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EDITORIAL COMMENT

Illuminating a Hidden Risk

The Genetic Contribution to Acute Myocarditis*

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A small and fascinating revolution is taking place in the field of myocarditis. Traditionally seen as an acquired disease, acute myocarditis results from viral infection (eg, enteroviruses and adenoviruses), and persistence of virus in the myocardium predisposes to subsequent dilated cardiomyopathy. An increasing number of reports have identified pathogenic (P) or likely pathogenic (LP) variants within genes related to structural elements of the cardiomyocyte in a subset of patients with myocarditis.[1-3] These new data suggest that some patients who suffer from myocarditis do so because of a susceptible genetic background. Myocarditis following an infection or immunogenic exposure can be the second hit that triggers acute cardiomyopathy or unstable arrhythmias in these individuals.

Several genotype-phenotype associations are suggested by the existing data. For example, P/LP variants in *DSP* (desmoplakin) have been noted in patients presenting with acute myocarditis characterized by normal or nearly normal left ventricular ejection fraction (LVEF), myocarditis recurrence, fibrosis involving the interventricular septum, greater risk of ventricular arrhythmias, and a family history of myocarditis.[2,4] These patients are at risk for developing arrhythmogenic biventricular or left-prevalent cardiomyopathy.[4] P/LP variants in *TTN* (titin) and other genes related to the sarcomere have been reported in patients presenting with acute myocarditis and reduced LVEF and dilated cardiomyopathy.[1,3,4]

In this issue of *JACC: Heart Failure,* Monda et al[5] summarize 8 studies reporting P/LP cardiac gene variants among patients with acute myocarditis. Their systematic review and meta-analysis were stratified into pediatric and adult age groups. They considered 2 clinical scenarios: "complicated" (acute myocarditis complicated by reduced LVEF, heart failure, or ventricular arrhythmias) and "uncomplicated" (absence of complicated features) forms. Of 586 patients with acute myocarditis, 85 had a P/LP variant in a cardiomyopathy-associated genes. The prevalence of P/LP variants in patients with uncomplicated myocarditis (4.2%) was less than that observed in either pediatric (44.5%) or adult (21.9%) patients with complicated presentations. P/LP variants in desmosomal genes were more frequently reported in uncomplicated myocarditis (64%), whereas sarcomeric gene variants were observed overall in 58% of adults and 71% of children with complicated presentation.

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Analyzing genetic associations in myocarditis is challenging due to the extreme heterogeneity of presentations and diagnostic methods used and reported in published reports. Myocarditis can present with cardiogenic shock, ventricular arrhythmia, or anginal chest pain. A fraction of myopericarditis may be misclassified as isolated pericarditis if high-sensitivity troponin or cardiac magnetic resonance is not obtained early after symptom onset. Nonuniversal adherence to formal established diagnostic criteria (based on histologic or cardiac magnetic resonance features) and contemporary evolution of these criteria are additional challenges. Limitations specific to this study include some small cohort sizes, which could lead to an overestimation of

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P/LP variant prevalence. Only 47 pediatric cases with complicated presentation were identified. Furthermore, of the 5 studies involving children, 3 were relatively small case series and 2 of these (with n = 8 and n = 12) contributed the highest burden of genetic testing positivity (>60%), far higher than has been reported in other case-control studies of genetic myocarditis in children. In the adults with myocarditis, the study by Lota et al[3] comprised 336 (57.3%) of the 586 identified cases and had a P/LP rate of only 8%. When smaller studies were included, this current meta-analysis estimated a higher P/LP gene prevalence in adults of 24.7%, raising the possibility that smaller cohorts with high P/LP rates biased the meta-analysis prevalence in adults as well.

Methods of classifying genetic variants as P/LP varied among the 8 included studies. Genetic variation is common and not all variants identified through genetic testing are disruptive to gene function. The ACMG (American College of Medical Genetics) has put forth a framework for variant interpretation based on several key features including strength of prior published variant-disease associations in multiple unrelated individuals or families, minor allele frequency in the general population, and putatively damaging characteristics.[6] Only 6 of 8 included studies listed these ACMG criteria as the basis for their variant classification. One study classified the variants more stringently in a way that adheres to ACMG guidelines but additionally required that missense variants be included only if they were previously reported as disease-associated by a validated clinical laboratory. The remaining study did not specify the method by which included variants were classified and did not provide the genomic coordinates or other variant characteristics. This is concerning, particularly because 8 of 11 variants were found in *TTN*. Truncating variants in *TTN* have previously been found to underlie ~15% of dilated cardiomyopathy, peripartum cardiomyopathy, alcohol cardiomyopathy, chemotherapy-induced cardiomyopathy, and myocarditis.[7] However, such variants are also found in ~3% of healthy reference populations. Previous studies have identified specific characteristics that inform whether or not a truncating *TTN* variant is disease-causing, including exonic position within particular transcripts (cardiac vs noncardiac expressed), and the particular domain in which the variant resides; eg, cardiomyopathy-associated variants are more likely to occur in the A-band domain of the gene and variants in healthy populations cluster in non-A-band domains.[7] Given these important specific characteristics of *TTN* variant pathogenicity, that 1 of 8 included studies in the meta-analysis withheld these details makes validation of these results difficult. In fact, this particular series had among the highest individual study prevalence of genetic myocarditis (~30%, nearly double that of most of the other studies), suggesting that some of the included *TTN* variants may not have been disease-causing and potentially introducing bias, particularly toward the conclusion of higher P/LP rates in "complicated" cases (because all were complicated in this series).

Future work is needed to establish and validate a "myocarditis gene set," which would likely include genes associated with dilated and arrhythmogenic cardiomyopathies as well as with neuromuscular diseases in which cardiomyopathy can be a manifestation (eg, *PRDM16, DNM2, RYR1, DYSF, SGCG,* and *TRDN*). Immune response gene variants may also affect the risk of myocarditis (eg, *DNAH11, FANCC,* and *SPAG1*). To advance the development of validated genetic panels, the National Institutes of Health has convened clinical domain expert working groups (ClinGen) for gene-disease associations across a number of relevant cardiovascular disorders including cardiomyopathies. The findings by Monda et al[5] support their conclusion that P/LP cardiomyopathic gene variants contribute to the risk of myocarditis. We recommend offering cardiomyopathy genetic counseling and testing to patients with acute myocarditis as is guideline-supported for other myocardial diseases.

On the horizon are novel genes that contribute to immune regulation (eg, BMP4 and BMP4 receptors) that are being linked to myocarditis. The interaction of cardiomyopathy and immune response genes on long-term outcomes is an expanding field. Longitudinal studies comparing genotype-positive with genotype-negative patients are needed to refine our understanding of the natural history of myocarditis and the impact of host genetic factors.

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