A Genetically Vulnerable Myocardium May Predispose to Myocarditis

Death from myocarditis requires the presence of myocardial inflammation, without any other structural heart disease, and is frequently associated with a viral infection (1). We postulate that genetic defects in structural proteins cause the myocardium to become vulnerable and predisposed to myocardial inflammation by a pathogenic agent. To prove this hypothesis, we prospectively collected 3 cases of myocarditis-related sudden death (SD), according to the Dallas criteria (2). To further investigate the genetic basis, we screened the most prevalent 55 sudden cardiac death-related genes (3). Family members were clinically and genetically investigated. The local ethics committee approved the study.

Family 1 (**Figure 1**). This was a 10-year-old healthy boy (III.1) who was experiencing canker sores, transmitted from his brother. Genetic analysis revealed 3 novel potentially pathogenic genetic variants (PPGV): p.R413X_*PKP2*, associated with arrhythmogenic right ventricular cardiomyopathy (CM060431), and 2 missense PPGV (p.L1591Q_*MYH7*, and p.A20252P_*TTN*). All were predicted as disease-causing in silico. His uncle died at age 15 years of unexplained SD (II.3), without autopsy. Three asymptomatic members had inherited the 3 variants and had abnormal CMR: the mother's CMR (II.2) had areas of right ventricular aneurisms, dyskinesia, and patches of interstitial fibrosis; the youngest uncle's CMR (II.6) had biventricular dilation, with no fibrosis or fatty infiltration; and the grandmother's CMR (I.1) had areas of RV dyskinesia and aneurysms with patchy fibrosis. An uncle (II.5) inherited the *MHY7* variant and had a normal electrocardiogram and exercise test. The 2 brothers (III.2 and III.3) had a normal echocardiogram. Individual III.2 had inherited the variation in *PKP2*. Individual III.3 had inherited the other 2 PPGV. We considered the *nonsense* variation in *PKP2* the culprit of the disease, whereas the additional variants could be modulators of the phenotype.

Family 2 (**Figure 1**). This was a 15-year-old boy who was experiencing low-grade fever, present in individuals in his school class. Genetic analysis revealed 4 missense variants. The variant *DSP*_p.E290K, rs397816974, not identified in global databases, was predicted in silico as deleterious. The variant *PKP2*_p.Q62K, rs199601548, present in very low frequency, was classified as of unknown significance. Other 2 genetic variants were predicted in silico as benign (*JPH2*_p.A181T) and deleterious (*TTN*_p.S30475G). His sister's CMR (III.2) showed wide fibrotic areas in the left ventricular myocardium. She carried *DSP* (p.E290K) and *TTN* (p.S30475G). The mother's CMR (II.2) showed fibrotic interstitial areas in the left ventricle. She carried *DSP* (p.E290K) and *JPH2* (p.A181T). His father (II.1) had normal CMR and carried *PKP2* (p.Q62K) and *TTN* (p.S30475G). Thus, the only segregating pathogenic variant was *DSP* (p.E290K). The grandfather (I.1) died suddenly at a young age without autopsy.

Family 3 (**Figure 1**). He was a healthy 40-year-old physician (III.1). During the previous days, he had been experiencing low-grade night fevers. Genetic analysis revealed a rare novel variant in *DSC2* (p.T305del), predicted in silico as deleterious. Family genetic screening identified the same variant in his mother (II.2) and his brother (III.4), as well as 1 of his children (IV.2) and a nephew (IV.4). All were asymptomatic and had normal clinical tests. This variant was classified as of uncertain significance due to the lack of segregation.

We compared the prevalence of these genetic variants in 100 cases of unexplained SD. We identified rare desmosomal variants in 14.7% of the population, much lower than in our cohort, although the numbers are too small to draw any conclusions.

Myocarditis is an inflammatory process, not suspected to be of familial origin. Thus, genetic analyses are not considered in myocarditis. We postulate that a genetic variation in structural proteins create a vulnerable myocardium prone to myocardial seeding by a pathogen. In a prospective investigation, we collected 3 cases with a diagnosis of death from myocarditis and identified PPGV in desmosomal genes. None of the index cases was suspected of having arrhythmogenic right ventricular cardiomyopathy at autopsy.

The history of events suggests that the genetic alteration in the desmosome has created the environment for the seeding of an infectious agent. Subsequently, it will cascade into an inflammatory process. These data suggest that myocarditis could be genetically predisposed; thus, family members need to be investigated clinically and genetically for structural abnormalities. This proof-of-concept work reinforces the need for further genetic investigation of larger cohorts with myocarditis.

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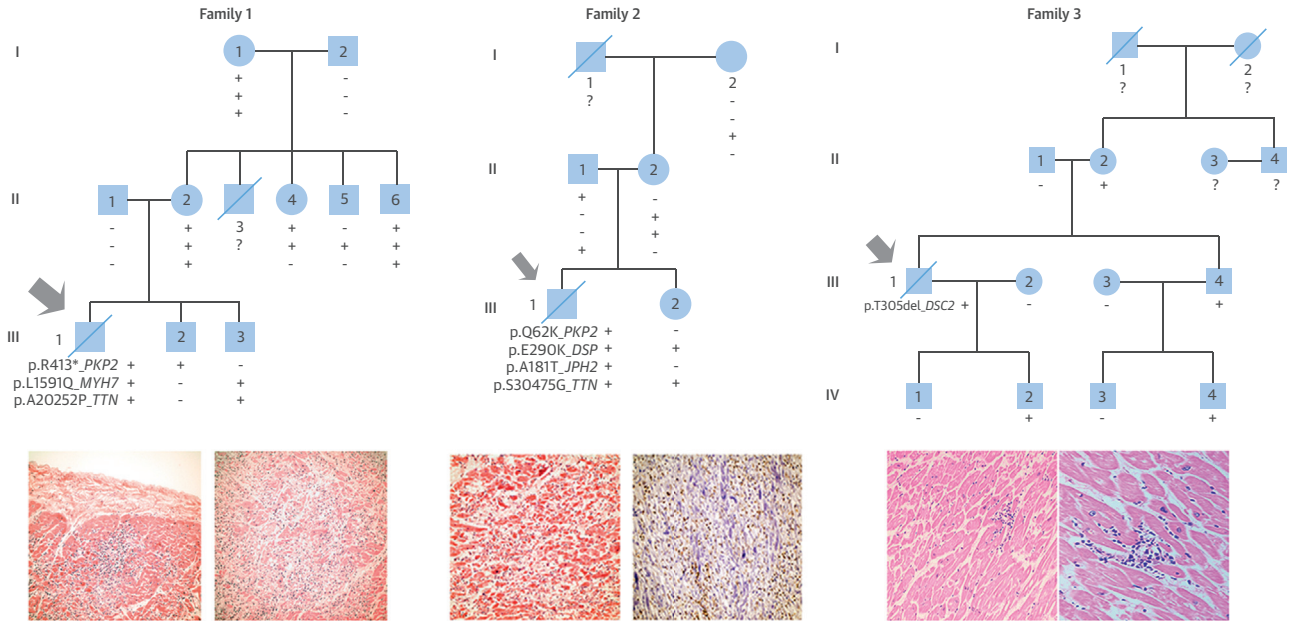
FIGURE 1 Data of Families



Pedigree: **arrows** indicate index case; **slashes** indicate deceased members; **gray** indicates structural heart alterations; **plus/minus** indicates carrier/noncarrier; and **question marks** indicate no genetic analysis. Family 1: inflammatory infiltrates (hematoxylin-eosin, left 4×, central 10× epicardium, right 10× myocardium). Family 2: inflammatory infiltrates (left 20×, hematoxylin-eosin, and right 20×, CD45). Family 3: inflammatory infiltrates (hematoxylin-eosin labeling, left 10×, right 20×).

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Echocardiographic Substrate for Biventricular Pacing

It is axiomatic that the presence of a substrate that is amenable to a specific treatment, coupled with effective delivery of that treatment, is likely to produce the most favorable clinical outcomes. In patients with heart failure, left bundle branch block (LBBB) and the associated abnormal electro-mechanical activation represents the substrate for biventricular