

More than meets the eye: Palmoplantar keratoderma and arrhythmogenic right ventricular cardiomyopathy in a patient with loss of the *DSP* gene



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Key words: arrhythmogenic right ventricular cardiomyopathy; cascade genetic testing; *DSP* gene; genetics; palmoplantar keratoderma; personalized medicine.

INTRODUCTION

Palmoplantar keratoderma (PPK) is a keratinizing disorder that can occur as an isolated phenomenon or in association with various systemic abnormalities. A woman with PPK was found through cascade genetic testing to have a heterozygous deletion in chromosome region 6p25.1p24.3 with loss of the *DSP* gene. Subsequent cardiac investigations revealed arrhythmogenic right ventricular cardiomyopathy (ARVC).

CASE REPORT

A 25-year-old woman with a 2.9-megabase heterozygous chromosomal deletion (6p25.1p24.3) was referred for phenotypic evaluation. This deletion was initially identified in her son, who had a ventricular septal defect, atrial septal defect, and patent ductus arteriosus surgically corrected. He is now 4 months old with normal development and no dysmorphic features. He has no features of palmoplantar keratoderma and no echocardiographic evidence of ARVC.

The patient herself is one of 4 children of nonconsanguineous parents. Although exact onset is unknown, she described having PPK for as long as she could recall. PPK initially affected only the soles of her feet. However, in the last 12 months, this progressed to involve her hands, in particular, her right first and second digits. She currently requires monthly podiatry appointments for paring of the soles. She had no other medical history and no hearing or visual impairment. She had no known

Abbreviations used:

ARVC: arrhythmogenic right ventricular cardiomyopathy
LV: left ventricle/left ventricular
PPK: palmoplantar keratoderma

cardiac issues and no limitations to exercise tolerance. Family history was also unremarkable with no known cardiac disease or PPK. Examination of the patient revealed large calluses on the plantar surfaces of both feet, predominantly affecting the pressure points (Figs 1, A and B). Small calluses were also noted on her hands consistent with nontransgradient PPK. There were neither stippling nor punctate lesions. She had no dysmorphic features or limb deformities. Her hair was wavy but not characteristic of woolly hair (Fig 2). She had no skin pigmentation changes, nail changes, or dental defects.

Detection of the deletion prompted cardiac investigations. Twenty-four-hour-Holter monitor found no arrhythmias. Transthoracic echocardiogram found left ventricular (LV) global hypokinesis and reduced ejection fraction (49%). Cardiac magnetic resonance imaging showed impaired LV function with an ejection fraction of 41% and extensive LV midwall and epicardial myocardium late gadolinium enhancement, suggestive of ARVC (Fig 3).

The heterozygous interstitial deletion on the short arm of chromosome 6: arr[hg19]6p25.1p24.3(58929

From The Royal Melbourne Hospital.

Funding sources: None.

Conflicts of interest: None disclosed.

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JAAD Case Reports 2020;6:804-6.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2020.06.025>



Fig 1. A and B, Palmoplantar keratoderma affecting patient's right and left soles.



Fig 2. Patient's hair.

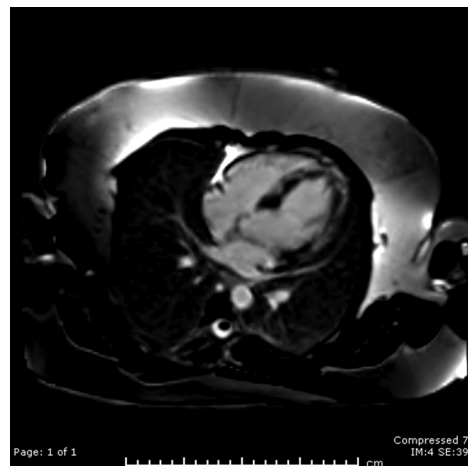


Fig 3. Cardiac magnetic resonance imaging. Long axis 4-chamber phase-sensitive inversion recovery acquisition of the heart following intravenous contrast, shows extensive mid myocardial and epicardial late enhancement.

65_8765236)x1 was initially detected with SNP microarray performed on her son. Segregation testing confirmed maternal inheritance of the deletion. This region contains 16 genes: *BLOC155*, *BMP6*, *CAGE1*, *DSP*, *EEF1E1*, ***F13A1***, ***FARS2***, *HULC*,

LY86, ***LYRM4***, *NRN1*, *RIOK1*, *RREB1*, *SLC35B3*, *SSR1*, *TXNDC5* (bold denotes disease association in OMIM).

Currently, the patient's son shows no signs of ARVC; because he carries the same heterozygous deletion as his mother, it is likely that he too will have ARVC in adulthood. The actual risk is difficult to quantify, as the penetrance of the *DSP* gene is not

well known. He will be advised to have lifelong cardiac follow up, considering ARVC in addition to congenital heart disease.

DISCUSSION

Chromosome 6pter-p24 deletion syndrome mostly involves 0.3-1.4Mb terminal deletions of 6p, with breakpoints within 6p25.3p23.¹ A 2.1Mb “commonly deleted region” is thought to confer the major syndromic features: developmental delay, craniofacial dysmorphism, hearing and language impairment, Dandy-Walker malformation, and eye anomalies. Cardiac abnormalities include atrial septal defect, patent foramen ovale, valvular defects and tetralogy of Fallot.²

Interstitial deletions of 6p25p25, excluding the commonly deleted region, as identified here, are rare.^{1,2} Features include orofacial clefting, short neck, clinodactyly/syndactyly, and brain, kidney, and heart abnormalities.¹ A 1.4-Mb deletion in 6p25.1p24.3 identified in 2 patients was associated with intellectual disability, feeding problems, and dysmorphism. Another 5.6-Mb interstitial deletion 6p25.1p24.3 manifested as developmental delay, hearing impairment, and dysmorphism.² No reports hitherto associate PPK or ARVC with a deletion in this region.

PPK are heterogeneous, often heritable disorders characterized by thickening of the palms and soles.³ Genes associated with PPK include *KRT9/1*, *SLURP1*, *GJB2*, *AQP5*, *SERPINB7*, *LOR*, *TRPV3*, *POMP*, *AAGAB*, *RHBDF2*, *DSG1*, *DSP*, *KRT6A/6B/16/17/14*, *CTSC*, *WNT10A*, *PKP1*, *JUP*, and *ATP2A2*, which all encode specific proteins.³ Thus, PPK often involves nails, teeth, and other organs. PPK is chronic and significantly affects quality of life. Furthermore, it can be associated with lethal cardiac abnormalities, hearing deficits, neuropathies, ophthalmic defects, and malignancies.

ARVC comprises fibrofatty myocardial replacement associated with syncope, ventricular arrhythmias, heart failure, and significant risk of

sudden death.⁴ Genes coding desmosomal proteins account for most pathogenic variations including ARVC. The first gene associated with ARVC was *JUP* causing Naxos disease (ARVC, PPK, and wooly hair).⁵

The *DSP* gene encodes desmoplakin, the major protein found in desmosomes, which are cell adhesion junctions in the epidermis and cardiac tissue.⁶ *DSP* mutations cause heterogeneous phenotypes with varying cardiac and dermatologic manifestations. Carvajal syndrome characterized by wooly hair, striate PPK, and dilated cardiomyopathy results from bi-allelic variants in *DSP*; 120 causative mutations identified are mostly at the 3' end of the *DSP* gene.⁶

To our knowledge, this is the first report of a heterozygous interstitial deletion in 6p25.1p24.3 removing the *DSP* gene causing PPK and ARVC. Although PPK is manageable, it may herald life-threatening cardiac conditions, here ARVC, warranting cardiac screening. This case also highlights the utility of genetic and cascade testing.

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