Editorial

A novel desmin mutation causing severe left ventricular arrhythmogenic cardiomyopathy/dysplasia

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Arrhythmogenic cardiomyopathy/dysplasia (AC) is a hereditary disorder characterized by degeneration of cardiomyocytes and their subsequent replacement by fat and fibrous tissue mainly, but not exclusively, in the right ventricle (RV) (1-3). Such changes lead to conduction abnormalities that provide the substrate for arrhythmogenesis (4,5). It is most frequently inherited in an autosomal dominant manner and is usually associated with mutations in genes encoding for desmosomal proteins (6,7), although non-desmosomal and ion channels gene mutations have also been described (8-10). Diagnosis is made according to the 2010 modified Task Force Criteria (11) and the average risk of ventricular arrhythmia can be very high, ranging from 3.7% to 10.6% per year depending on the specific AC population (12). The initial reported cases of AC affected exclusively the RV (13). However, over the recent years, cases of AC involving both ventricles or indeed only the left ventricle (LV) have been reported (14-17). Risk stratification of asymptomatic patients, however, remains a significant unresolved clinical problem. Consequently, the specific population who is at high risk of sudden cardiac death (SCD) and therefore will be benefit from an implantable cardioverter defibrillator (ICD) implantation is not well determined. A recent meta-analysis concluded that male gender, unexplained syncope, the extent of T-wave inversion, right ventricular dysfunction and previously documented VT/VF were significantly associated with higher risks of ventricular arrhythmias in AC patients (12). In addition to these established risk factors, strenuous exercise and inducibility of arrhythmia at electrophysiological studies also confer a higher arrhythmic risk even in borderline AC patients. Moreover, the presence of symptoms was linked to adverse outcomes in mutation carriers (12). However, reduced LV ejection fraction was not apparently associated with increased arrhythmic risk in definite and borderline AC patients (12).

Regarding the genetic basis of AC, an increasing number of AC-associated genes have been discovered with the expanding use of the next-generation sequencing (NGS) techniques in cardiovascular genetics. However, the molecular pathogenic mechanisms causing the AC-related desmin (*DES*) mutation phenotype remain unknown. The existing data shows an association of DES mutations with restrictive or dilated cardiomyopathy with conduction abnormalities or skeletal muscle

disorders (18,19).

In a recent article published in the journal *Circulation*, Bermúdez-Jiménez *et al.* demonstrated the pathogenicity of the novel *DES* mutation p.Glu401Asp in a large family with an inherited LV-dominant AC and a high incidence of adverse clinical events (20). This study evaluated 66 family members of Spanish origins across six generation and identified a new variant not previously described in the existing public databases. Genetically sequencing for *DES*-p.Glu401Asp revealed 23 members with the mutation. There were 8 additional non-tested individuals; 6 who died before sequencing and considered obligate carriers and 2 with a history of SCD, giving a total of 31 affected individuals. Furthermore, the genotype correlated well with phenotype after performing co-segregation analysis. An interesting finding was that primary myocardial disease was present in 100% of carriers while non-carriers did not show traces of cardiomyopathy. The mutation carriers were mainly asymptomatic (65.2%) at presentation while four patients presented with palpitations, three with heart failure symptoms and one with syncope. Bermúdez-Jiménez *et al.* showed that abnormal electrocardiographic findings were common in 97% of the mutation carriers (negative T-waves in inferior and antero-lateral leads (V2–V6), wider QRS complex, longer S wave duration, generalized low voltage and presence of Q wave), whilst in Holter recordings, non-sustained ventricular tachycardia was found in 32% of carriers and high density ventricular ectopy in 23% of the cases. There were no statistical significant differences in PR duration or frequency of epsilon wave or sinus rhythm between carriers and cases. Another interesting finding was that the missense *DES*-p.Glu401Asp mutation was not correlated with skeletal myopathy or abnormal creatine kinase levels. Echocardiography and cardiac magnetic resonance studies showed a near-exclusive LV affection, with hypokinesia localized on the mid-apical inferolateral wall of the LV, mildly depressed LV ejection fraction and no ventricular dilation while RV involvement was demonstrated only in 5 cases who presented concomitant moderate/severe LV ejection fraction impairment. During follow-up, a high incidence of cardiac events (39%) was noticed (4 SCD, 2 heart transplantations, 2 heart failure deaths and 1 atrioventricular block). This study also confirmed a higher prevalence of cardiac events in males, a finding that is also observed in other DES mutations.

DES mutations are known to influence the alpha-helical structures with deleterious consequences as the conformation of these helices is critical for desmin filament assembly and stability (21). The authors showed that the p.Glu401Asp mutation influences segment 2B of the central rod domain of desmin. However, it was not associated with conduction abnormalities or skeletal muscle disturbances, highlighting the role of aspartic acid in position 401 that gives rise to the specific phenotype. However, cell cultures showed that p.Glu401Asp mutation disrupted the intermediate filament structure in the transiently transfected cells in a manner similar to the p.Glu401Lys mutation (20). Another unique and important aspect of this study was the correlation of the p.Glu401Asp mutation with histological findings. Specifically, degenerative changes in the subepicardial myocardium, increased deposition of disorganized collagen fibers, the presence of infiltrating adipose tissue and groups of cardiomyocytes showing degenerative changes without inflammatory reaction. In the rest of the myocardium, the tissue organization was preserved but irregular cell thickness, increased perinuclear space, less density and less prominent intercalary discs of sarcoplasm, fewer and poorly organized contractile myofibrils were observed. Important functional proteins of cell-cell junctional complexes were preserved in mutation carriers but desmoplakin and plakoglobin were weakly stained as compared to controls. Cell cultures isolated from patients with the DES mutation and mild symptomatology showed similar cell morphology, but a slower growth and proliferation. Moreover, cell cultures from the index patient showed a typical mesenchymal morphology but a slower and different growth pattern. Furthermore, cells carrying the *DES*-p.Glu401Asp did not reveal higher *DES* expression after cardiomyogenic differentiation while over 30 genes encoding for a variety of potassium and sodium channels were found to be down- or up-regulated compared to healthy control samples.

In conclusion, the authors described for the first time a DES mutation in an LV dominant AC presenting without the specific conduction abnormalities known to occur in other DES mutations, or skeletal muscle disturbance that is associated with high incidence of arrhythmic events particularly in males. Detection of this specific mutation can help risk-stratify patients more precisely than with symptomatology and imaging alone. However, further research is needed for more accurate risk stratification strategies in this specific patient population to elucidate the group at high risk of malignant arrhythmias that will benefit from an ICD for primary prevention of SCD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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