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RESEARCH LETTER

Prevalence of Pathogenic Variants in Cardiomyopathy-Associated Genes in Myocarditis

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The relationship between myocarditis and genetic cardiomyopathies has been described previously,[1–3] but genetic testing in patients with myocarditis is not yet currently advocated. With the aim to clarify its value, we have genetically analyzed a retrospective cohort of 28 patients with myocarditis admitted in a 10-year period to further deepen the understanding of this association.

Myocarditis was diagnosed following the European Society of Cardiology criteria,[4] taking into account clinical presentation, ECG, myocardial cytolysis markers, echocardiography, and tissue characterization by cardiac magnetic resonance imaging or endomyocardial biopsy. Patients were classified into 2 groups depending on clinical severity. Severe myocarditis was defined as severe ventricular dysfunction (left ventricular ejection fraction, <30%), cardiogenic shock, or sustained ventricular arrhythmias. The rest of cases were classified as nonsevere myocarditis. Family history was obtained by clinical interview.

A genetic test including 71 cardiomyopathy-associated genes was performed. Pathogenicity of variants was defined according to the current American College of Medical Genetics and Genomics guidelines. The genetic study was considered positive when a pathogenic variant (PV) or a likely PV (P/LPV) was detected.

The data supporting the findings of this study are available from the corresponding author upon request. The study conforms to the principles of the Helsinki II Declaration. The study was approved by the institutional review board.

The cohort with severe myocarditis (n=12) was composed of 7 men (mean age, 41 years; range, 25–74) and 5 women (mean age, 30 years; range, 15–54). A total of 4 genetic rare P/LPVs were identified: a novel frameshift deletion in *FLNC* (p.Pro1555Leufs*52) in a 25-year-old man presenting with sustained ventricular arrhythmias, a novel gross deletion from exons 2 (partial) to 5 in *RBM20* (c.1104_1585+467del) in a 37-year-old woman presenting with cardiogenic shock (Figure [A–C]), and a previously reported nonsense variant in *BAG3* (p.(Gln88*)) identified in 2 unrelated patients, both presenting with cardiogenic shock and requiring heart transplantation: a 30-year-old man (Figure [D–F]) without family history of cardiomyopathies and a 15-year-old woman with family history of dilated cardiomyopathy.

Among remaining patients with severe myocarditis (n=8), either the genetic study was negative or a variant of unknown significance was detected. None of them had a family history of cardiomyopathies.

The cohort with nonsevere myocarditis (n=16) was composed of 15 men (mean age, 35 years; range, 18–68) and one 20-year-old woman. One nonsense PV was identified in *DSP* (p.(Gln113*)) in the woman. She presented with chest pain, elevated cardiac enzymes, pericardial effusion, and normal left ventricular ejection fraction and had a family history of arrhythmogenic cardiomyopathy.

In remaining patients with nonsevere myocarditis (n=15), either the genetic study was negative or variants of unknown significance were detected. None of them had a family history of cardiomyopathies.

Several recent studies have demonstrated the existence of rare PV in cardiomyopathy-associated genes in patients with myocardial diseases that had been so far exclusively attributed to environmental factors. Therefore, it has been seen that up to 12% of patients with alcoholic and chemotherapy-induced cardiomyopathy[5] are carriers of novel rare P/LPV in cardiomyopathy-associated genes.

Key Words: cardiomyopathies ■ genetics ■ myocarditis

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To date, myocarditis has also been considered mainly an environmental disease, but it has been seen that sudden cardiac death cases attributed to myocarditis after autopsy carry rare PV-causing cardiomyopathies in their relatives,[2] and a high proportion of rare PV has been found in selected patients with myocarditis and right ventricular involvement or sustained ventricular arrhythmias.

In the present work, 5 of 28 patients (17.9% [95% CI, 7.9–35.6]; 3 women and 2 men) experiencing myocarditis carried a P/LPV in cardiomyopathy-associated genes. Regarding pathogenicity classification, 4 of them were novel, suggesting a deleterious role, and one has been previously described as definitively disease causing.

According to predefined clinical groups, 4 of 12 patients with severe myocarditis (33.3% [95% CI, 13.8–60.9]) carried a P/LPV. Among patients with nonsevere myocarditis, only 1 of 16 (6.3% [95% CI, 1.1–28.3]) carried a PV. This difference in P/LPV frequency between severe and nonsevere myocarditis has not been described before. The data suggest that genetics could not only influence myocardium vulnerability to inflammation but also severity of presentation.

In this series, 2 of 2 (100%) patients with a family history of cardiomyopathy carried a P/LPV. Thus, a detailed family history in a patient presenting with myocarditis is of paramount importance.[1,2]

In summary, our data confirm the role of genetic testing in cardiomyopathy-associated genes in severe forms of myocarditis patients and in those with a family history of cardiomyopathy for early identification of relatives at risk.

This study was performed in a limited number of patients. Further studies in larger cohorts and family screening should be performed to confirm our results. It should be noted that being a retrospective study, patients who died have not been included. Though, our previous results, in autopsy patients, also confirmed this genetic hypothesis.[2]

ARTICLE INFORMATION

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Disclosures

Dr Brugada is a consultant for Genincode. The other authors report no conflicts.

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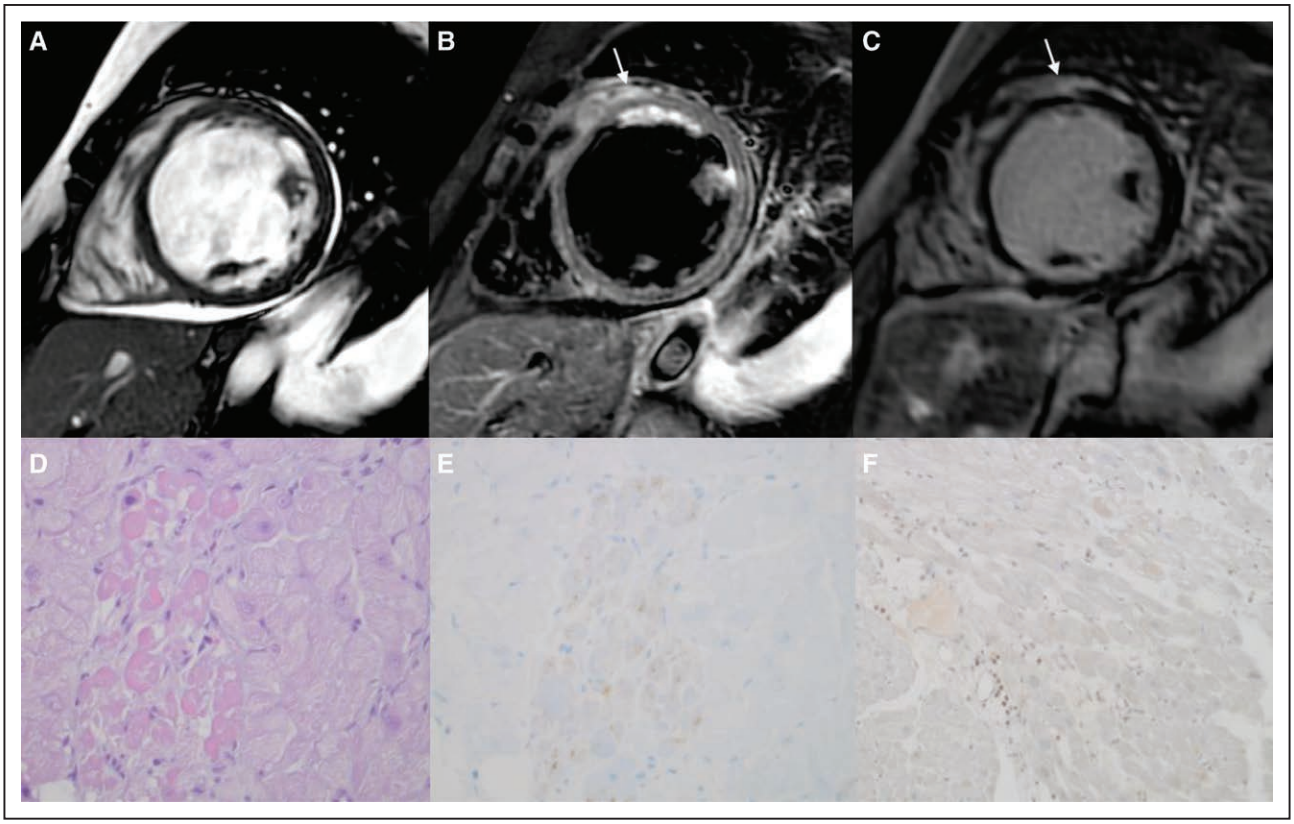

Figure. Cardiac magnetic resonance images (MRIs) of the patient with a likely pathogenic variant in RBM20.
A, End diastolic frame from short-axis cine MRI shows severe left ventricular dilatation with mild pericardial effusion. **B**, Short-axis T2-weighted STIR image shows subepicardial increased signal (arrow) indicating focal edema in the anterior wall of the left ventricle, and (**C**) short-axis delayed-enhancement image shows an area of subepicardial enhancement in the anterior wall with nonischemic distribution suggesting acute myocarditis.Endomyocardial biopsy images of the patient with a pathogenic variant in *BAG3*. **D**, Endomyocardial biopsy shows a focus of necrotic cardiomyocytes with few lymphocytes, ×400. **E**, C9 stain highlights the necrotic myocardial cells, ×400. **F**, CD3 stain shows mild lymphocytic infiltrate at the periphery of a necrotic area.