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A novel Desmoplakin mutation associated with left dominant arrhythmogenic cardiomyopathy and cutaneous phenotype

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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DSP gene encodes the desmoplakin which is a protein that anchors intermediate filaments to desmosomal plaques and forms an obligate component of functional desmosomes. Mutations in *DSP* are the cause of several cardiomyopathies including left dominant arrhythmogenic cardiomyopathy (LDAC) with cutaneous phenotype.[1,2] However, the true prevalence of LDAC with cardio-cutaneous phenotype and dominant type of inheritance seems to be underestimated.[3,4]

In this study we report a family, in which three members across three generations carry the same *DSP* variant associated with cutaneous phenotype alone, or in concomitance with cardiomyopathy.

A 47-y-old female (case index-II(III) patient) (Figure 1A) presented to a local hospital after an episode of chest discomfort with a subsequent syncopal episode. Her family history was negative for cardiomyopathy or premature sudden death. High sensitivity-troponin T levels reached the value of 1446 pg/ml (normal <15 pg/ml). Basal electrocardiogram (ECG) showed low voltages in inferior and lateral leads with depolarization abnormalities (Figure 1B). Echocardiography revealed a moderately depressed left ventricular ejection fraction (43%) with diffuse hypokinesia. Right ventricle was normal. Coronary angiogram demonstrated normal coronary arteries. During hospitalization the patient suffered an episode of sustained ventricular tachycardia. The patient was evaluated in our cardiomyopathy outpatient clinic two months later and a cardiac magnetic resonance was performed, which evidenced extensive sub-epicardial fibrosis primarily in the inferior, posterior, lateral and anterior left ventricular walls (Figure 1C). The right ventricle was normal. An implantable cardioverter defibrillator (ICD) was implanted for sudden cardiac death's secondary prevention. Moreover, amiodarone, metoprolole and ramipril was administered to the patient. During evaluation specific patient features were

evidenced like a curly hair appearance concomitantly with palmoplantar keratoderma (Figure 1D).

The case index-I(II) and case index-III(V) patient, the father and daughter of case index-II(III) patient respectively, were also evaluated in our outpatient clinic. The father was 72-y-old and presented curly hair and extensive palmoplantar keratoderma. Although his echocardiogram was normal, his ECG displayed low voltages in limb leads and multifocal premature ventricular extrasystoles. 24h holter monitoring revealed over 1000 ventricular extrasystoles. The daughter (case index-III(V) patient) was 19-y-old and had curly hair and mild palmoplantar keratoderma. Her ECG and echocardiogram were normal. No medication was administered to these cases.

During annual follow-up, the proband (case index II(III) patient) was asymptomatic, without any appropriate ICD discharges, and amiodarone was discontinued. Accordingly, her father and her daughter did not demonstrate any structural cardiac abnormality at follow-up. Moreover, the 24h holter monitoring of the daughter was normal, without ventricular extrasystoles. Annual follow-up was recommended to these genotype (+)/phenotype (-) patients.

The proband, followed by her father and her daughter, were subjected to genetic testing in order to identify a potential causal gene mutation. Next Generation Sequencing (NGS) exome study was carried out on DNA extracted from peripheral blood, in order to identify genomic variants in 74 genes known to be associated with cardiomyopathy

The variant DSP:c.2811_2812dupAT was identified in heterozygosity in the case-index II(III) patient. It is considered a pathogenic variant which we confirmed with sanger sequencing (Figure 1E). This variant is new and never previously reported. It

is predicted to cause an interruption of protein synthesis and the formation of a truncated protein p.Ser938Tyrfs*. Segregation studies in order to determine the inheritance pattern of the identified variant were done and the same variant was identified at the father and daughter in heterozygosity.

DSP:c.2811_2812dupAT is a novel variant of the gene coding for desmoplakin presumed to cause LDAC associated with cutaneous phenotype (keratoderma and curly hair) with a dominant pattern of inheritance.

The red flags to raise the suspicion of LDAC are the presence of ventricular arrhythmias of left ventricular origin, the low voltage in inferior and lateral ECG leads and the moderately depressed left ventricular ejection fraction.[5] If curly hair or palmoplantar keratosis are present, the diagnosis is more consistent. CMR is of great importance since it may reveal subepicardial fibrosis or fibro-fatty replacement in inferior, posterior and lateral left ventricular wall and in many cases circumferential pattern.[6] As in many cases of arrhythmogenic cardiomyopathy, the first clinical manifestation of the disease in our case was that of acute myocarditis. [7]

In the pedigree of our study, two members (the father and the daughter of the proband) carried the same variant. The father presented cutaneous phenotype and high arrhythmogenicity without structural heart abnormalities and the daughter only cutaneous manifestations. The management (participation in sport activities, follow-up frequency and examinations) of the genotype(+)/phenotype(-) individuals remains unclear.[8]

REFERENCES

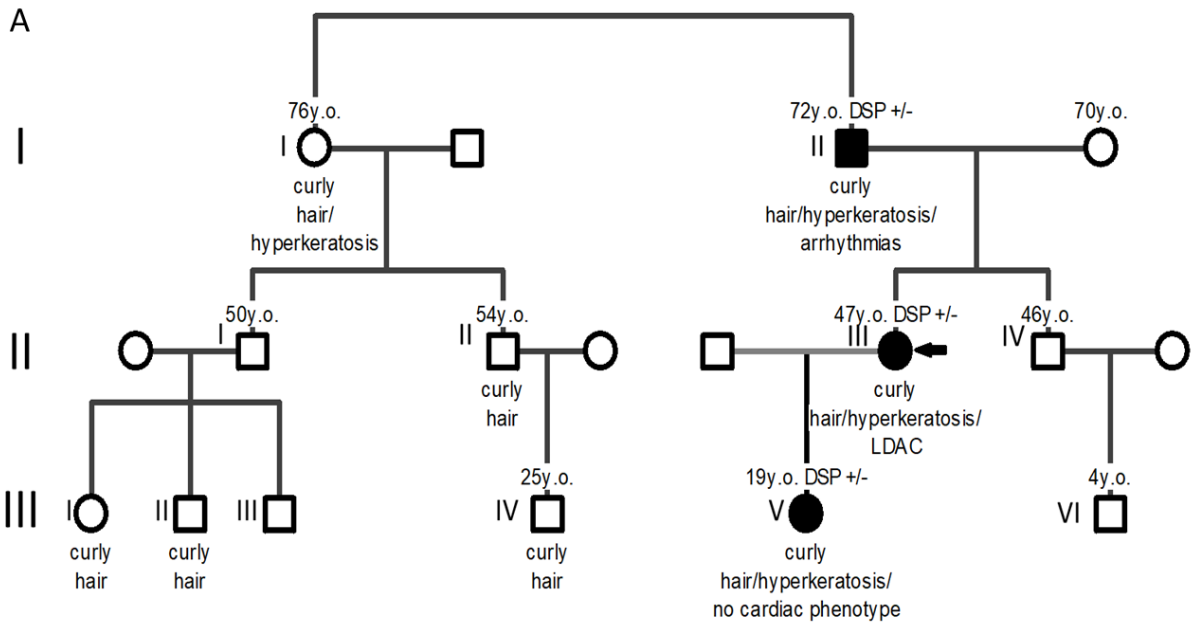
1. Corrado D, Basso C, Judge DP. Arrhythmogenic Cardiomyopathy. *Circ Res.* 2017;121:784-802.
2. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet.* 2000;9:2761-2766.
3. Norgett EE, Lucke TW, Bowers B, Munro CS, Leigh IM, Kelsell DP. Early death from cardiomyopathy in a family with autosomal dominant striate palmoplantar keratoderma and woolly hair associated with a novel insertion mutation in desmoplakin. *J Invest Dermatol.* 2006;126:1651-1654.
4. Pigors M, Schwieger-Briel A, Cosgarea R, et al. Desmoplakin mutations with palmoplantar keratoderma, woolly hair and cardiomyopathy. *Acta Derm Venereol.* 2015;95:337-340.
5. Bakalakos A, Ritsatos K, Anastasakis A. Current perspectives on the diagnosis and management of dilated cardiomyopathy Beyond heart failure: a Cardiomyopathy Clinic Doctor's point of view. *Hellenic Journal of Cardiology.* 2018;59:254-261.
6. Sen-Chowdhry S, Syrris P, Prasad SK, et al. Left-Dominant Arrhythmogenic Cardiomyopathy. *Journal of the American College of Cardiology.* 2008;52:2175.
7. Corrado D, Basso C, Judge DP. Arrhythmogenic Cardiomyopathy. *Circulation Research.* 2017;121:784-802.

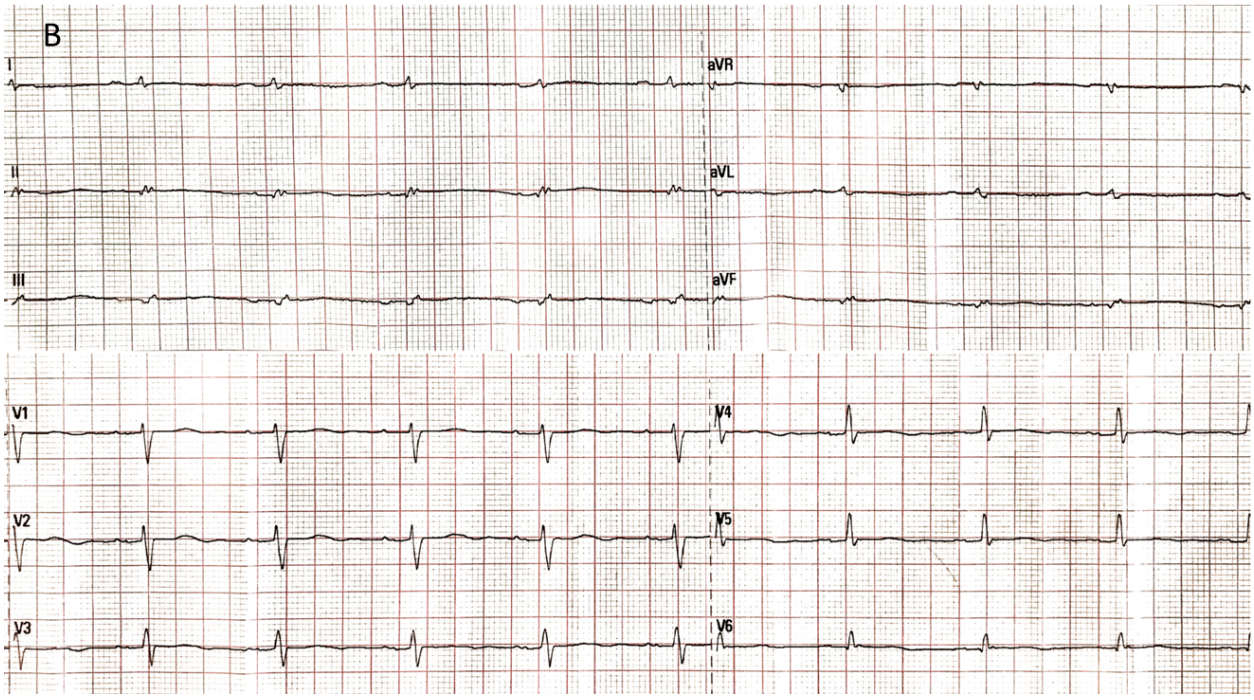
8. Gatzoulis KA, Kanoupakis E, Antoniou C-K, Sideris A, Kolettis TM. Reconsidering arrhythmic risk stratification in dilated cardiomyopathy – Beyond ventricular contractility and gene mutability. *Hellenic Journal of Cardiology*. 2019;60:196-197.

FIGURE LEGENDS

Figure 1. A. Pedigree chart. Case-index II(III) is the proband (arrow). Squares represent males and circles females. Black colour filled schemes represent patients with the pathogenic *DSP* variant. +/- indicates heterozygosity. LDAC: left dominant arrhythmogenic cardiomyopathy. B. The electrocardiogram of the proband.

Figure 2. A. Cardiac magnetic resonance images demonstrating sub-epicardial late gadolinium enhancement. B. The curly hair and palmoplantar keratoderma of the proband. C. Results of Sanger method. The duplication is pointed out by the arrow.


A
I
II
III
76y.o.
curly hair/ hyperkeratosis
72y.o. DSP +/-
curly hair/hyperkeratosis/ arrhythmias
70y.o.
50y.o.
curly hair
curly hair
curly hair
54y.o.
curly hair
25y.o.
curly hair
47y.o. DSP +/-
curly hair/hyperkeratosis/ LDAC
19y.o. DSP +/-
curly hair/hyperkeratosis/ no cardiac phenotype
46y.o.
4y.o.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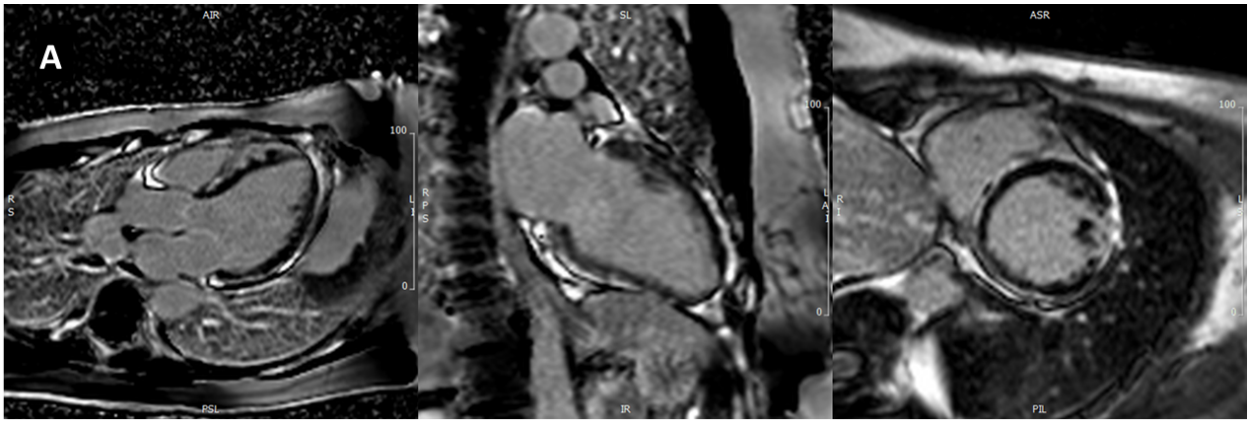
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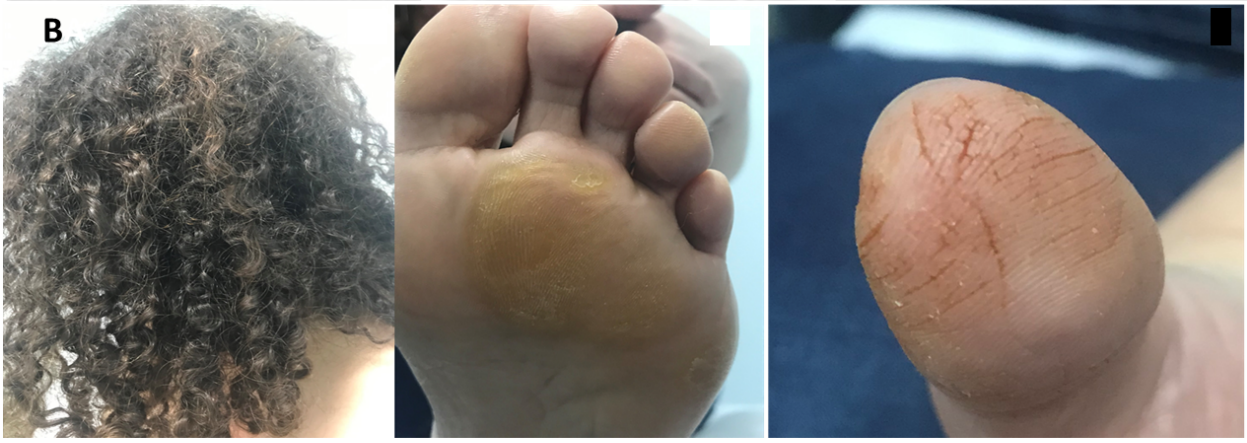
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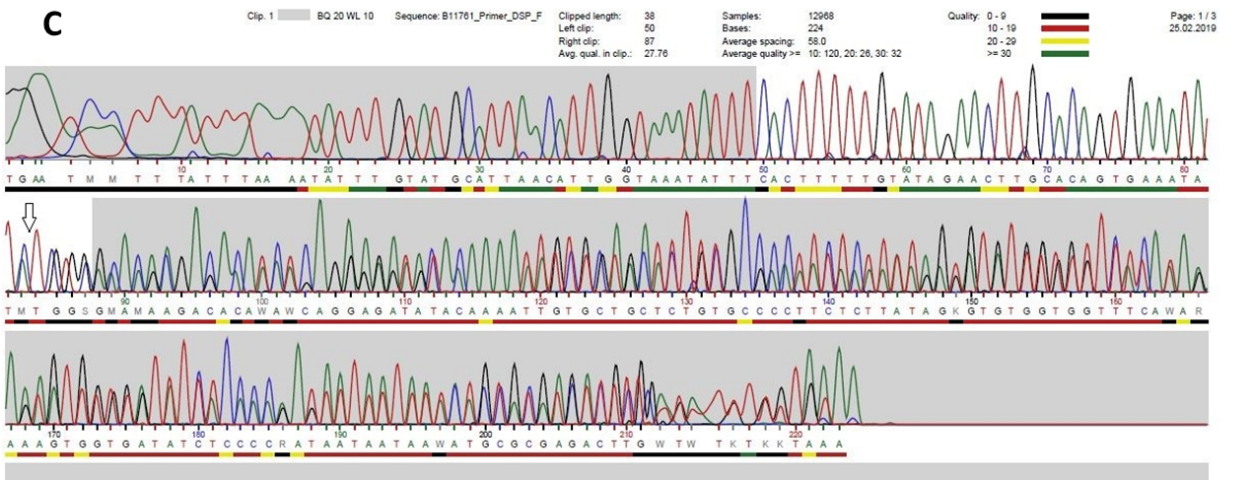
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