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Authors: Lidia Ziółkowska, Elżbieta Ciara, Karolina Borowiec, Maciej Sterliński, Elżbieta Katarzyna Biernacka

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Carvajal syndrome related to two distinct molecular variants in desmoplakin gene

Lidia Ziółkowska[1], Elżbieta Ciara[2], Karolina Borowiec[3], Maciej Sterliński[4], Elżbieta Katarzyna Biernacka[3]

[1]Department of Cardiology, The Children's Memorial Health Institute, Warsaw, Poland

[2]Department of Medical Genetics, The Children's Memorial Health Institute, Warsaw, Poland

[3]Department of Congenital Heart Diseases, Cardinal Stefan Wyszyński National Institute of Cardiology, Warsaw, Poland

[4]1st Department of Arrhythmia, Cardinal Stefan Wyszyński National Institute of Cardiology, Warsaw, Poland

* Both authors equally contributed to the study

Corresponding author:

Karolina Borowiec, MD, PhD

Department of Congenital Heart Diseases

Cardinal Stefan Wyszyński National Institute of Cardiology

Alpejska 42, 04-628 Warsaw, Poland

Tel.: +48 (22) 343 44 00

e-mail: kborowiec@ikard.pl

We report a case of 19-year-old woman with palmoplantar keratoderma and woolly hair (Fig. 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. Extensive subepicardial and intramural fibrosis of inferolateral LV wall and subepicardial fibrosis in RV wall were present (Fig. 1B, Suppl. 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 (Suppl. Figure S2). A 24-hour Holter monitoring showed multiple polymorphic premature ventricular contractions (1400/24 h) originating from both ventricles and episodes of non-sustained ventricular tachycardia (Fig. 1D). Echocardiography demonstrated significant RV impairment (RV end-diastolic area = 40.2 cm^2, fractional area change = 21%) with severe tricuspid regurgitation (Fig. 1C, Suppl. Video S1–S2), as well as LV dilatation with reduced ejection fraction (LVEF = 15%) (Suppl. Video 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 revealed 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) (Fig. 1E). Both variants result in an absent/disrupted desmoplakin so an autosomal recessive (AR) inheritance was suspected, however dominant effect of 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 severe form (early cardiac lethality, with blistering) or mild (palmar-only or minor palmoplantar keratoderma, curly to woolly hair) [2]. To our knowledge, c.1339C>T *DSP* variant, has been 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 C-terminal desmoplakin domain, respectively.

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

Article information

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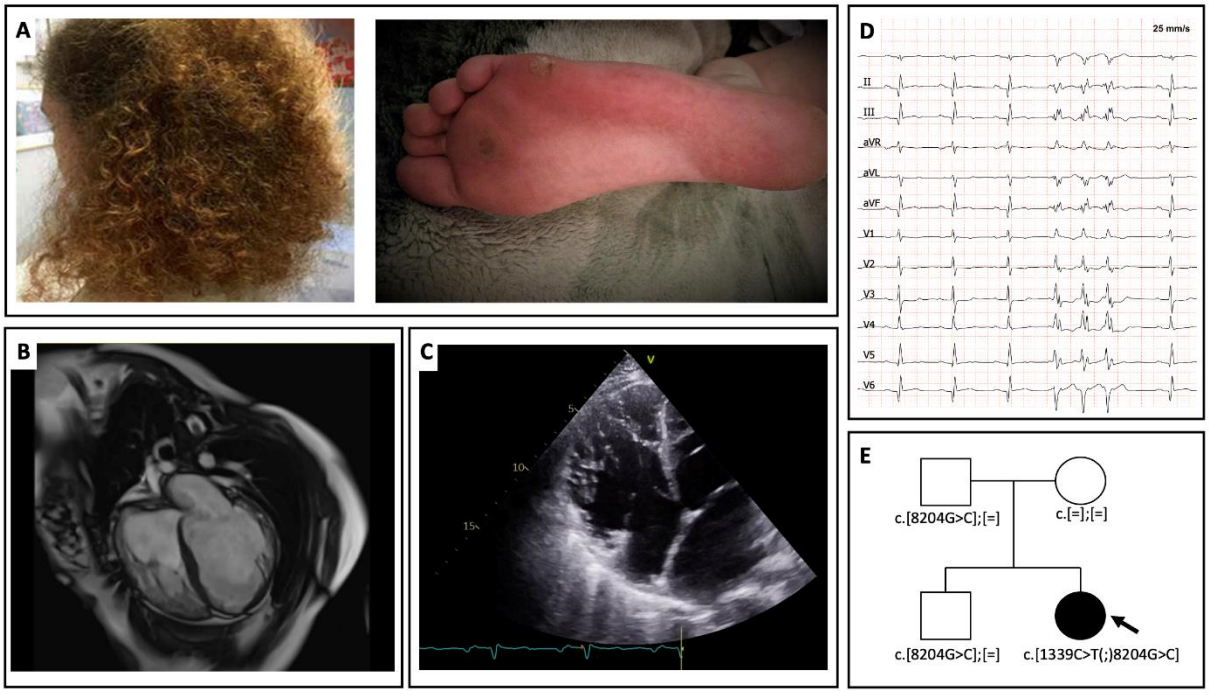
Figure 1. A. Cutaneous symptoms of Carvajal syndrome: woolly hair and palmoplantar keratoderma. **B.** Cardiac magnetic resonance (CMR). Significantly dilated both ventricles with reduced systolic function (4-chamber view). **C.** 2-dimensional echocardiogram. *Focused right ventricular (RV) apical 4-chamber view. Dilated RV* (RV end-diastolic area, RVA 40.2 cm2) with impaired systolic function (fractional area change, FAC 21%). **D.** 24-hour Holter monitoring. Episodes of non-sustained ventricular tachycardia (NSVT). **E.** Pedigree of the family. Filled symbol – affected individual. Molecular variant NM_004415.4(DSP):c.1339C>T p.(Gln447*) causes a stop gained change predicted to results in nonsense mediated mRNA decay. Loss-of-function variants in desmoplakin gene (*DSP)* are known patomechanism of the disease. This variant was reported in ClinVar as Pathogenic and was absent in control chromosomes in GnomAD database. The nonsense variant is localised in critical protein SH3 domain, that contributes to the stability and rigidity of this subfamily of spectrin repeats (SRs) containing proteins. The NM_004415.4(DSP):c.8204G>C p.(Gly2735Ala) variant causes a missense change involving the alteration of a conserved nucleotide. This is very rare variant in general population (was found at a frequency of 0.0000007 in 1 461 886 control chromosomes in the GnomAD database, with no homozygous occurrence). In-silico tool predicts a deleterious effect, so likely pathogenic outcome for this substitution. This missense variant is localised in the C-terminal desmoplakin domain that appear to be mutation hot spots in *DSP*.



Supplementary Figure S1. Cardiac magnetic resonance (CMR). Extensive subepicardial and intramural fibrosis of inferolateral left ventricular wall and subepicardial fibrosis in right ventricular wall (short axis view).

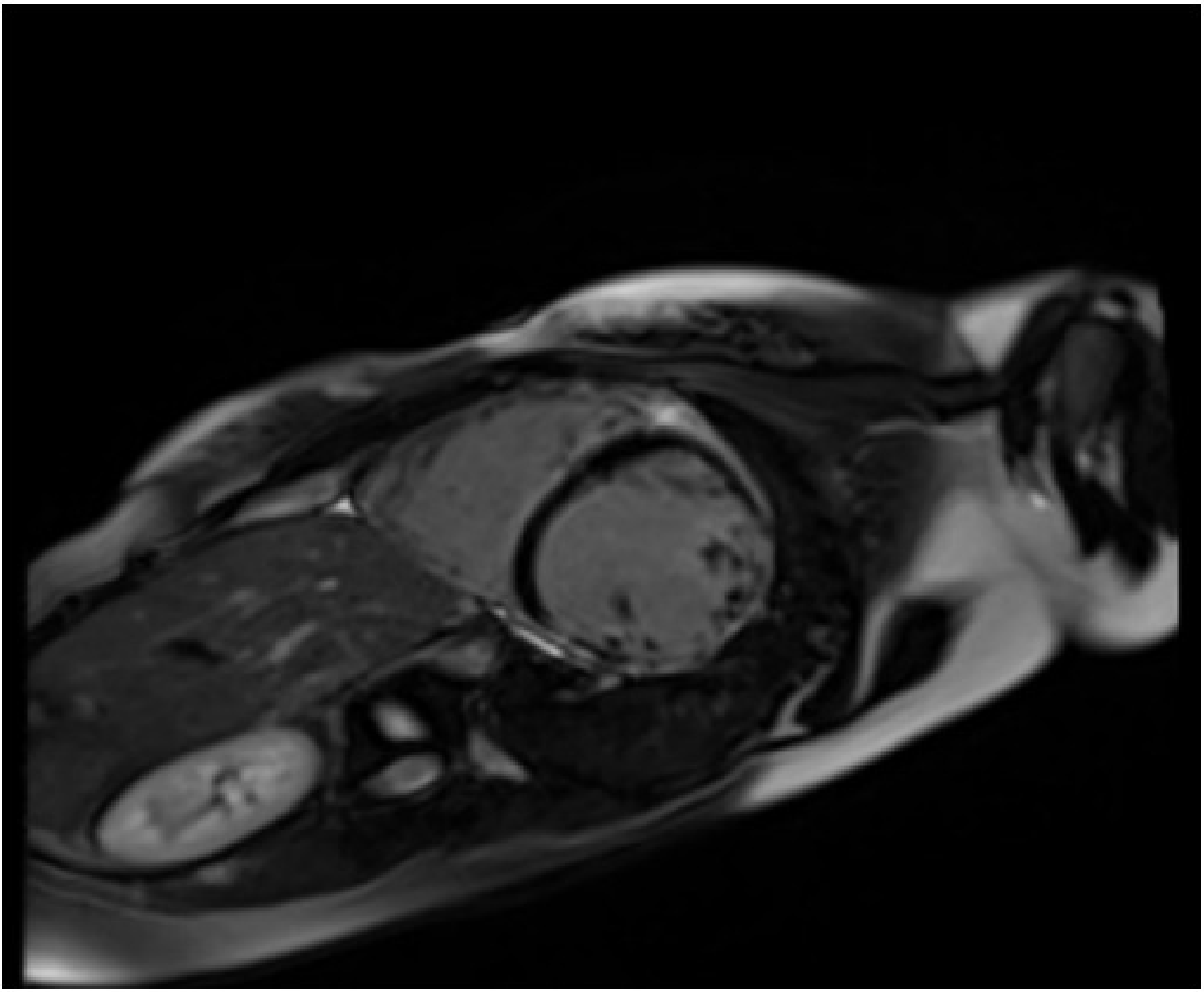
Supplementary Figure S2. 12-lead electrocardiogram. Low voltage in limb and precordial leads, non-specific repolarization abnormalities.

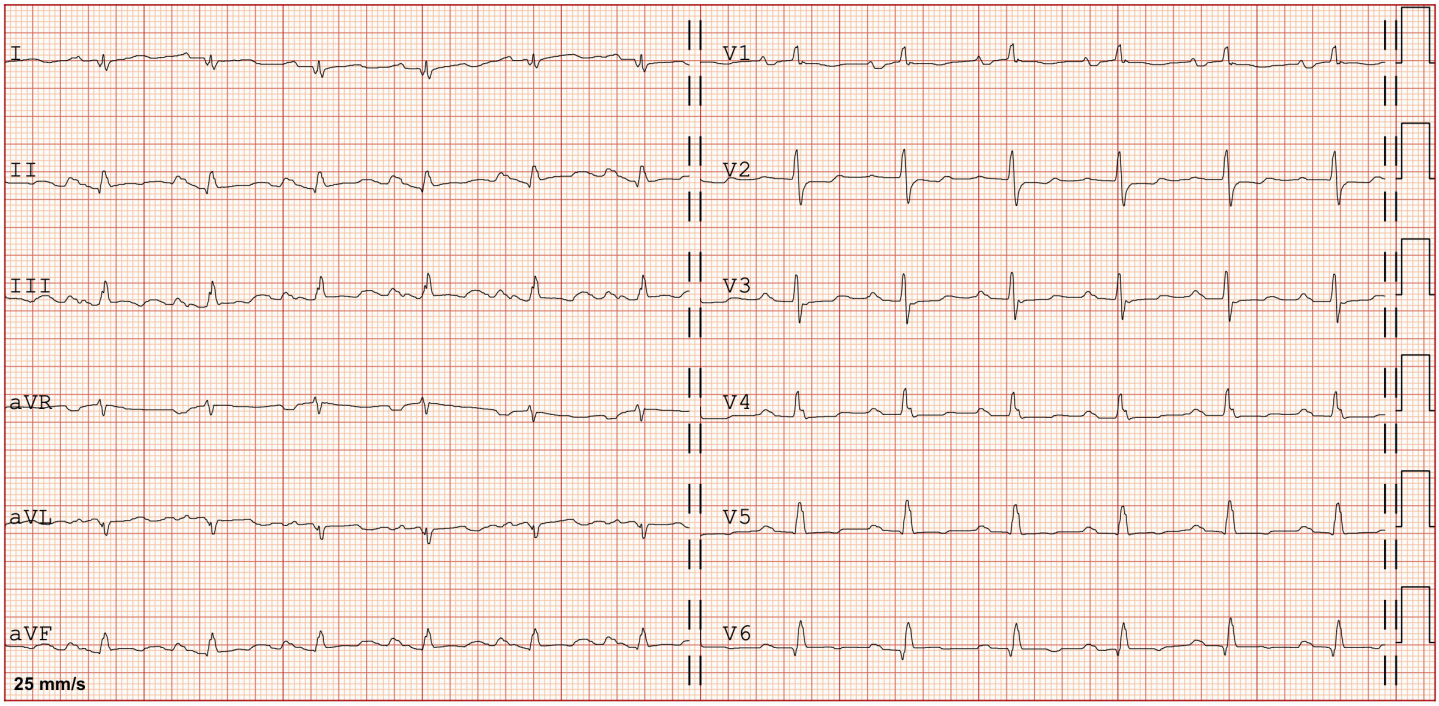
Supplementary Video S1. 2-dimensional echocardiogram. *Focused right ventricular (RV) apical 4-chamber view. Dilated RV* (RV end-diastolic area, RVA 40.2 cm2) with impaired systolic function (fractional area change, FAC 21%).

Supplementary Video S2. 2-dimensional colour Doppler echocardiogram. *Focused right ventricular (RV) apical 4-chamber view.* Severe tricuspid regurgitation.

Supplementary Video S3. 2-dimensional echocardiogram. *Apical 4-chamber view.* Dilatation of the left ventricle (LV) (LV end-diastolic volume, LVEDV 240 ml) with excessive trabeculation and severely reduced ejection fraction (EF 15%).

Supplementary Video S4. 2-dimensional colour Doppler echocardiogram. *Apical 4-chamber view.* Moderate mitral regurgitation.

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