The development of serious, potentially lethal cardiac arrhythmias is determined by a complex integration of factors, including, but not limited to, common and rare genetic variants that determine the responses to gene-gene and gene-environment interactions. Even the rare “simple” channelopathies that cause long-QT syndrome (LQTS) and a host of other potentially lethal arrhythmias exhibit a complex set of phenotypes of varying severity and overlapping features. Ankyrins are a family of adapter proteins, first identified in the erythrocyte membrane, that mediate the localization of a diverse group of cellular proteins. Three genes in the mammalian genome encode ankyrins that share a similar global architecture but exhibit distinct expression patterns and functions: ANK1 encodes ankyrin-R, which exhibits a more restricted expression; ANK2 (chromosome 4q25–27) encodes the more broadly distributed ankyrin-B; and ANK3 encodes the ankyrin-G for general or global. Ankyrins bind a number of ion motive proteins essential to normal cardiac electrophysiology, including the Na\(^+\)-Ca\(^{2+}\) exchanger; inositol 1,4,5-triphosphate receptor; Na\(^+\)-K\(^+\) ATPase; and the voltage-dependent sodium channel (Na\(_{a,1.5}\)). By the very nature of the role of ankyrins in excitation and contraction in cardiac myocytes, it is understandable that variants in ankyrin-B originally described in a family with congenital LQTS\(^1\) would exhibit protean electrical phenotypes. Indeed, in the original LQTS cohort, sinus node dysfunction and atrial fibrillation have been described,\(^1,2\) and other electrophysiological abnormalities such as conduction block, idiopathic ventricular fibrillation, and catecholaminergic ventricular tachycardia have been included under the rubric of ankyrin-B syndrome.\(^3\) A mutation in the ankyrin binding domain of Na\(_{a,1.5}\) has been associated with defective ankyrin-G binding and Brugada syndrome.\(^4\)

Our understanding of the precise role of ankyrin-B in cellular electrophysiology continues to evolve. Limitations in the understanding of the function of ankyrins in cardiac excitation and contraction contribute to difficulties in interpreting the role of genetic variants in this protein in generating or exaggerating the risk for cardiac arrhythmias. This problem is not unique to variants in ankyrins but is magnified by the recognition that ankyrins have a functional impact on a number of ion channels and transporters that in turn influence cardiac excitability and probably the risk of arrhythmias.\(^5,6\) So how does one interpret the presence of an ankyrin-B variant, and what is the risk of a serious, life-threatening arrhythmia in a carrier of such a variant? What are the phenotypic features that might identify an individual to be at high risk at baseline or after exposure to an environmental stress such as a drug or structural heart disease?

Mohler and coworkers\(^1\) screened an ethnically diverse human genetic panel and a group of patients with diverse cardiac arrhythmias for variation in the ANK2 gene. They identified a number of ANK2 variants in control subjects and patients with a variety of congenital and presumably acquired cardiac arrhythmias. The functional importance of the variants studied is supported by the clustering of the amino acid changes in the regulatory domain of ankyrin-B. A number of missense alterations in the same region appear to be of little consequence to control subjects and family members of some of the probands, however. To understand the role of these variants in arrhythmogenesis, they expressed the ankyrin-B variants in wild-type neonatal mouse ventricular myocytes (NMVMs) and NMVMs that had the ANK2 gene knocked out in a homozygous or heterozygous fashion. The work extends previously published work by this group using a cellular phenotype to assess the risk of specific ankyrin-B variants.\(^3\) They examined the expression pattern of ankyrin-B and ion transporters regulated by ankyrin B (including the Na\(^+\)-Ca\(^{2+}\) exchanger, inositol 1,4,5-triphosphate receptor, and Na\(^+\)-K\(^+\) ATPase), spontaneous contraction rates, and the frequency of calcium release events. On the basis of the degree to which a normal phenotype was restored in knockout cells and the severity of disruption of transporter expression, rates of contraction, and phasic changes in intracellular Ca\(^{2+}\) in normal NMVMs, the variants were classified as normally functioning or exhibiting varying severities of loss of function.

All of the variants identified in the screen of anonymous subjects of varying ethnicity revealed normal or, at most, a mild loss of function in vitro. Of note, 1 of the variants in this screen, E1813K, exhibited a mild loss of function and was present in 2 newly identified patients with drug-associated LQTS. In general, the severity of the cellular phenotype correlated with significance of the clinical arrhythmias in some of the patients, with more malignant ventricular arrhythmias with an earlier onset being more common in patients harboring variants that more severely disrupted cellular function. The correlation is intuitively pleasing and...
importantly addresses the functional and clinical significance of the identified variants in ankyrin-B. The molecular mechanism of disruption of cell function requires further elucidation. In other autosomal-dominant inherited arrhythmia syndromes, altered channel proteins may adversely affect the normal, wild-type gene product within the same cell, thus behaving as a dominant negative. This usually occurs if the protein can still interact with the same elements as the wild type but blocks its function in some way. It is possible, but not clearly demonstrated, that the ankyrin-B variants that have the greatest effect on cellular function work by a dominant-negative mechanism. For example, a gain-of-function variant may produce a dominant effect in a heterozygous context without affecting the function of the normal gene product. In the latter case, increasing the function of the normal variant may overcome the adverse effects of the variant gene product; in the case of a dominant-negative mechanism, this may not be the case.

It is notable that the arrhythmias described in patients are predominantly but not exclusively ventricular. The presence of bradycardias and atrial arrhythmias suggests that abnormal channel function is present in other cell types such as the sinus node and atria. The functional changes in NMVMs include alterations in the spontaneous contraction rates and changes in the calcium transient. In some cases, it is clear how the cellular phenotype may produce the clinical arrhythmia; in other cases, the alterations in cellular functions measured reflect the severity of disruption of ankyrin function, not necessarily the specific arrhythmogenic defect.

Variants in ANK2 were associated with a number of different types of cardiac arrhythmias, some congenital with mendelian inheritance patterns (LQTS) and others more classically considered to be acquired (nonfamilial atrial fibrillation and drug-induced LQTS). Additionally, the genetic contribution to apparently acquired cardiac arrhythmias is highlighted by this study. The familial basis of a number of arrhythmias, including atrial fibrillation, cardiac conduction system disease, and sudden death, has been recognized, but the genetic determinants are only now being identified. Rare and more common variants in a number of genes will continue to be identified in late-onset cardiac arrhythmias that occur in the context of complex acquired heart diseases. Larger association and ultimately mechanistic studies are required to determine whether the specific variants play a role in the genesis of specific arrhythmias. As more complex phenotypes associated with single gene defects are described and more susceptibility loci for acquired arrhythmias are discovered, the genetic distinction between congenital and acquired arrhythmias becomes blurred.

The article by Mohler et al highlights the more general issue that common variants in a number of channel and nonchannel genes will contribute to the risk of serious, potentially lethal cardiac arrhythmias. The effect may be due to a direct alteration in the function of the variant protein, as shown in the in vitro studies of a number of ion channel variants, or as result of influencing the function of other excitability proteins as in the ankyrin-B variants. In any case, the challenge is clear; defining genetic variation in proteins of interest is important but only the first step in understanding the mechanism of arrhythmias associated with these variants. Despite the recognized limitations in the cell platform and readouts, this work provides important insights into the mechanisms of the defects associated with variant ankyrin-B proteins. The data provide a framework for helping to understand the severity and latency of the congenital and acquired arrhythmias associated with defective ankyrin-B.

Disclosures

None.

References


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Gordon F. Tomaselli

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