Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy
A Family Affair

Daniel P. Judge, MD

The report from investigators at The Heart Hospital in London is also commendable for its thorough assessment of family members (cascade screening), which was not simply performed as part of their study protocol, but serves as a model for how we should tailor our own clinical practices. One of the highlights of their analysis was their focus on sudden cardiac death (SCD) among probands. Among 100 families reported, the initially diagnosed family member (proband) was deceased in 51. By focusing on both genetic characterization of these deceased probands when possible and genetic and phenotypic characterization of living affected relatives in the remainder, the authors were often able to assign a probable genetic cause of SCD. This is a remarkable feat, but one that could be improved by systematic policies among pathologists internationally who perform autopsies to ensure the availability of DNA postmortem in cases of inherited disease or unexplained SCD, as consensus guidelines have also recommended. Each of these families, and many more like them, undoubtedly hopes for answers like this. Such testing helps not only to understand the cause of unexpected death of the proband, but also to recognize others within the family at highest risk of SCD. Although phenotypic evaluation of at-risk family members may avert subsequent SCD, cascade genetic testing should offer a more cost-effective and focused assessment, as has been shown in hypertrophic cardiomyopathy.

Quarta et al carefully describe 4 families that should make the reader uncomfortable, as the authors undoubtedly must be in bringing them to our attention. Within each of these families, ambiguous genotype/phenotype data are highlighted to show the dangers of misinterpretation and incomplete evaluations. In 3 of the 4 cases, the putative disease-causing mutation was not present in family members who show concerning phenotypic features. In the fourth family, an out-of-frame deletion in the terminal portion of desmocollin-2 that has been shown to occur among family members with desmosome gene mutations. Their data help to clarify prior reports of 3 gene variants that were previously considered nonpathogenic. Notably, they included in their methods a technique called multiplex ligation-dependent probe amplification to identify large insertions, deletions, or gene rearrangements that would not be picked up with traditional DNA sequencing. Although rare, 3 of the 149 probands (2%) had such a mutation in PKP2, similar to the overall prevalence of DSC2 or JUP mutations in cohorts like this. Other technologies are also available and currently used to recognize copy number variation in DNA, and this report justifies further assessment of large alterations in desmosome genes in ARVD/C.
the London group compares their use in a cohort to the former criteria.7,8 They note only 91% specificity for the former criteria because of 2 individuals who could have received the diagnosis of ARVD/C on the basis of a major criterion for the diagnosis of ARVD/C in a family member on autopsy in addition to the presence of 2 minor criteria. The revised diagnostic criteria place a greater emphasis both on genetic testing and on quantitative phenotypic assessment of structural right ventricular disease. The quantification of the structural aspects of RV disease is unquestionably welcomed, because minor structural RV abnormalities are a frequent cause of inappropriate diagnosis of this condition.9 However, this very report raises questions about the correct interpretation of rare DNA variants in these genes, and time will tell if reliance on a putative mutation is better or worse.2

In the cardiac desmosome, DNA variants of uncertain significance remain a vexing challenge. Without decades of experience or in vitro functional assays to help with the assignment of pathogenicity, the field has relied so far on imperfect pathological criteria, consisting of the absence of the variant in an unaffected control population that is matched for ethnicity, cosegregation of the variant with the disease phenotype in the family when discernible, and protein prediction software that uses a combination of conservation among species, determination of functional domains, and differences in amino acid properties. However, several lines of evidence discount the significance of these characteristics. Each of us probably harbors ∼10 rare missense DNA variants,10 and most rare missense alleles are thought to be deleterious in humans,11 yet most of us do not have rare genetic disorders. Within families who have ARVD/C and a desmosome gene mutation, the penetrance is remarkably low.12–14 There must be considerable influence by other genetic variants and environmental factors on the development of ARVD/C. Difficulties with the overinterpretation or underinterpretation of cosegregation of DNA variants and phenotypic features of ARVD/C are nicely highlighted in this report.2 In addition, current software is far from perfect at predicting the functional significance of variation in protein sequence, with both low sensitivity and specificity.15 Accordingly, the field continues to strive for better functional assays to determine the significance of novel desmosome alleles.

Quarta et al12 provide further support for a longstanding yet unproven hypothesis that the presence of >1 rare desmosome variant contributes to this disorder. In their analysis, an additional rare desmosome variant was associated with a 5-fold increased risk of developing penetrant disease among family members. In contrast, a study of early-onset ARVD/C that was restricted to probands did not find increased prevalence of young individuals with ARVD/C and >1 rare desmosome variant compared with people with a diagnosis of ARVD/C at average or later age.16 Several other large studies of ARVD/C probands have identified >1 rare desmosome variant among 5% to 10% of the total cohort with variable phenotypic consequences.4,17,18 Further investigation of penetrance and other consequences of multiple rare desmosome variants should help to clarify this issue.

How can the field improve its use of desmosome genetic testing for ARVD/C? Technological advancements are increasing the efficiency and lowering the costs of DNA sequencing. The cost of complete DNA sequencing of the first human genome was estimated at $300 000 000 in 2001; just 9 years later, that price had fallen to an estimated $50 000.19–21 Today, complete DNA testing of the human exome (the portion of the genome known to directly encode proteins) can be performed with a cost for reagents that is less than $2000. It should not be surprising that clinical genetic testing laboratories have capitalized on this technology and expanded the range and scale of cardiovascular genetic tests that can be used in clinical practice. Increased use and reporting of these tests and online databases will improve our ability to interpret them.22

Many other monogenic forms of cardiovascular disease are well suited to the use of genetic testing. The diagnostic criteria for Marfan syndrome have recently been updated to account for recognition of FBN1 mutations, and assessment for a related disorder, Loeys-Dietz syndrome, is improved by analysis of TGFBR1 and TGFBR2 DNA sequence.23,24 Decades of quantitative functional analysis of novel ion channel variants by cellular patch clamping have led to much greater certainty about variation in genes encoding the cardiac ion channels, leading to wider calls for use of genetic analysis not only in the patient who presents with LQT, but also among family members who are at risk of this condition.25 After ∼20 years of analysis of variation in elements of the cardiac sarcomere in hypertrophic cardiomyopathy, clinical application of genetic testing for hypertrophic cardiomyopathy has become more widespread and more readily interpreted. These disorders have advantages with regard to time and functional associations for novel DNA variants. Although the interpretation of genetic sequencing for ARVD/C is improving, it is not yet as robust as for many other monogenic disorders.

Where does this leave clinical application of genetic testing for ARVD/C? Such testing can be helpful for understanding the cause of disease, for recognizing family members who are at risk of this condition, for family planning, and for limited prognostic information.26,27 As we strive for more accurate predictions from genetic tests, we must be very careful about correct interpretation, about the possibility of a change in the interpretation of a DNA variant, and about the other unrecognized genetic factors that influence our patients’ conditions and the risk of disease within their families. DNA variants of uncertain significance can sometimes create more questions than answers, and incorrect interpretation can cause life-threatening errors in medical practice. Such challenges are not as obvious for a person who is clearly affected with ARVD/C as for the unaffected family member whose risk may be misinterpreted by errant test interpretation. Genetic testing for ARVD/C has great potential for both benefits and problems. It should only be used with caution in this setting.

Disclosures

None.

References


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