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

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FIGURE 1  A – cardiac magnetic resonance: diffuse foci of late gadolinium enhancement in the proband (arrows)
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, while the splice variant was reported in patients with arrhythmogenic right ventricular cardiomyopathy. 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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