Is the Phenotype–Genotype Relationship Necessary to Understand Cardiomyopathies?

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Although the vast majority of genotyped patients with arrhythmogenic right ventricular dysplasia (ARVD)²,³ carry desmosomal gene mutations, with plakophilin 2 (PKP2) being the most frequent,⁴ several nondesmosomal genes responsible for other cardiomyopathies/myopathies have been found that they can produce ARVD-like phenotypes, the so-called overlap syndromes.⁵–⁷ Phospholamban (PLN) is a transmembrane protein of the sarcoplasmic reticulum that plays a key role in calcium homeostasis a determinant of the force of cardiac contraction. PLN R14del, a founder gene mutation responsible for dilated cardiomyopathy (DCM),⁸⁹ can produce ARVD-like phenotype as well.¹⁰¹¹ By conducting a multicenter study, van Rijssingen et al ¹² reported the clinical course of 403 mutation carriers from 83 families in this issue of the journal. Among 295 individuals with clinical information available, DCM phenotype is predominant, where 1% shows both DCM and ARVD and 6% with ARVD only. Among mutation carriers, no death or major cardiac events occurred before the age of 15 years. Symptomatic patients were older. Syncope, sustained, and nonsustained ventricular tachycardia, sudden cardiac death, and death caused by end-stage heart failure occurred in individuals with either DCM or ARVD phenotypes. Among inherited arrhythmias, mutations in a single gene causing multifacet phenotypes are mostly reported in SCN5A, a sodium channel gene, with a variety of phenotypic presentations, such as type-3 long-QT syndrome, Brugada syndrome, conduction abnormalities, DCM,¹³,¹⁴ and ARVD.¹⁵,¹⁶ Uncovering the genetic basis of complex phenotypes of single-gene disorders have created new opportunities to investigate the disease-causing mechanisms, clinical courses that can be factored in the therapeutic decision making.

The histological investigation¹¹ revealed that in the PLN R14del hearts from patients undergone heart transplants, myocardial fibrosis was found predominantly in the left ventricle (LV) and to a lesser extent in the RV, whereas fatty changes were more pronounced in the RV. Those findings may partially explain the ARVD-like phenotype because there are no histological data showing apoptosis of cardiomyocytes, the gradual loss of myocardium/regional wall thinning, and the signs of inflammation. It is possible that the histological differences between the typical cases of ARVD caused by desmosomal gene mutations and ARVD-like phenotype produced by PLN R14del are genetically predetermined.

Irreversible heart failure has been recognized as a major concern in the late stage of ARVD.¹⁷ The worsening of cardiac function may be the outcome of disease progression from the RV to LV, or the progression developed in the same time, leading to the rare form of biventricular dysplasia with major loss of LV contractility. Using induced pluripotent stem cells technique,¹⁹ it may be possible to test novel drugs or small molecules in-the-dish by targeting specific mutations hoping that they can slow down or block the disease progression in human.

The ECG phenotype of ARVD is characteristic¹⁹ in the majority patients meeting the revised task force criteria.²⁰ Among PLN R14del mutation carriers, no epsilon waves have been reported. The most striking ECG change is the reduced QRS amplitude especially in those with LV dilatations.⁹¹²¹ Reduced QRS amplitude is common in patients with heart failure of all causes, ARVD,¹⁹ presence of peripheral edema, and in other conditions.²²

Patients with all types of cardiomyopathies, including congenital and acquired forms, are prone to ventricular arrhythmias and sudden cardiac death. It is important to differentiate one from another by appropriate naming or nomenclature. Frequent ventricular arrhythmia with left bundle-branch block morphology is typically seen in ARVD because the disease is predominantly involving the RV. ARVD description captured most of the main features of the disease since it was first named.¹ Same is perhaps true for hypertrophic cardiomyopathy, restrictive cardiomyopathy, and DCM. In the latter ectopic beats, mostly arise from the LV. Ventricular arrhythmias and end-stage heart failure are the main contributing factors to sudden cardiac death and total mortality in DCM.²³–²⁶ Calling it an arrhythmogenic cardiomyopathy may better describe the phenotype characteristics of PLN R14del. Replacing ARVD with arrhythmogenic cardiomyopathy, however, can cause confusion, making ARVD indistinguishable from DCM, hypertrophic cardiomyopathy, and other types of cardiomyopathies.

The arrhythmogenic substrate in DCM is likely related to the structural abnormalities, such as myocardial fibrosis and stretching of myocardial fibers, induced by increased LV end-diastolic volume. In the overlap syndromes, especially the concealed cases that fatal arrhythmias occur before the macroscopic structural damage, the final common pathways may explain the arrhythmogenesis.²³ The loss of integrity in the sarcolemma, cytoskeleton, sarcomere, or the intercellular

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links caused by gene mutations could ultimately disrupt the ion channel function of cardiomyocytes and, therefore, cause arrhythmias. ARVD-causing PKP2 mutations, for example, can drastically reduce sodium channel currents (INa) and PKP2 variants downregulate INa is seen in Brugada syndrome as well.27 SCN5A mutations are found in 1.7% DCM families with patients showing a strong arrhythmia pattern.28 Sharing the final common pathways, nevertheless, does not necessarily mean everything is the same. Naming a disease must take clinical applications into considerations to avoid confusion because confusion can lead to misdiagnosis and mistreatment.

Because sudden cardiac death can be the first presentation of the disease, it is important to identify the high-risk individuals as demonstrated in this study.12 Challenge remains as how to not miss the high-risk individuals while eliminate the overuse in those in whom implantable cardioverter defibrillators are not necessary.

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None.

References

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