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EDITORIAL COMMENT

Inherited Arrhythmia Syndromes

Exome Sequencing Opens a New Door to Diagnosis*

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Idiopathic ventricular fibrillation is a major clinical and diagnostic challenge. Because the heart is structurally normal and a culprit gene defect is not identified in the proband, family members cannot undergo clinical or genetic risk stratification. With low overall survival from ventricular fibrillation and small numbers of subjects available for study, traditional kindred-based approaches for identification of novel genes are low yield in idiopathic ventricular fibrillation. Whole exome sequencing has emerged as a complementary approach for the identification of genetic variants associated with inherited human diseases. In this issue of the *Journal*,

See page 259

Marsman et al. (1) report on their use of whole exome sequencing for investigation of genetic defects in 2 affected siblings presenting with idiopathic ventricular fibrillation and early onset sudden cardiac death (SCD). They identified a missense variant within calmodulin 1 (*CALM1*) associated with idiopathic ventricular fibrillation and SCD in childhood and adolescence. These findings are clearly of immediate clinical relevance to the extended family members of these 2 subjects, as they finally provide the means to assess SCD risk among yet unaffected individuals.

This new information also represents another important chink in the armor of idiopathic ventricular fibrillation, which is slowly yet steadily yielding to better-defined primary arrhythmia syndromes such as the long-QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. Calmodulins are proteins with important roles in calcium signaling and myocardial contractility that mediate the control of several ion channels and a large number of proteins regulated by calcium (2). Interestingly, mutations in *CALM1* and *CALM2* have been previously implicated in primary arrhythmia disorders (3,4). Nyegaard et al. (3) identified 2 missense mutations: the first mutation was Asn53Ile in a large Swedish family that presented with well-documented catecholaminergic polymorphic ventricular tachycardia, and a second de novo mutation, Asn97Ser, was identified in a subject of Iraqi origin. Functional characterization of these variants showed a significant reduction in Ca^{2+} affinity, and for the Asn97Ser, an aberrant interaction with the *RYR2* receptor at low calcium concentrations (3). Crotti et al. (4) performed whole exome sequencing in 4 subjects presenting with recurrent cardiac arrest and neurodevelopmental delay in early infancy. They found 3 mutations within *CALM1* and *CALM2* and showed that all 3 mutations have reduced Ca^{2+} affinity in the C domain (4). The paper by Marsman et al. (1) provides additional evidence for the role of calmodulin mutations in familial arrhythmia disorders, this time due to a novel, presumably causal mutation (Phe90Leu) resulting in idiopathic ventricular fibrillation and early onset SCD. However, there is an important caveat to keep in mind. The 2 subjects who survived idiopathic ventricular fibrillation, as well as their mother, had mild QT prolongation with exercise. Because electrocardiographic recordings are not available for the extended family, it is difficult to rule out long-QT syndrome with certainty. The authors did not perform functional characterization of the Phe90Leu variant. However, there is previous evidence suggesting that alterations of phenylalanine residues in calmodulin may have a specific role in calcium binding activation (5,6). Nonetheless, further work is needed to evaluate the role of Phe90Leu in additional families presenting with idiopathic ventricular fibrillation. Different mutations in the same gene could lead to different molecular mechanisms, as pointed out by the authors. Thus, calmodulins are attractive candidate genes for the investigation of molecular pathways associated with arrhythmias. In addition, *CALM1* has been nominally associated with severe coronary artery disease (7) and stroke (8), leaving open the tantalizing possibility that calmodulins may be involved in more common, complex forms of ventricular arrhythmias, such as those associated with coronary artery disease.

While diagnosis by whole exome sequencing holds promise, what will it take for this tool to be incorporated into mainstream clinical practice? The process of whole exome sequencing provides a generous list of candidates that need to be "filtered" to identify a shortlist that eventually leads to a single gene variant. This process is currently labor intensive, with at least some likelihood of a false positive result, but improvements in ongoing analysis software are likely to have a favorable impact on the efficiency and specificity of whole exome sequencing. As whole exome sequencing provides more candidate gene variants in abundance, the field will need to keep up with evaluation of the functional significance of these variants in order to establish a pathophysiological

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link to the specific disease condition. Recent publications from the ENCODE consortia highlight the importance of noncoding regions in human diseases (9), but exome sequencing covers only coding regions, representing about 1.2% of the human genome. However, in addition to its use as a diagnostic tool, there are emerging examples of utilizing whole exome sequencing for precision therapeutics. Worthey et al. (10) diagnosed a child with X-linked apoptosis deficiency by identifying a missense mutation within NOD2. This finding allowed the clinicians to design a specific treatment based on bone marrow transplantation.

Marsman et al. (1) are to be commended for their careful approach. Their findings highlight the promise of whole exome sequencing to make a diagnosis, even among small numbers of affected subjects in families with inherited sudden death syndromes. They have contributed to the understanding of idiopathic ventricular fibrillation while providing additional evidence for the role of *CALM1* in ventricular arrhythmias and sudden death. It would be important to evaluate these findings in other families with idiopathic ventricular fibrillation and to also assess the specific functional role of the culprit genetic mutation they have identified.

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Key Words: calmodulin ■ genetics ■ idiopathic ventricular fibrillation ■ ventricular arrhythmia ■ whole exome sequencing.