Carvajal syndrome related to two distinct molecular variants in desmoplakin gene

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We present the case of a 19-year-old woman with palmoplantar keratoderma and woolly hair (Figure 1A), diagnosed with arrhythmogenic right ventricular cardiomyopathy (ARVC) with left ventricular involvement. Family history was negative for cardiomyopathies, arrhythmias, or sudden cardiac death (SCD). The disease was initially identified at the age of 9, followed by exacerbation of ventricular arrhythmia at the age of 14. At that time, echocardiography showed significant dilatation and systolic dysfunction of both ventricles, which was confirmed by cardiac magnetic resonance (CMR), where left ventricular (LV) and right ventricular (RV) ejection fraction were reduced to 20% and 23%, respectively (Figure 1B). Extensive subepicardial and intramural fibrosis of inferolateral LV wall and subepicardial fibrosis in RV wall were present (Supplementary material, *Figure S1*). Treatment included pharmacotherapy (β-blockers, mexiletine, and optimal treatment for heart failure), primary prevention implantable cardioverter-defibrillator (ICD), and catheter ablation of recurrent ventricular arrhythmias.

During a 4-year follow-up, progression of heart failure symptoms, syncope, and multiple appropriate ICD interventions due to ventricular fibrillation were observed. Additionally, the patient underwent an episode of stroke. Electrocardiogram indicated low voltage in limb and precordial leads, along with repolarization abnormalities (Supplementary material, *Figure S2*). 24-hour Holter monitoring showed multiple polymorphic premature ventricular contractions (1400/24 h) originating from both ventricles, and episodes of non-sustained ventricular tachycardia (Figure 1D). Echocardiography demonstrated significant RV impairment (RV end-diastolic area = 40.2 cm^2, fractional area change = 21%) with severe tricuspid regurgitation (Figure 1C; Supplementary material, *Videos S1–S2*), as well as LV dilatation with reduced ejection fraction (LVEF 15%) (Supplementary material, *Videos S3–S4*). The patient was referred for orthotopic heart transplantation (HTx), and the procedure was carried out successfully. One year after HTx, the patient is in good health, and echocardiography indicates favorable function of the transplanted heart.

Next-generation panel sequencing showed two heterozygous desmoplakin gene (*DSP*) molecular variants: known pathogenic c.1339C>T (occurred *de novo*) and a novel likely pathogenic c.8204G>C (inherited from a healthy father) (Figure 1E). Both variants result in absent or disrupted desmoplakin, so autosomal recessive (AR) inheritance was suspected, although the dominant effect of a single *de novo* variant cannot be excluded. Pathogenic *DSP* variants involved in cardiocutaneous phenotypes including autosomal recessive Carvajal syndrome are mainly located in the rod domain or close to the C-terminus [1]. Compound heterozygotes for a truncation and a missense change have been described in Carvajal syndrome, including a severe form (early cardiac lethality, with blistering) and a mild form (palmar-only or minor palmoplantar keratoderma, curly to woolly hair) [2]. To the best of our knowledge, c.1339C>T *DSP*

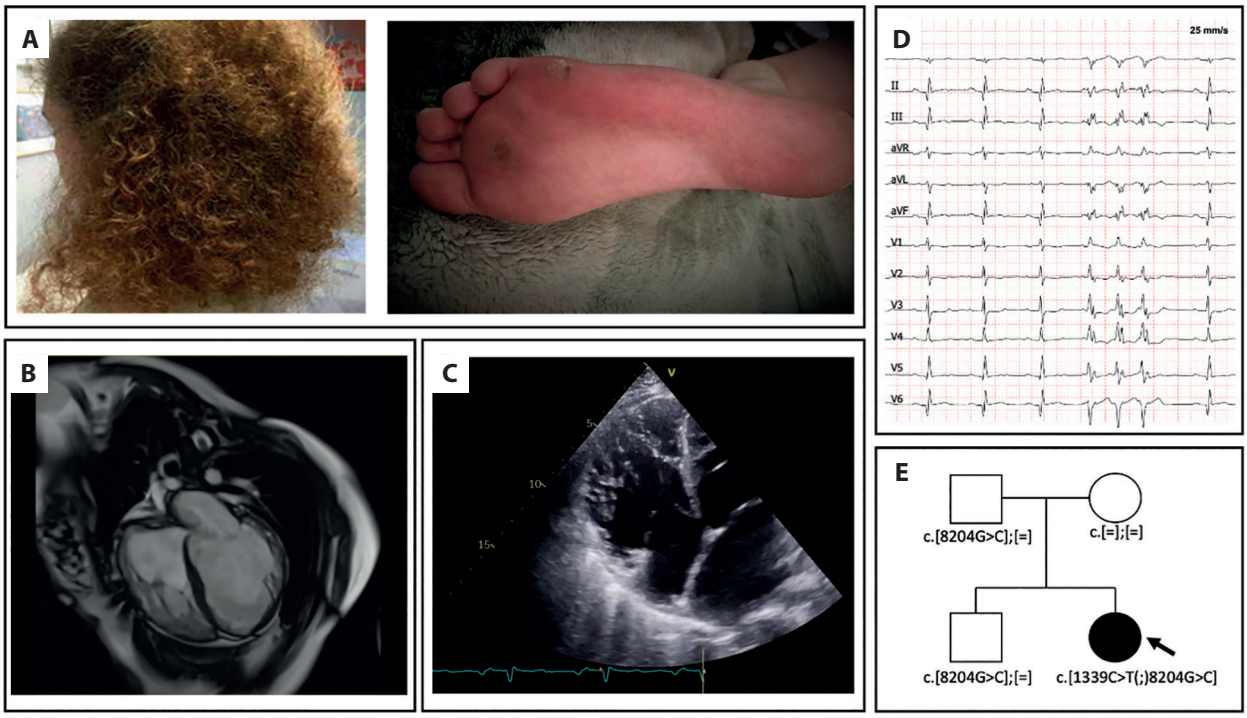

Figure 1. A. Cutaneous symptoms of Carvajal syndrome: woolly hair and palmoplantar keratoderma. **B.** Cardiac magnetic resonance (CMR). Both ventricles significantly dilated with reduced systolic function (4-chamber view). **C.** 2-dimensional echocardiogram. *Focused right ventricular (RV) apical 4-chamber view. Dilated RV* (RV end-diastolic area, RVA 40.2 cm^2) with impaired systolic function (fractional area change, FAC, 21%). **D.** 24-hour Holter monitoring. Episodes of non-sustained ventricular tachycardia (NSVT). **E.** Pedigree of family. Filled symbol — affected individual. Molecular variant NM_004415.4(DSP):c.1339C>T p.(Gln447*) causes a stop gained change predicted to result in nonsense-mediated mRNA decay. Loss-of-function variants in desmoplakin gene (*DSP)* are a known pathomechanism of disease. This variant was reported in ClinVar as Pathogenic and was absent in control chromosomes in GnomAD database. Nonsense variant is localized in critical protein SH3 domain that contributes to stability and rigidity of this subfamily of spectrin repeats (SRs) containing proteins. NM_004415.4(DSP):c.8204G>C p.(Gly2735Ala) variant causes a missense change involving alteration of a conserved nucleotide. This is a very rare variant in the general population (and was found at a frequency of 0.0000007 in 1 461 886 control chromosomes in GnomAD database, with no homozygous occurrence). In-silico tool predicts a deleterious effect, so likely pathogenic outcome for this substitution. This missense variant is localized in C-terminal desmoplakin domain that appears to be a mutation hot spot in *DSP*

variant has been previously described only in patients with familial autosomal dominant left ventricular cardiomyopathy [3]. Our patient is the first case with recessive Carvajal syndrome related to *de novo* c.1339C>T, co-occurring with novel paternal c.8204G>C substitution, located unusually in the SH3 and typically in the C-terminal desmoplakin domain, respectively.

This report expands the existing knowledge of the phenotype, molecular pathomechanism and background of Carvajal syndrome.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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