CLINICAL IMAGE

Novel truncating desmoplakin mutation as a potential cause of sudden cardiac death in a family

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Sudden cardiac death (SCD) of young, apparently healthy individuals raises questions about whether other family members are also at risk of SCD.

A 30-year-old patient treated with bisoprolol (5 mg once daily) for ventricular arrhythmia for 6 months was admitted to our hospital for evaluation. A family history of SCD was identified: the patient's brother died suddenly at the age of 39 years while working at the computer. A physical examination of our patient was unremarkable. A standard 12-lead electrocardiogram showed sinus bradycardia (47 bpm) and low voltage, fragmented QRS in limb leads (FIGURE 1A). A transthoracic 2-dimensional echocardiogram revealed a nondilated left ventricle with borderline ejection fraction; however, the right ventricle was dilated with mild global contractile dysfunction. Subsequent cardiac magnetic resonance (CMR) revealed a significantly enlarged right ventricle and a slightly enlarged left ventricle (right ventricular [RV] end-diastolic volume, 151 ml/m^2, n <111, and left ventricular [LV] end-diastolic volume, 111 ml/m^2, n <101) with slightly reduced LV and RV ejection fractions (49% and 46%, respectively) and global hypokinesis. Additionally, diffuse changes on late gadolinium enhancement (LGE) were found (FIGURE 1B–D).

On 24-hour Holter monitoring, sinus bradycardia (without pauses), single premature ventricular contractions, ventricular couplets, and episodes of nonsustained ventricular tachycardia (2 polymorphic triplets) were observed.

A family history revealed that the proband's father died of heart failure at the age of 75 years, and a paternal cousin died suddenly (FIGURE 1E). Noninvasive clinical cardiac screening was performed in available family members (mother and sister) and revealed no abnormalities. A genetic study was performed to gain insight into SCD in the family and identify family members at potential risk. DNA was extracted from peripheral blood by phenol extraction. Next-generation sequencing (NGS) in the proband was performed using the TruSight One (TSO, Illumina, San Diego, California, United States) sequencing panel. Selected genetic variants identified by NGS were followed up in the proband and relatives, using Sanger sequencing.

We identified the frameshift deletion p.Thr2625fs (c.7871_7872delAC), annotated to transcript NM_004415.2 of the desmoplakin (DSP) gene, in the proband, but not in his healthy mother or sister (FIGURE 1F and 1G). Desmoplakin is a critical component of desmosome structures in the cardiac muscle, and the role of DSP mutations, including protein-truncating mutations, in the pathogenesis of cardiomyopathies is well established.[1,2] The identified variant has not been described in the literature before or found in genomic databases (Phase 3 of 1000 Genomes, NHLBI GO Exome Sequencing Project [ESP] 6500 and Version 0.3 of ExAC).

Although the recommendation of an implantable cardioverter defibrillator (ICD) as primary prevention remains controversial,[3] it was necessary in this case. ICD was implemented owing to signs of biventricular involvement on CMR, the family history of SCD, and the result of genetic study in the patient with complex ventricular arrhythmia.

A 2-year follow-up revealed that the patient remained asymptomatic, and cardiac function was stable with readings from the ICD memory

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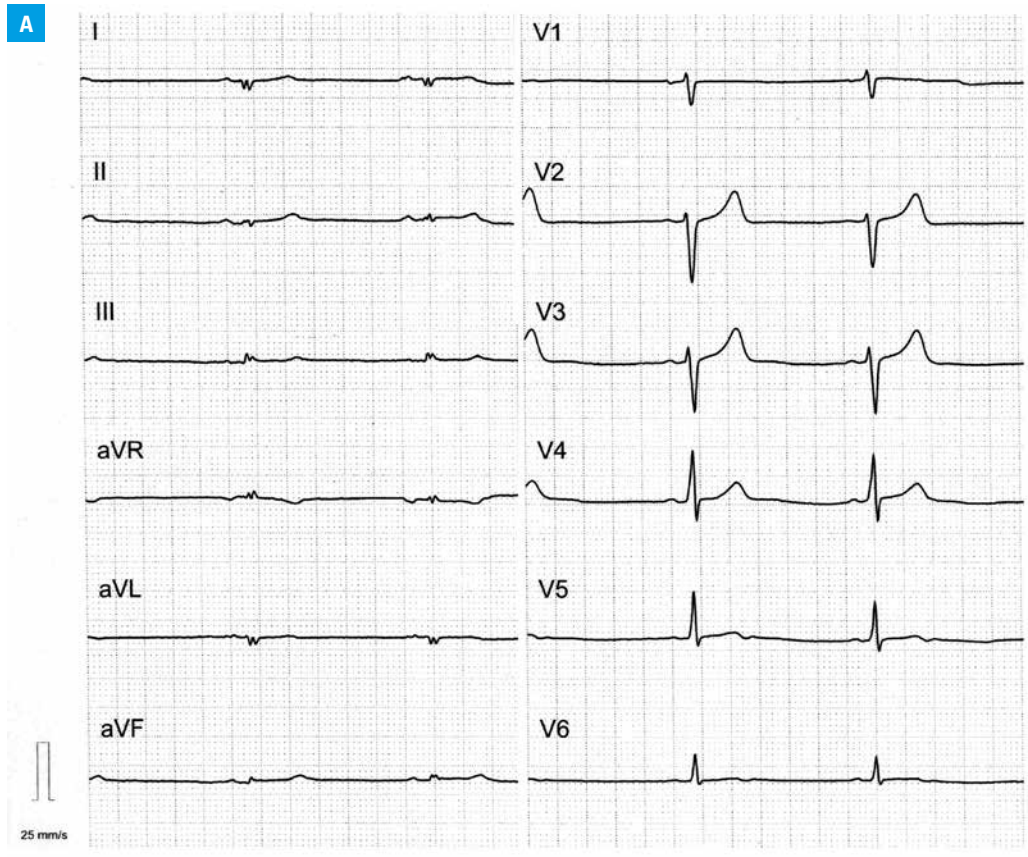
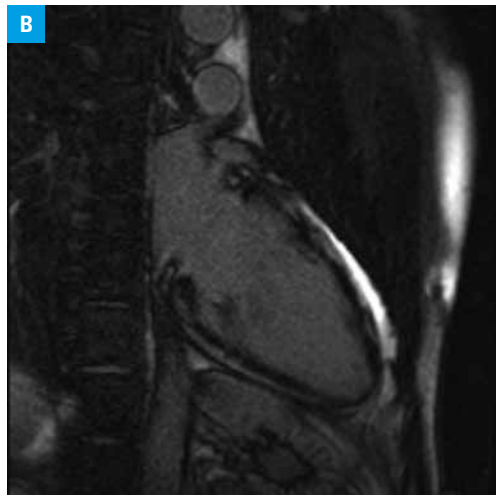
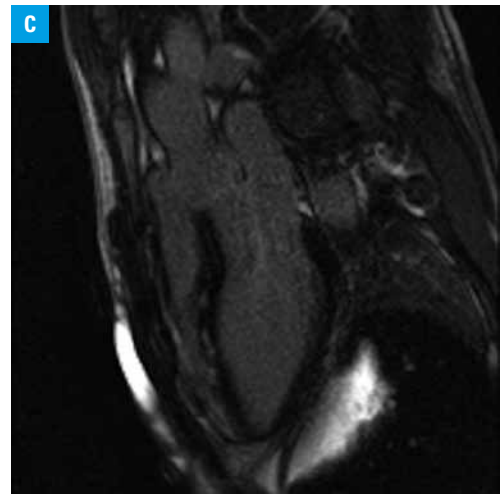






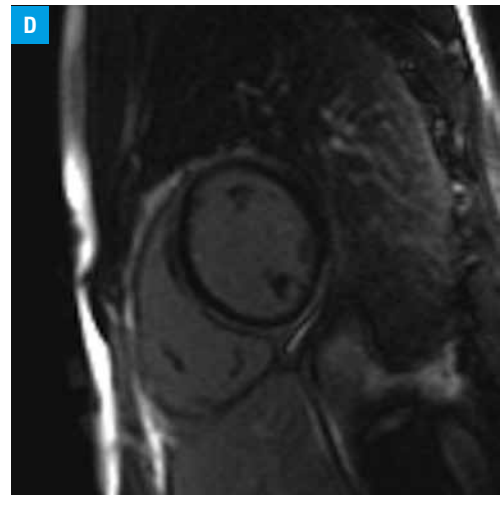
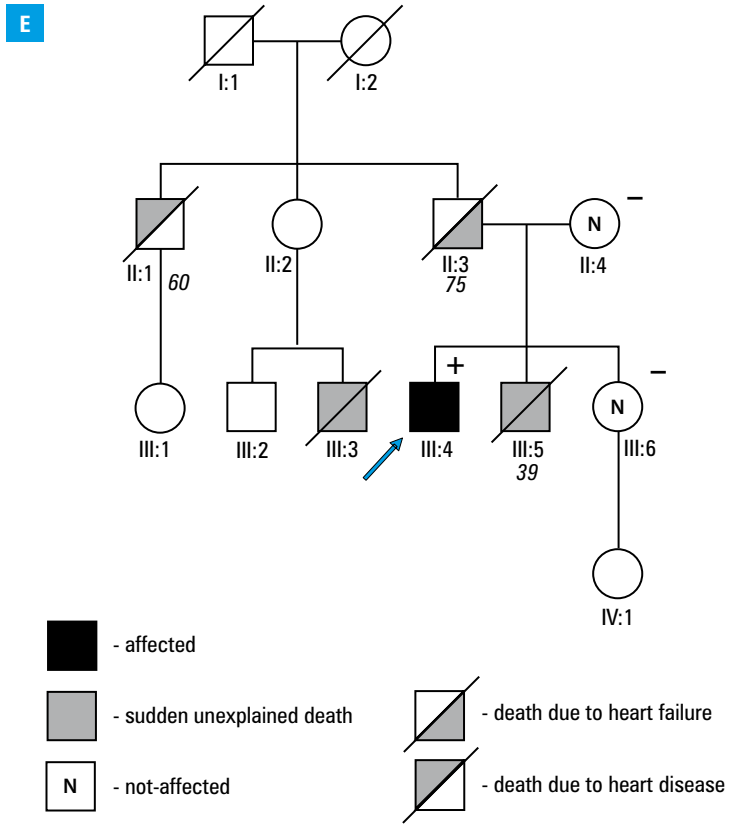


FIGURE 1 **A** – sinus bradycardia, 47 bpm, low voltage, fragmented QRS in limb leads; **B**, **C**, **D** – cardiac magnetic resonance; late gadolinium enhancement (LGE) images (inversion recovery; 1,5T; Siemens; Avanto Erlangen, Germany) in 2-chamber (**B**), 3-chamber (**C**), and short-axis views (**D**); intramyocardial and subepicardial areas of LGE are seen: linear subepicardial areas of LGE in the inferior wall and irregular LGE areas in anterior wall (**B**); irregular, patchy areas of LGE in the interventricular septum (**C**); linear mid-wall LGE areas in the interventricular septum as well as LGE located in the inferior and inferolateral segments with subepicardial distribution (**D**)



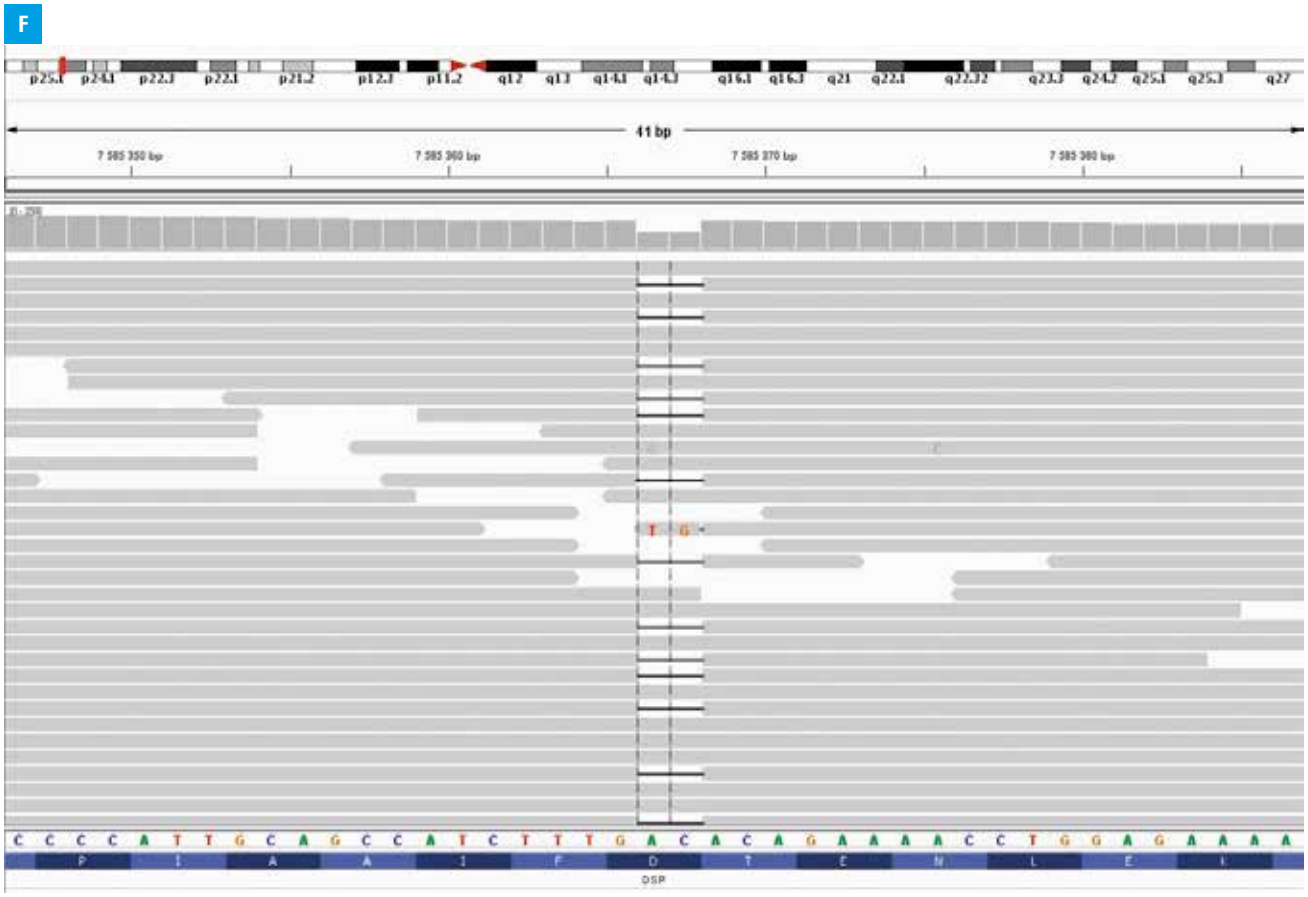
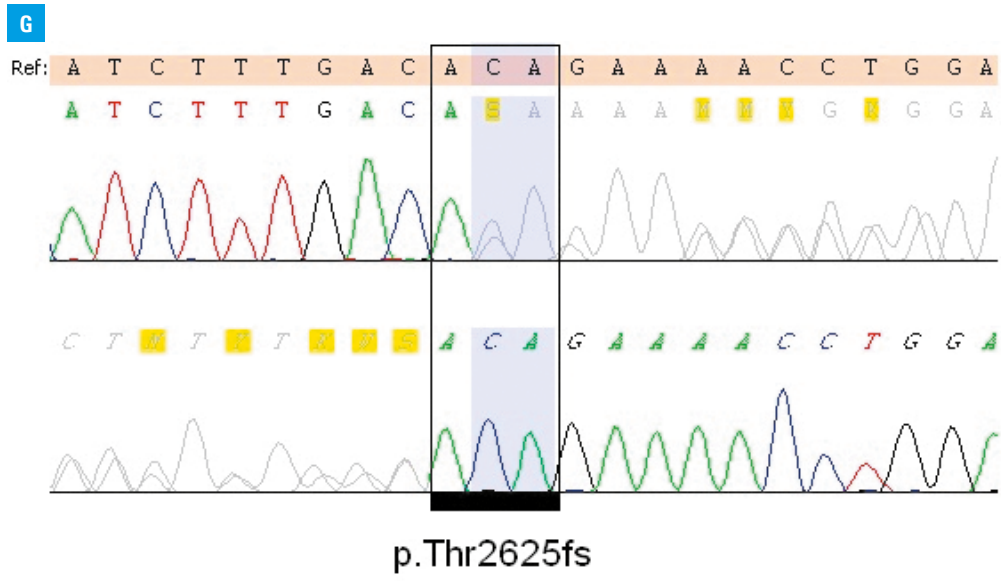


FIGURE 1 **E** – pedigree of the family. Squares represent males and circles represent females. An arrowhead denotes the proband. A diagonal line marks deceased individuals. Solid symbols denote affected individual. Open symbols with "N" denote unaffected individuals with clinically normal echocardiogram/electrocardiogram. Other features are shown in the bottom of the figure. The presence or absence of a desmoplakin (DSP) gene mutation is indicated by "+" or "–", respectively. **F** – a view of the DSP (NM_004415.2) frameshift deletion p.Thr2625fs (c.7871_7872delAC) found in the proband (visualized using the Integrative Genomics Viewer)

FIGURE 1
G – chromatograms from direct Sanger sequencing showing the p.Thr2625fs mutation in the proband



not showing any activity over set detection criteria for zone VF (12 consecutive beats with a frequency of 214 bpm).

Our patient did not fulfill the current diagnostic criteria for arrhythmogenic RV cardiomyopathy/dysplasia (ARVC/D),[4] although the presence of the mutation alone allowed us to make a borderline diagnosis. We also found LV involvement to be consistent with the findings of Bhonsale et al,[5] who studied a large cohort of 577 patients with ARVC/D-associated mutations and reported that DSP mutation carriers were considerably more likely to develop LV involvement and heart failure.

This case illustrates the clinical difficulties in diagnosing the cause of global biventricular dysfunction and infrequent complex ventricular arrhythmia. Furthermore, it highlights the role of genetic studies in identifying potentially pathogenic, disease-causing variants that might have been responsible for SCD in this family.

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