current, associated with a negative shift of steady-state Na+ channel inactivation, and an increase in the

**Figure 1.** Schematic of the primary structure of the cardiac channel alpha-subunit with location of the SCN5A mutations associated with clinical overlap of LQT3 and Brugada syndromes.
tetrodotoxin-sensitive late Na⁺ current in HEK293 cells expressing the mutated (L1786Q) Na⁺ channels. These changes in electrophysiological properties have been commonly observed in mutated Na⁺ channels responsible for the overlap phenotype of LQT3 and BrS.1–5 It has been assumed that a persistent (late) inward Na⁺ current during the action potential plateau phase can lead to prolongation of the QT interval whereas a reduction of the peak Na⁺ current, especially in epicardial ventricular cells, may produce coved ST elevation on the ECG (Figure 2). However, the precise electrophysiological mechanisms by which a single Na⁺ channel mutation causes a phenotype of combined LQT3 and BrS, leading to sudden cardiac death, remain to be established.

In terms of pharmacological treatment of the overlap phenotype of LQT3 and BrS, selection of an appropriate antiarrhythmic drug is difficult. According to the HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with congenital long QT syndrome, β-blocker use is recommended for the treatment of the inherited cardiac arrhythmia regardless of genotype.6 In LQT3 patients, β-blockers are less effective than in LQT1 or LQT2 patients.7 In addition, administration of a β-blocker to a patient with combined LQT3 and BrS should be avoided because treatment with a β-blocker is known to worsen the symptoms and sometimes induce ventricular fibrillation in patients with BrS.8 For the treatment of LQT3 in isolation, class Ib antiarrhythmic drugs such as mexiletine are recommended. Although the drug may not unmask BrS in patients with overlap syndrome, BrS should be avoided because treatment with a β-blocker may produce Brugada-type ECG changes. Kanter et al9 postulate that ranolazine may be a new alternative pharmacotherapy because the drug is reported to preferentially inhibit a late Na⁺ current without suppressing the peak current.10 However, the pharmacotherapy of overlap syndrome with LQT3 and BrS may be unreliable, and implantation of an ICD would be more appropriate treatment. Phenotypic overlap of LQT3 in BrS patients seems to be not uncommon. For the patients diagnosed as LQT3, a flecainide provocation test would be appropriate to check for concealed BrS. Clinical evaluation of phenotype in patients with sodium channelopathies would facilitate risk stratification and identification of patient-specific treatment strategies.

Figure 2. Schematic of the electrophysiological mechanisms underlying the overlap phenotype of LQT3 and Brugada syndromes caused by a single SCN5A mutation. A persistent (late) inward Na⁺ current during the action potential plateau phase can lead to prolongation of the QT interval. A reduction of the peak Na⁺ current, especially in epicardial (Epi) ventricular cells, may produce Brugada-type ST elevation on the ECG.

References