Multiple causative genes for various inherited arrhythmia syndromes have been identified. Most of the genes encode ion channels and some genes are responsible for multiple arrhythmia syndromes because they are critical for normal cardiac function, especially cardiac electrophysiological activity. For example, sodium channels play an important role in the generation and propagation of electrical signals in the heart, and SCN5A encoding the predominant cardiac sodium channel a subunit is causative for various arrhythmia syndromes, including sinus node dysfunction, atrioventricular block, atrial fibrillation, long QT (LQT) syndrome, and Brugada syndrome (BrS).

In addition to ion channel genes, variants in other genes have also been associated with inherited arrhythmia syndromes. Genes that regulate the expression levels and function of ion channels can cause arrhythmia syndromes. Mutations in GPD1-L decrease sodium channel expression and are causative for BrS, in which one of the important mechanisms is decreased sodium currents. Ankyrin-B, which is encoded by ANK2, is critical for the membrane targeting of ion channels, transporters, and pumps located at the transverse tubule and sarcoplasmic reticulum, such as the voltage-gated sodium and potassium channels, sodium/potassium ATPase, the sodium/calcium exchanger, ammonium transporter, inositol 1,4,5 trisphosphate receptor, and the anion exchanger. Because ankyrin-B affects various proteins that are essential for normal cardiac function, ankyrin-B dysfunction represents a wide variety of arrhythmias and cardiomyopathies (Table).

During the decade from the initial report showing the association of ANK2 mutations with arrhythmia syndromes, a small number of studies describing mutations in ANK2 had been reported but only from Western countries. The reasons may be the low frequency of ANK2 mutations in arrhythmia syndromes and the difficulty with genetic screening because of the large size of ANK2, which includes ~50 exons.

However, recent advances in DNA sequencing technology have dramatically increased sequencing speed. After the development of next-generation sequencing, the number of studies of ANK2 variants associated with arrhythmia syndromes increased. In this issue of the Journal, Ichikawa et al report how they successfully identified mutations in ANK2 using next-generation sequencing in a large cohort of 533 Japanese patients affected by various arrhythmia syndromes, indicating the importance of ANK2 as the pathogenesis of arrhythmia syndromes in Asia.

Initially, ANK2 was identified in 2003 as a causative gene in LQT syndrome, and the first gene encoding a protein other than ion channels. Mutations in ANK2 have also been associated with acquired LQT syndrome. The frequency of ANK2 mutations in LQT syndrome seems rare. Mutations in ANK2 have been identified in 8 out of 341 probands (2.3%) with LQT syndrome who were negative for mutations in 3 major genes: KCNQ1, KCNH2, and SCN5A. Because mutations in these 3 genes account for 60–70% of patients with congenital LQT syndrome, the estimated prevalence of ANK2 mutations in LQT syndrome is ~1%. In fact, screening of 855 patients with LQT syndrome identified 1 mutation in ANK2. That screening also identified 30 rare variants in ANK2 in which the pathogenesis was uncertain. Sinus node dysfunction often occurs in patients with LQT syndrome who carry an ANK2 mutation, and the prevalence of ANK2 mutations increases if patients have sinus node dysfunction. Actually, 3 out of 4 patients with congenital LQT syndrome had bradycardia in the study by Ichikawa et al. In addition to rare variants of ANK2 that can cause LQT syndrome, common variants of ANK2 modulate the QT interval in the general population.

Mutations in ANK2 are associated with ventricular tachyarhythmias in the absence of QT prolongation. Among patients with idiopathic ventricular fibrillation, a mutation in ANK2...
was identified in one of 226 patients in 1 study\textsuperscript{13} and in one of 40 patients in the study by Ichikawa et al.\textsuperscript{16} Furthermore, recent studies have shown that ANK2 is a causative gene of BrS\textsuperscript{8,10}. Among patients with BrS who are negative for mutations in SCN5A, which is the most common causative gene, accounting for 20–25% of patients with BrS, a mutation in ANK2 was identified in 4 out of 45 patients in 1 study\textsuperscript{8} and in 2 out of 58 patients in the study by Ichikawa et al.\textsuperscript{10} Interestingly, all 3 patients with idiopathic ventricular fibrillation or BrS had bradycardia in the study by Ichikawa et al.,\textsuperscript{10} similarly to those with LQT syndrome.\textsuperscript{3} Although a mutation in ANK2 was identified in 1 patient with catecholaminergic polymorphic ventricular tachycardia in 1 study, mutations were not identified in 27 patients in another study and there has been no study showing mutations in ANK2 in catecholaminergic polymorphic ventricular tachycardia thereafter.\textsuperscript{10,13}

In addition to ventricular tachyarrhythmias, mutations in ANK2 also increase susceptibility to atrial tachyarrhythmias such as atrial fibrillation and atrial flutter.\textsuperscript{6} The incidence of atrial fibrillation is high and usually develops from a relatively young age in individuals carrying a mutation in ANK2.\textsuperscript{6} Atrial fibrillation usually occurs in combination with other arrhythmia phenotypes, including LQTS syndrome and sinus node dysfunction, but atrial fibrillation can also develop in the absence of other arrhythmia phenotypes.\textsuperscript{5,6}

Because ANK2 is a causative gene of lethal inherited ventricular tachyarrhythmias, it is not surprising that its mutations are associated with sudden death. Among 16 cases of sudden cardiac death aged less than 35 years, 1 subject carried a mutation in ANK2 that has previously been shown to result in a loss of ankyrin-B function.\textsuperscript{5,13} Interestingly, rare variants in ANK2 were also identified in one out of 12 cases of epilepsy-related sudden unexpected death.\textsuperscript{8} However, whole-exome analysis, which resequences all of the expressed genes in a genome, did not identify possibly pathogenic mutations in ANK2 in cases of sudden cardiac death in other studies.\textsuperscript{14,15}

References