CLINICAL IMAGE

Autosomal recessive transmission of familial nonsyndromic dilated cardiomyopathy due to compound desmoplakin gene mutations

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Familial nonsyndromic dilated cardiomyopathy (DCM) has a heterogeneous genetic background and is most often transmitted in an autosomal dominant way. Sudden cardiac arrest may be the first manifestation of the disease.[1,2] Mutations identified in the desmoplakin (*DSP*) gene are a recognized cause of arrhythmogenic right ventricular cardiomyopathy, DCM, and keratodermas.[3]

We present a case of a 16-year-old male patient after aborted sudden cardiac arrest due to ventricular fibrillation, which occurred during a football match at school. Resting 12-lead electrocardiography (ECG) performed after clinical stabilization showed sinus rhythm with prolongation of the QT interval (QT, 550 ms; corrected QT [QTc], 470 ms), not sufficient to diagnose long QT syndrome. Echocardiography revealed left ventricular dilation (left ventricular end-diastolic diameter [LVEDD], 6.4 cm), with moderately impaired global systolic function (left ventricular ejection fraction [LVEF], 44%). During 24-hour ECG monitoring, approximately 1000 ventricular extrasystoles of different morphologies were observed. Laboratory tests were positive for tetrahydrocannabinol use. The family history was negative for sudden cardiac death. Cardiac magnetic resonance imaging confirmed DCM with diffused areas of late gadolinium enhancement (FIGURE 1A). Treatment with propranolol and enalapril was started, and an implantable cardioverter-defibrillator was implanted as secondary prevention. The family

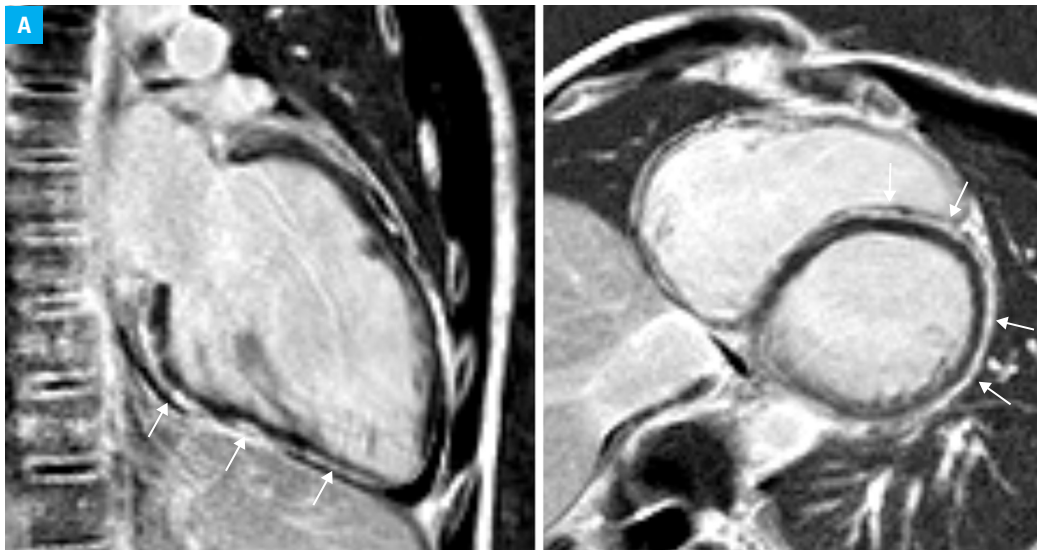

FIGURE 1 A – cardiac magnetic resonance: diffuse foci of late gadolinium enhancement in the proband (arrows)

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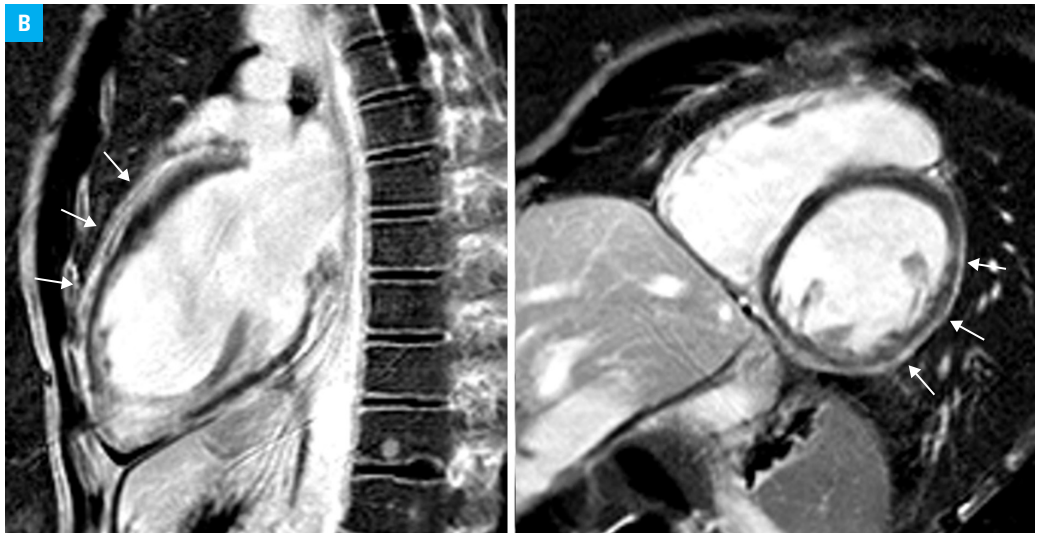

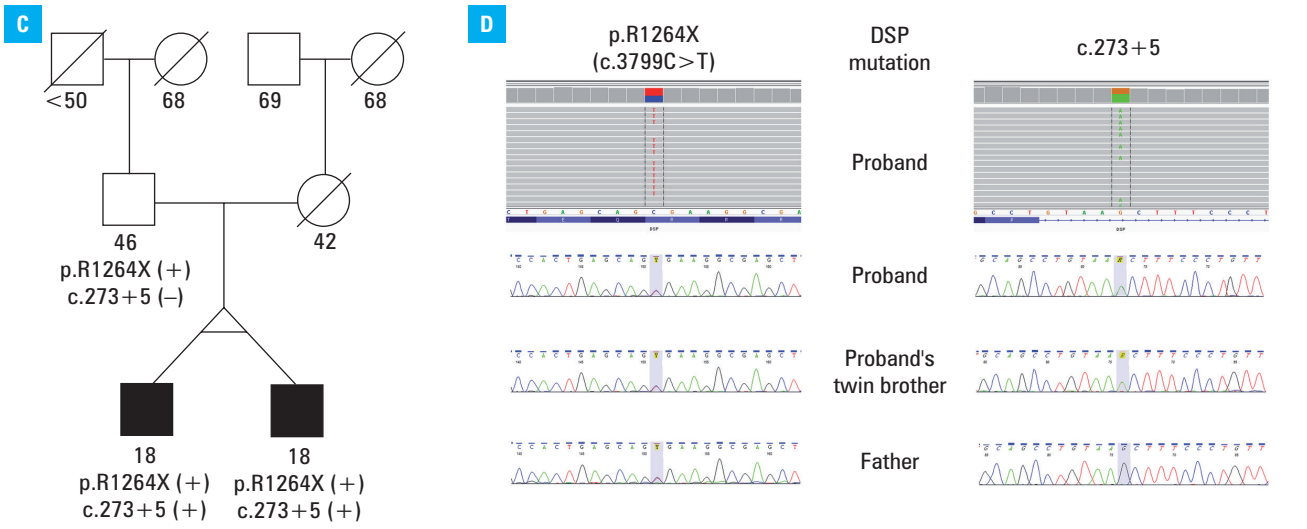

FIGURE 1 **B** – cardiac magnetic resonance: diffuse foci of late gadolinium enhancement in the proband's twin brother (arrows); **C** – the pedigree of the family with double desmoplakin mutation; **D** – integrative Genomics Viewer and Sanger sequencing views of both desmoplakin variants in the proband, proband's twin brother, and their father

history was negative for heart disease; the patient's mother died of extracardiac disease.

An asymptomatic twin brother of the patient was subsequently screened. Echocardiography confirmed DCM (LVEDD, 6.0 cm), with moderately impaired LVEF (41%). On 12-lead ECG, a borderline prolonged QT interval was observed (QTc, 450–480 ms). A few ventricular extrasystoles and about 1000 supraventricular extrasystoles were recorded on 24-hour ECG monitoring. Cardiac magnetic resonance imaging also showed signs of DCM with diffused areas of late gadolinium enhancement (FIGURE 1B). Treatment with metoprolol and ramipril was started.

Cardiovascular screening of a 46-year-old asymptomatic father revealed sinus rhythm with a borderline prolonged PR interval (207 ms) and nonspecific intraventricular conduction delay (QRS, 116 ms) on ECG. Echocardiography revealed normal left ventricular size (5.3 cm) and function (LVEF, 72%).

No evidence of right ventricular involvement was found in any of the patients. Genetic counseling and testing were performed in the proband, with subsequent testing in the proband's brother and father. Next-generation sequencing (TruSight Cardio Sequencing Panel, Illumina; mean coverage, 269.7x; ge20, 98.7%) identified the heterozygous nonsense variant p.R1267X/c.3799C>T (rs121912997) and the heterozygous splice region variant c.273+5G>A (rs200473206) in the *DSP* gene (NM_004415) (FIGURE 1C). Genetic testing of the brother and father revealed the p.R1267X mutation in both patients and c.273+5G>A only in the brother, thus confirming autosomal recessive transmission. The analysis did not reveal any genetic cause of the borderline prolonged QT interval in the brother.

The homozygous nonsense variant R1267X was previously reported in a 4-year-old child with arrhythmogenic DCM, with left and right ventricular involvement, epidermolytic palmoplantar keratoderma, and wooly hair,[4] while the splice variant was reported in patients with arrhythmogenic right ventricular cardiomyopathy.[3,5] No skin abnormalities were found in our family.

In conclusion, compound heterozygotic *DSP* variants cause early-onset nonsyndromic DCM, while the truncating variant R1267X alone is weakly penetrant.

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