**E1784K Mutation in SCN5A and Overlap Syndrome**

Naokata Sumitomo, MD, PhD

**Table. SCN5A Mutations and Associated Inherited Arrhythmias**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Phenotype</th>
<th>Possible cause of the syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT3</td>
<td>Prolonged QT</td>
<td>Persistent Na current</td>
</tr>
<tr>
<td>BrS</td>
<td>RBBB type QRS, ST elevation in the right precordial leads</td>
<td>Reduction in the initial opening of the Na channels in the epicardial right ventricular outflow tract cells</td>
</tr>
<tr>
<td>PCCD</td>
<td>BBB, AVB</td>
<td>Fibrosis and conduction disturbance of the conduction system</td>
</tr>
<tr>
<td>SSS</td>
<td>Sinus bradycardia, SA block</td>
<td>Failure of conduction from the sinus node (exit block), morphological changes in the atrial cells</td>
</tr>
<tr>
<td>Atrial standstill</td>
<td>Junctional rhythm without P waves</td>
<td>Failure of conduction in the atrium</td>
</tr>
<tr>
<td>AF</td>
<td>AF</td>
<td>Morphological changes of the atrial cells</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>LQT3, BrS, SSS</td>
<td>Persistent Na current and reduction in the initial Na current</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; AVB, AV block; BBB, bundle branch block; BrS, Brugada syndrome; LQT3, long QT type 3; PCCD, progressive cardiac conduction system disturbance; RBBB, right bundle branch block; SA block, sino-atrial block; SSS, sick sinus syndrome.

C ongenital long QT syndrome (LQTS) is characterized by prolongation of the QT interval on the surface ECG and may cause syncopal and seizures; there is a certain risk of fatal ventricular arrhythmias, torsade de pointes or ventricular fibrillation.\(^1\) The QT interval is determined by the cardiac action potential duration and is related to the many ion channels in the myocardial cells. The most important state of the ion currents for prolonging the QT interval is a decrease in the outward K current, and increase of the inward Na or Ca current.\(^2\) Some PCCD patients develop this phenotype with aging, because the increased chance of fibrosis in association with the conduction system disturbance; RBBB, right bundle branch block; SA block, sino-atrial block; SSS, sick sinus syndrome.

In contrast, a reduction in the initial opening of the Na channels in the right ventricular epicardial cells may cause ST elevation in the right precordial leads and lead to BrS (Table).\(^3\) Some PCCD patients present with ECG findings characteristic of BrS (overlap syndrome), and one of the causes of this overlapping syndrome can be explained by E1784K.\(^4\) Sodium-channel blockers are commonly used in patients with LQT3 because of the blocking effect on persistent Na currents.\(^5\) However, in overlap syndrome, sodium-channel blockers shorten the QT interval, possibly reducing the peak Na current, and thus uncover a concealed BrS resulting in typical ST segment elevation in the right precordial leads, and may provoke malignant ventricular arrhythmias.\(^6\)

In this issue of the Journal, Takahashi et al report that the E1784K mutation in SCN5A is the most prevalent mutation in school children with LQTS in the Okinawa islands.\(^7\) The most common mutation in LQTS is reported to be a KCNQ1 mutation.\(^8\) It is noteworthy that there is a high prevalence rate of...
LQT3 (63%) in the Okinawa islands, and all the mutations are E1784K in SCN5A.23 From this result, the ancestors of the Okinawa islands may differ from those of the other islands in Japan. As reported, BrS is much more prevalent in the Asian region,24 and we need to investigate the prevalence of LQT3 incidence and also E1784K mutations in SCN5A.

In the study by Takahashi et al.,21 one in 8 of the phenotypes was revealed to have the BrS-type ST elevation while taking mexiletine. Those patients may have an overlapping syndrome of LQT3 and BrS. A closer look at the ST changes in the right precordial leads and 3rd intercostal space right precordial lead recording may be needed when an LQT3 gene anomaly is found, especially an E1784K mutation in SCN5A. Further, great care also must be taken when using sodium-channel blockers and β-blockers in patients with LQT3.

References