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EDITORIAL COMMENT

Connexin-45 as a New Gene Underlying Syndromic AV Block*

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Gap junction channels are formed by connexin (Cx) proteins and directly connect the cytoplasm of neighboring cells to facilitate impulse propagation. Three main connexins are expressed in the heart: Cx43, the most common isoform, is expressed in ventricular and atrial myocardium; Cx40 is present in the atrioventricular node, His-Purkinje system, and atrial myocytes; and Cx45 is localized to the sinoatrial node, atrioventricular node, and His-Purkinje system, but has also been shown to be expressed in atrial and ventricular myocytes (1). Gap junctions in the cardiac conduction system, made up of the sinoatrial node, the atrioventricular node, and the His-Purkinje system (1), allow for unified cardiac contraction.

In adults, abnormalities in cardiac conduction, such as sinoatrial or atrioventricular nodal dysfunction, are most commonly associated with aging. In contrast, most cases of congenital heart block are due to neonatal lupus (2), congenital heart disease (3), or more rarely, attributed to a range of primary genetic syndromes (4).

SEE PAGE 358

In this issue of the *Journal*, Seki et al. (5) report a novel inherited syndromic bradyarrhythmia in 2 unrelated families: an isolated case in a boy of European ancestry and a 3-generation Japanese family with autosomal dominant inheritance. The affected individuals presented with progressive atrioventricular block and ultimately atrial standstill with normal ventricular conduction. They also exhibited similar extracardiac craniofacial, finger, and dental malformations. Through whole exome and targeted exon sequencing, the affected individuals were found to share a common mutation in the third exon of gap junction C1 (p.R75H), the gene encoding Cx45.

The R75H-Cx45 mutation was characterized in detail and was found to have no effect on connexin subcellular localization, or gap junction plaque formation. However, the mutation was found to inhibit transfer of Lucifer yellow dye between adjacent cells, and to markedly reduce macroscopic conductance in heteromeric or homomeric mutant channels compared with wild type channels. The authors then examined the effects of knocking out Cx45 in the heart by using an inducible, cardiac-specific mouse Cx45 knockout (*Gjc1*-CKO). Interestingly, the loss of Cx45 in mice was unable to recapitulate the atrioventricular block and atrial standstill observed in humans. Instead, the major finding in the *Gjc1*-CKO mice was a prolongation in the sinus node recovery time.

The strengths of the current study include the identification of the same mutation in multiple, independent families with a similar phenotype and the detailed characterization of the mutant protein. As with any study, there are a number of potential limitations to consider. First, in addition to the R75H Cx45 mutation, there were other variants identified in each of the affected families that may contribute to the phenotype or modify the disease course. Second, it would have been interesting to see if the extracardiac manifestations observed in the individuals with the R75H Cx45 mutation could be recapitulated in mice. Finally, it would have been helpful to directly demonstrate Cx45 knockout in the *Gjc1*-CKO mice. Prior studies have demonstrated that homozygous, cardiac-specific Cx45 knockout results in embryonic lethality due to heart failure with conduction block

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JULY 18, 2017:371–2

(6), whereas heterozygous Cx45 knockout results with atrioventricular septal defects, and slowed atrioventricular conduction (7). Further, other investigators have found that a conditional knockout of Cx45 in adult mice causes impaired atrioventricular nodal function (8), which is more in keeping with the phenotype observed in the current families.

Despite the differences observed in mice, the genetics, protein biochemistry, and cellular electrophysiology combine to elegantly implicate the R75H Cx45 mutation as the basis for the syndromic bradyarrhythmias observed in these families. Although this variant has provided a unique mechanism for the role of Cx45 in atrial conduction, mutations in this gene are likely to remain a rare cause of atrial or atrioventricular nodal dysfunction.

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