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CASE REPORT

A Novel Variant in the *Desmoplakin* Gene in One Case of the Rare Carvajal Syndrome with Dilated Cardiomyopathy: A Case Report and Literature Review

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Abstract: Carvajal syndrome is a rare hereditary cardiocutaneous syndrome caused by the variants of the *desmoplakin* (*DSP*) gene. In this study, we report a patient of Carvajal syndrome with a novel homozygous missense variant of *DSP* gene. We diagnosed a 7-year-old female patient with Carvajal syndrome characterized by dilated cardiomyopathy, palmoplantar keratoderma, woolly hair, and dental dysplasia, who disclosed a novel homozygous missense variant c.4597C > T (p.Q1533X) in exon 6 of the *DSP* gene found for the first time. Both her parents were heterozygous for the identified nonsense variant c.4597C > T (p.Q1533X) in *DSP* gene but neither showed evidence of Carvajal syndrome, indicating that this novel variant causes the disease in an autosomal recessive manner. Genotypes of Carvajal syndrome are even broader than so far anticipated. When patients with dilated cardiomyopathy, palmoplantar keratoderma, woolly hair, and dental dysplasia are found in clinical practice, Carvajal syndrome should be highly suspected, and family gene sequencing should be actively carried out.

Keywords: Carvajal syndrome, *desmoplakin*, genotype, variant, novel

Introduction

As a hereditary cardiocutaneous syndrome, Carvajal syndrome is characterized by dilated cardiomyopathy, palmoplantar keratoderma, woolly hair, and dental dysplasia.[1] Carvajal syndrome was first identified by Rao et al in 1996[2] and then was described in detail by Carvajal-Huerta in 1998.[3] Soon thereafter, in 2000, Norgett et al first found its etiology was mainly the variants of the *desmoplakin* (*DSP*) gene.[4] Carvajal syndrome tends to develop in childhood and is mainly autosomal recessive, with occasional autosomal dominant inheritance.[5] This syndrome is rare, and not many cases have been reported worldwide. Recently, we diagnosed one 7-year-old female with the Carvajal syndrome who visited hospital mainly due to the manifestations of de novo heart failure, which will be reported below with a literature review.

Case Presentation

The 7-year-old female patient was born normally as the first child of no-consanguineous parents of Chinese Han, with yellow-brown woolly hair on her forehead at birth. Before she was 4 years old, she had no health problems. Since then, palmoplantar keratoderma began to present on her palms and soles, and gradually spread to the fingers and toes. Meanwhile, she received irregular external ointment treatment. She developed dysplasia of deciduous teeth at the age of 5 years, with bilateral multiple incisors and molars oligodontia and dentition irregularity. At the age of 6 years, the child began to suffer from chest tightness, shortness of breath, and dyspnea when she was active, which gradually

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aggravated, and then unable to tolerate moderate daily activities. Shortly before coming to Shijiazhuang Great Wall Cardiovascular Hospital, she had been examined at Chongqing Children's Hospital, diagnosed with dilated cardiomyopathy and the corresponding treatment. The patient has a healthy 4-year-old younger brother and their parents are also healthy. There is no similar patient in the family.

On physical examination, the patient was not in acute distress. Her intelligence was normal. Her weight was 21kg (25–30 centile), and her height was 125cm (25–30 centile). Her body temperature was 36.4 °C, pulse 76 beats/min, respiratory rate 20 breaths/min, and blood pressure 88/65mmHg. She had sparse, dark-brown, and woolly hair (Figure 1A and B). She also suffers from agenesis of primary teeth with multiple oligodontia (7 teeth) and odontoloxia (Figure 1C). Bilateral jugular veins were dilated slightly. Thick breath sounds could be heard in bilateral lungs, without obvious dry or wet rales. The apical beat was diffuse, cardiac boundaries were enlarged to both sides, and apical pulsation was located at the 7th intercostal of the left axillary-front line. The heart rate was 76 beats/min with premature beats, and a grade 2/6 systolic blowing-like murmurs could be detected at the mitral valve auscultation area. The abdomen was flat and soft, with no tenderness. The liver was palpable 3 cm below the costal margin, and the spleen was not touched. Striate palmoplantar keratoderma was observed on both palms, fingers, soles, halluces, and heels, with a rough and chapped surface (Figure 1D and F). Leukonychia also could be found on toenails (Figure 1E). There was mild edema in both legs and joints movements barrier-free.

Laboratory tests showed that routine blood tests, blood glucose, liver function, renal function, electrolytes, myocardial enzymes, coagulation function, erythrocyte sedimentation rate, thyroid function, immunoglobulin (IgA, IgG, IgM), complement (C3, C4), procalcitonin, 25-hydroxyvitamin D3, trace elements were all normal. Screening indicators of hepatitis B virus, hepatitis C virus, adenovirus, Coxsackie, Epstein-Barr, syphilis, and human immunodeficiency virus were all negative and/or within the normal range. The B-type natriuretic peptide was 18,883.5 pg/mL (reference value: 0–450pg/mL). The 24-hour dynamic electrocardiogram indicated sinus rhythm, increased P wave amplitude, average heart rate of 74 beats/min, lowest heart rate of 55 beats/min, fastest heart rate of 139 beats/min, and 3561 ventricular premature beats (Figure 2A). Chest X-ray showed double-lung texture increased, together with heart shadow enlarged (Figure 2B). Cardiac magnetic resonance imaging (MRI) revealed that the heart was enlarged, especially the left heart,

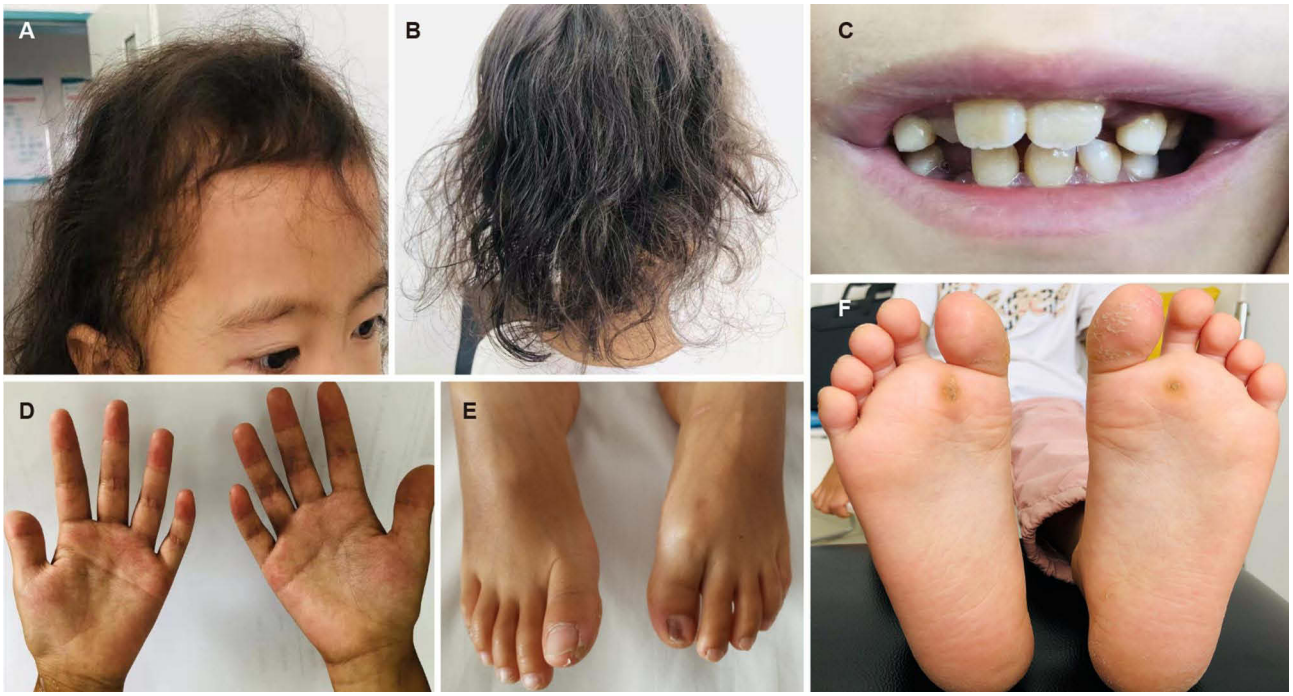

Figure 1 Clinical manifestations of our Carvajal syndrome patient with novel variants in the *desmoplakin* (*DSP*) gene. (**A** and **B**) Sparse, dark-brown, and woolly hair; (**C**) Oligodontia and odontoloxia; (**D**) Palmoplantar keratoderma (PPK) on both palms; (**E** and **F**) PPK on both toes and soles.

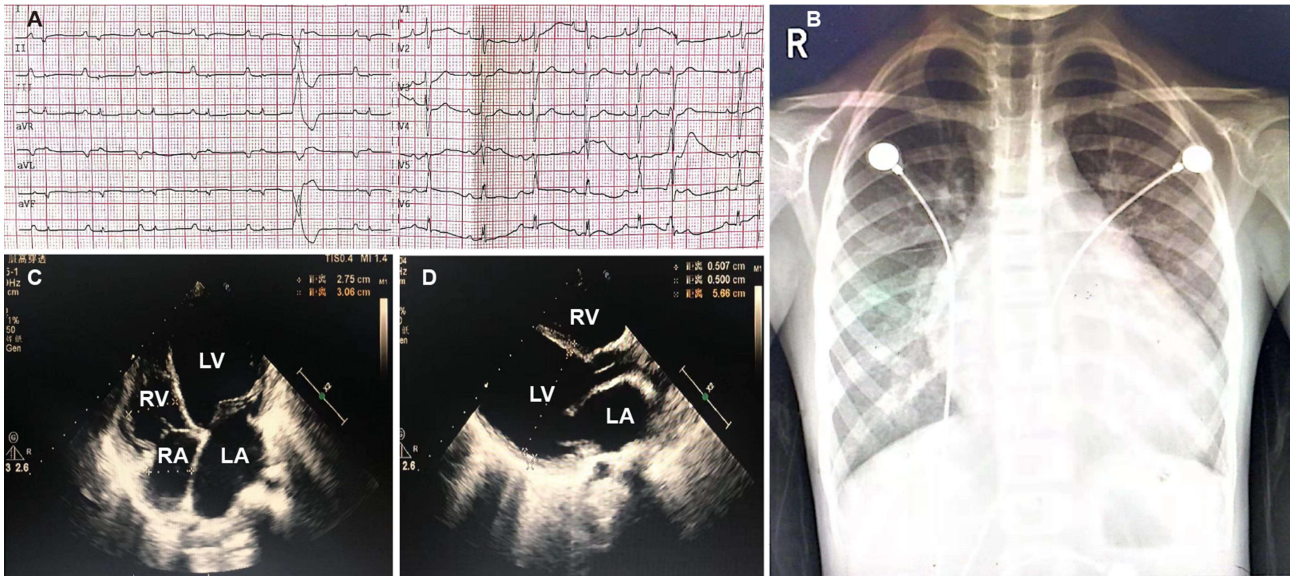

Figure 2 Electrocardiogram (ECG), Chest x-ray, and Echocardiography of our Carvajal syndrome patient with novel variants in the *desmoplakin* gene. (**A**) Echocardiography showing ventricular premature beats; (**B**) Chest x-ray showing dilated heart and increased cardiothoracic ratio; (**C** and **D**) Echocardiography showing dilated left and right ventricles.

and the ventricular systolic and diastolic functions decreased. Color Doppler echocardiography demonstrated left ventricular end-diastolic diameter was 55 mm, left atrium 28*36*56 mm, right ventricular end-diastolic diameter 29 mm, right atrial diameter 33mm, left ventricular ejection fraction 25%, global heart enlargement, partial myocardial non-compaction of the left ventricle, diffuse decrease in ventricular septum and left ventricular wall motion amplitude, mild aortic regurgitation, moderate mitral regurgitation, mild tricuspid regurgitation, pulmonary hypertension (mild), mild pulmonary artery regurgitation, the main pulmonary artery and its branches widened. The diastolic and contractile functions of the left and right ventricles all decreased (Figure 2C and D). Abdominal color ultrasound suggested mild hepatic congestion.

Genetic testing was performed by high-throughput whole-exome sequencing (MyGenostics Inc., Beijing, China). The proband disclosed a homozygous missense variant c.4597C > T (p.Q1533X) in exon 6 of the *DSP* gene, ie the nucleotide at position 4597 in the coding region changed from cytosine to thymine, resulting in a senseless variant of the amino acid (Glutamine) at position 1533 (Figure 3). In reference to relevant document database, ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/), Gnomad database (http://www.gnomad-sg.org/), and the Human Gene Mutation Database (https://www.hgmd.cf.ac.uk/ac/index.php), up to now, there is no report on the variation of this gene locus. The proband's parents were verified by Sanger sequencing (MyGenostics Inc., Beijing, China): they both carried the heterozygous variant c.4597C > T (p.Q1533X) in *DSP* gene and were both healthy (Figure 4).

According to clinical manifestations and *DSP* gene test results, the patient was diagnosed as (1) Carvajal syndrome; (2) dilated cardiomyopathy, heart failure (NYHA grade III), and arrhythmia as ventricular premature contraction. Then, the patient received comprehensive treatments: for heart failure and ventricular premature, using the diuretic, cardiotonic, inhibition of myocardial remodeling, inhibition of sympathetic excitation, traditional Chinese medicine decoction, and the symptoms were significantly improved; for palmoplantar keratoderma, oral vitamin A and E capsules were given once every other day, and 0.1% retinoic acid ointment and urea ointment were applied externally twice a day. One month later, the hand and foot palmoplantar keratoderma was better than before. The electrocardiogram remained premature ventricular contraction. Three months later, there was a significant improvement in palmoplantar keratoderma, and premature ventricular contraction was found to be reduced, but there was no significant change in color Doppler echocardiography. At present, the cardiology department and dermatology department are following up.

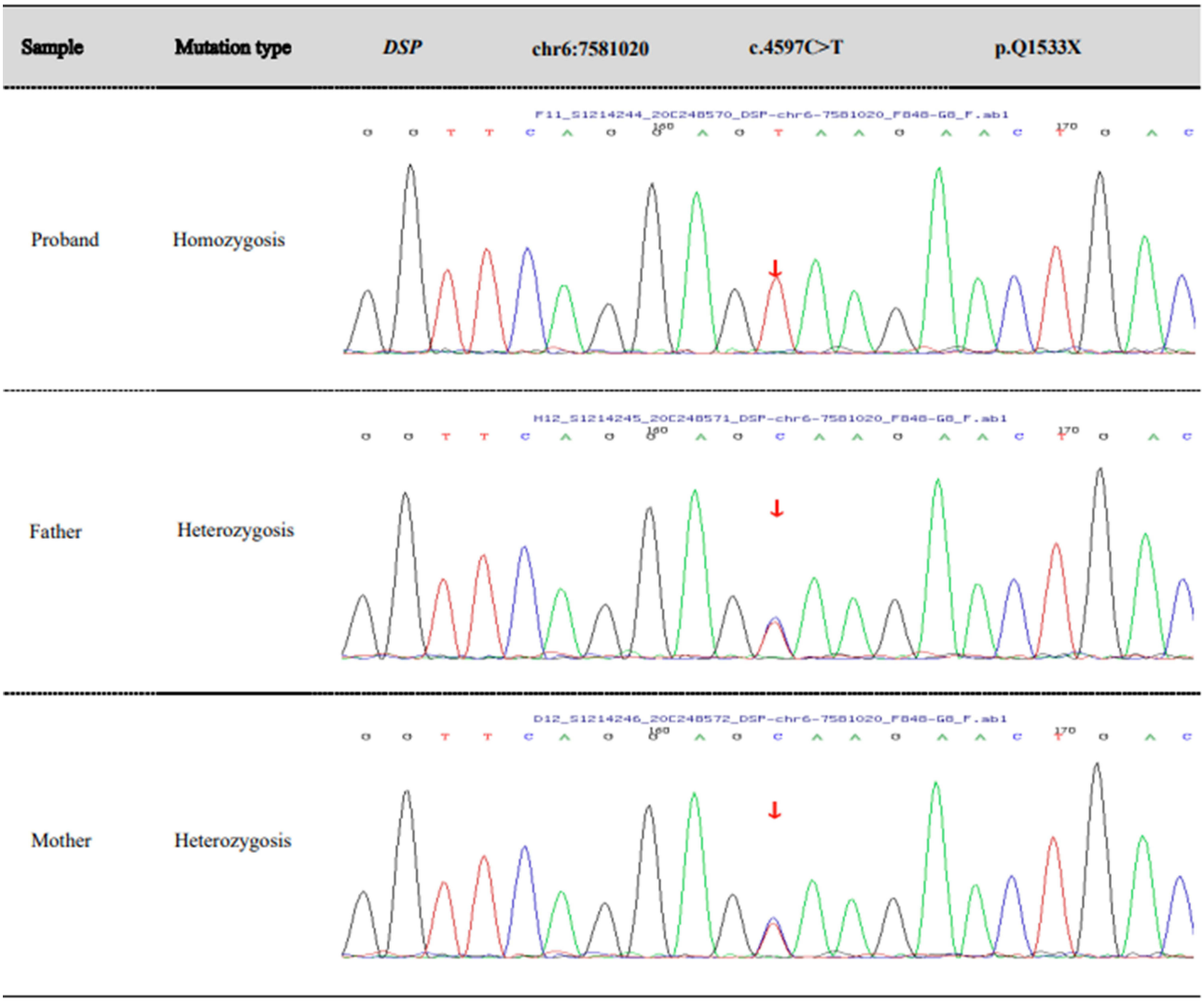

Figure 3 Variant analysis in the proband and her parents. Both the parents carried a heterozygous variant c.4597C > T (p.Q1533X) in *DSP* gene; Proband disclosed a homozygous missense variant c.4597C > T (p.Q1533X) in exon 6 of *DSP* gene.

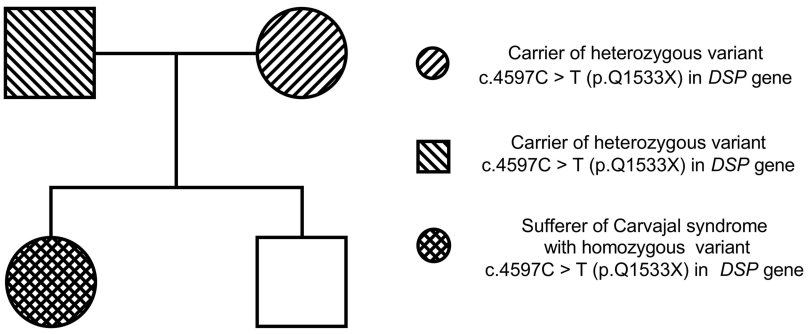

Figure 4 Pedigree chart of the family.

Discussion

This study, for the first time, identified a novel *DSP* variant of c.4597C > T (p.Q1533X) in exon 6, leading to the Carvajal syndrome in a sporadic case of patient, who manifested as dilated cardiomyopathy, woolly hair, palmoplantar keratosis,

and teeth loss. Both the parents carried this variant in a heterozygous state, and they were both healthy, which indicated that this novel variant causes Carvajal syndrome in an autosomal recessive manner.

At present, Carvajal syndrome is believed to be mainly secondary to *DSP* gene variant.[5] Desmosomes are tough and strong intercellular junctions, particularly abundant in the myocardium and epidermis, and *DSP* is the most abundant protein of desmosome.[6] Therefore, once the *DSP* gene variant occurs, the desmosome undergoes structural changes, resulting in phenotypic changes in the heart, skin and other related organs and tissues. We summarized the characteristics of patients with Carvajal syndrome in published literature in Table 1. Most patients with Carvajal syndrome are autosomal recessive inheritance, and the variant hotspots are mainly located in exons 23[7–12] or 24[4,13–16] of *DSP* gene, while a few of them were autosomal dominant inheritance, and the variant regions were mainly in other exons of *DSP* gene.[6,17–20] Furthermore, the earliest and most reports related to Carvajal syndrome were homozygous variants in *DSP* gene c.7901delG.[4] To date, apart from a few special cases of Carvajal syndrome without *DPS* variant,[5] many other *DSP* gene variants have been discovered successively[4,6–32] (Table 1). While, in this case, a novel homozygous missense variant c.4597C > T (p.Q1533X) in exon 6 of the *DSP* gene was found for the first time.

The phenotype of *DSP* variant is related to its inheritance mode. In the past, it was believed that Carvajal syndrome caused by *DSP* variant was a recessive inheritance, and in fact most cases were reported to be so.[4,7,10,11,13–17,24,26,27,32] Nevertheless, with the gradual increasing and deepening of studies, some reports have also found spontaneous variant[9,10,16,20,21,28] and dominant inheritance.[18,19,23,25,30] Whether inherited or acquired, the main clinical manifestations of Carvajal syndrome are woolly hair, palmoplantar keratoderma, and cardiomyopathy involving more frequently the left ventricle.[33] However, some cases showed biventricular[7,14,17,18,21] or right ventricular[4,12,13,21,23] involvement, and even no cardiac abnormalities.[16,19,20,24,32] In this case, the main manifestations of the proband were global dilated cardiomyopathy, partial left ventricular myocardial no-compaction, wool hair, palmoplantar keratoderma, and leukonychia. Other reports suggest that other features of Carvajal syndrome include paratrichosis (alopecia[11,12,27] or hypotrichosis)[4,7,14,20,21,24,28,29,32], dental anomalies (oligodontia[5,18–22,25] or enamel abnormalities)[14], fingernail/toenail abnormalities (onychodystrophy,[5,11,14,20,21] leukonychia,[19,21,22,28] onychorrhexis,[18] or onychogryphosis)[24], recurrent syncopes,[13,18,25] mucocutaneous blisters,[11,14,24] and other rare manifestations papules (such as bilateral external rotation of the fifth toe,[24] recurrent pharyngeal infections, recurrent diarrhea, left-sided hypoacusis,[25] and hand wart-like lesions).[26] The clinical phenotypes of Carvajal syndrome are varied, which is closely related to the variants of different *DSP* genes and their influence on the changes of N-terminal and C-terminal domain.[4,14,17]

Furthermore, what counts is some related diseases with similar clinical phenotypes need to be differentiated, especially the Naxos disease. With the main clinical features of arrhythmogenic right ventricular cardiomyopathy (ARVC), woolly hair, and palmoplantar keratoderma, Naxos disease was first described by Protonotarios et al in four families from Naxos island of Greece in 1986.[34] Because both show similar heart, hair and skin lesions, earlier studies considered Carvajal syndrome and Naxos disease as one syndrome, or Carvajal syndrome as a variant of Naxos disease.[8,23,35,36] However, with the increasing number of case reports and the deepening of investigations, researchers began to realize that Carvajal syndrome and Naxos disease are two different diseases. First, left cardiac involvement was more common in Carvajal syndrome,[5,9–11,21,22,24–26,28,29,31] while right-ventricle involvement was more common in Naxos disease.[23,36–38] Second, the plantopalmar keratoderma in Carvajal syndrome was often striate,[4,18,21,29,32] which in Naxos disease was often diffuse.[33,35–38] Third, Carvajal syndrome was often accompanied by dental abnormalities[5,14,18–22,25] or nail abnormalities,[5,11,14,18–22,24,28] while Naxos disease was less seen. However, with the increasing number of cases reported, the phenotypic differences between them gradually become less obvious. Then, genetic testing can be used to differentiate them——Carvajal syndrome is mainly caused by *DSP* gene variant,[4,7–32,34] while Naxos disease is mainly caused by *plakoglobin* gene variant.[34,37,38]

Moreover, woolly hair is generally the first sign that patients with Carvajal syndrome may be detected at birth. However, woolly hair is not unique to Carvajal syndrome; it is also found in Naxos disease, mentioned above, and in other rare diseases such as Menkes disease (MD),[39,40] skin fragility/woolly hair syndrome (SFWHS),[41,42] and tricho-dento-osseus syndrome (TDOS).[43,44] MD occurs due to X-linked genetic variant in the *ATP7A* gene. Woolly, sparse, lusterless, and tangled hair usually together with progressive neurodegeneration and connective tissue disturbances become the main features of MD.[39,40] Similar to Carvajal syndrome, SFWHS is also caused by variants of *DSP* gene

Table 1 Characteristics of Patients with Carvajal Syndrome in Published Literatures

First Author [Reference]	Pub	Patient Characteristics											
		Sex	Age	Country	DSPGM	He/ Ho	AD/AR	Initial Disease	At time	Clinical Features	CSP	Family	Outcome
Norgett[4]	2000	4M and 7F	NR	Ecuador	Exon 24, c.7901delG	Ho	AR	PPK and DCM	NR	DCM, WH, PPK	NR	3 families, 2 families CS and DSPGM	NR
Alcalai[13]	2003	F	NR	Israel	Exon 24, c.7402G > C (p. G2375R)	He	AR	RCS	16 y	ARVD, WH, PPK, RCS	NR	No CS, eight members DSPGM and SD	NR
Norgett[6]	2006	F	18 y	UK	Exon 14, c.608ATinsA (QSQFTDARKI)	He	NR	PPK	3 y	ARVD, BCM, WH, HoT, PPK	NR	Father CS and SD, no DSPGM	ICD, Cardiac death
Uzumcu[7]	2006	M	4 y	Turkey	Exon 23 c.3799C > T (p. R1267X), and exon 13 of JUP c.2089 T > A (p.L697M)	Ho	AR	DCM	3.5 y	ABVC, WH, PPK	Yes	No CS, Parents JUPGM	NR
Prompona[8]	2007	M	12 y	Germany	Exon 23, DSP (2bp deletion, details NR)	Ho	NR	PPK	2 y	DCM, WH, PPK	Yes	Brother CS and Cardiac death, NR DSPGM	ICD, HT
Tanaka[17]	2009	F	5	Brazilian	Exon 18, c.2516del4 (p. H839fsX23); exon 23, c.3971del4 (p.N1324fsX23)	He	AR	Face erosions	Birth	BCM, PPK, alopecia	No	No CS, parents DSPGM	NR
Mahoney[14]	2010	F	14 y	Finland	Exon 24 c.6310delA (p.A2655D)	He	AR	Skin fragility	Birth	BCM, WH, HoT, PPK, MCB, OCD, ED	No	No CS, parents and two siblings DSPGM	Cardiac death
Krishnamurthy[9]	2010	F	11 y	India	Exon 23, c.3901C > T (p.Q1301X)	Ho	SM	HF	11 y	DCM-L, WH, PPK	Yes	No CS	MT
Chalabreysse[18]	2011	M	22 y	France	Exon 14 c.1790 C > T (p. S597L)	He	AD	Fainting	17 y	DCM-B, WH, PPK, OD, OCR, RCS	NR	Father and brother CS and DSPGM	HT
Williams[10]	2011	M	6 y	Germany	Exon 23, c.5208_5209delAG (p.G1737fsX1742)	Ho	SM	DCM-L	5 y	DCM-L, WH, PPK	Yes	Brother CS and DSPGM	HF death
		M	10 y	Germany	c.5208_5209delAG (p.G1737fsX1742)	Ho	SM	PPK	2 y	DCM-L, NCLVM, WH, PPK	Yes	Brother CS and DSPGM	HT

Keller[21]	2012	NR	15 y	NR	c.1748T > C (p.L583P)	He	SM	VVP	2 m	DCM-B, WH, HoT, PPK, OCD	NR	Normal	ICD
		F	22 y	NR	c.1691C > T (p.T564I)	He	NR	NR	13 y	DCM-R, WH, HoT, LN, OD	No	NR	ICD
Boulé[22]	2012	M	29 y	France	c.1691C > T (p.T564I)	He	NR	DCM-L	12 y	DCM-L, WH, PPK, LN, OD	NR	Son CS and DSPGM	ICD
Nehme[5]	2012	M	57 y	France	No DSPGM	NI	NI	CD	3 y	DCM-L, NCLVM, WH, PPK, OD, OCD	No	Normal	NR
Tomberli[23]	2013	F	37 y	Italy	c.878A > T (p.E293V)	NR	AD	CA	37 y	ARVC, PPK	NR	CS and DSPGM NR, Brother SCD	NR
Antonov[11]	2015	M	3 y	DR	Exon 23, c.4198C > T (p.R1400X), c.6850C > T (p.R2284X); exon 16, c.2636A > G (p.D879G)	He	AR	Skin blisters	2 y	DCM-L, alopecia, PPK, OCD	NR	Normal	HT
Pigors[32]	2015	M	6 y	Romania	Exon 24, c.7566_7567delAAinsC (p.R2522Sfs*39), c.7756C > T (p.R2586*)	He	AR	HoT	5 y	HoT, PPK,	No	No CS, parents DSPGM	NR
		M	14 y	Germany	Exon 9, c.1067C > A (p.T356K); exon 16, c.2131_2132delAG (p.S711Cfs*4)	He	AR	HS	1 y	DCM, WH, HoT, PPK	NR	Brother CS and DSPGM	HT
		F	10 y	Germany	Exon 9, c.1067C > A (p.T356K); exon 16, c.2131_2132delAG (p.S711Cfs*4)	He	AR	HoT	Birth	DCM, WH, HoT, PPK	NR	Sister CS and DSPGM	NR
Molho-Pessach[24]	2015	M	5 y	Israel	c.3924delG (H1309Tfs*1348)	Ho	NR	PPK	1 y	DCM-L, WH, PPK, and bilateral external rotation of the fifth toe	NR	No CS, parents DSPGM	ICD
		F	59 y	Israel	c.7111C > A (p.Q2371K)	Ho	AR	Plantar blisters and erythema	Birth	WH, PPK, HoT, OCG	NR	Sister CS and DSPGM, siblings SD	ICD

(*Continued*)

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Table 1 (Continued).

First Author [Reference]	Pub	Patient Characteristics											
		Sex	Age	Country	DSPGM	He/ Ho	AD/AR	Initial Disease	At time	Clinical Features	CSP	Family	Outcome
		F	NR	Israel	c.7111C > A (p.Q2371K)	Ho	AR	Plantar blisters and erythema	Birth	WH, PPK, papules, HoT	NR	Sister CS and DSPGM, siblings SD	SCD
Bitar[19]	2016	M	17 y	USA	Exon 14, c.1865T > C (p.L622P)	He	AD	CD	Birth	WH, PPK, OD, LN	NR	Normal	NR
Finsterer[25]	2016	F	43 y	Austria	c.1678A > T (p.I560F)	NR	AD	Weakness and vertigo	13	LVHT, WH, PPK, OD, RPI, RCS, LSH, RDI	No	Father and brother CS, brother DSPGM	ICD
Ramoğlu[26]	2017	F	12 y	Turkey	c.4650_4651delTG (p.V155Efs*75)	Ho	AR	HF	5 y	DCM-L, WH, PPK, HWLL	Yes	Siblings CS, parents DSPGM	LVAD, HT
		F	10 y	Turkey	c.4650_4651delTG (p.V155Efs*75)	Ho	AR	HF	6y	DCM-L, WH, PPK, HWLL	Yes	Siblings CS, parents DSPGM	MT
Paller[27]	2017	F	10 y	Ireland	c.1748T > C (p. L583P)	He	AR	PPK	9 m	DCM, alopecia, PPK, DA, recurrent impetigo and bacteremia	NR	NR	HT
Erolu[12]	2018	M	4 y	Turkey	Exon 23, c.3564T > A (p.Y1188X), c.4395T > A (p.Y1465X)	He	AR	VT	4 y	ARVD, Alopecia, PPK	NR	No CS, parents DSPGM	ICD
Akdogan[28]	2018	F	8 y	Turkey	c.4650_4651delTG (p.V155Efs*75)	Ho	SM	PPK	1 y	DCM-L, WH, HoT, PPK, LN	Yes	Sister CS and DSPGM	NR
Yermakovich[15]	2018	M	11 y	Belarus	Exon 24, c.7123G > C (p.G2375R), c.6986T > C (p.L2329P)	He	AR	PPK	2 y	DCM-B, WH, PPK	NR	Sister CS, sister and parents DSPGM	HT
Guerra[29]	2019	F	5 y		Exon 23, c.4788delA (p.E1597Sfs*5); exon 24, c.6091_6092delTT (p.L2031Gfs*29)	He	NR	PPK	5 y	ALVC, WH, HoT, PPK	NO	NR	ICD
Zhang[20]	2019	M	10 y	China	Exon 14, c.1790C > T (p.S597L)	He	SM	PPK	3 y	WH, HoT, PPK, OCD, OD	No	Normal	MT

De Gregorio[30]	2020	F	37 y	Italy	c.878A > T (p.E293V)	He	AD	CA	37 y	RV wall aneurysms, PPK	NR	No CS, mother and uncle DSPGM, brother SCD	ICD
Wu[16]	2020	F	3 y	China	Exon 24, c.5152dupT (p.L1718Ffs*15), c.C6478T (p.R2160X)	NR	SM	PPK	8 m	WH, PPK	No	No CS, mother DSPGM	MT
Akintoye[31]	2021	M	47 y	USA	c.6510_6511insCT (p.N2171Lfs*17), c.27315G > A (Intronic)	NR	SM	HF	47 y	DCM-L, WH, PPK	NR	Siblings NS and SCD, no DSPGM	ICD

Abbreviations: ABVC, arrhythmogenic biventricular cardiomyopathy; AD, autosomal dominant; ALVC, arrhythmogenic left-sided ventricular cardiomyopathy; AR, autosomal recessive; ALVC, arrhythmogenic left ventricular cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; ARVD, arrhythmogenic right ventricular dysplasia; BCM, biventricular cardiomyopathy; CA, cardiac arrest; CD, cutaneous disease; CM, cardiomyopathy; CSP, consanguineous parents; CS, Carvajal syndrome; DA, dental abnormalities; DCM, dilated cardiomyopathy; DCM-B, dilated cardiomyopathy with bi-ventricles; DCM-L, dilated cardiomyopathy and left ventricle more obvious; DCM-R, dilated cardiomyopathy and right ventricle more obvious; DSPGM, desmoplakin gene mutation; DR= Dominican Republic; ED, enamel dysplasia; F, female; He, heterozygosis; HF, heart failure; Ho, homozygosis; HoT, hypotrichosis; HWLL, hand wart-like lesions; JUP, plakoglobin gene; LCM, left cardiomyopathy; LDCM, dilated cardiomyopathy; LSH, left-sided hypoacusis; LV, left ventricle; LVAD, left ventricular assist device; LN, leukonychia; LVHT, left ventricular hypertrabeculation; HS, hair shedding, HT, heart transplantation; m, months, M, male; MCB, mucocutaneous blisters; MT, medication treatment; NB, neuroblastoma; NCLVM, non-compaction of the left ventricular myocardium; NI, not involved; NR, not reported; NS, Naxos syndrome; OCD, onychodystrophy; OCG, onychogryphosis; OCR, onychorrhexis; OD, oligodontia; PPK, plantopalmar keratoderma; Pub, publication year; RCM, right cardiomyopathy; RCS, recurrent syncopes; RDI, recurrent diarrhea; RPI, recurrent pharyngeal infections; RV, right ventricular; RVDP, right ventricular dysplasia; SCD, sudden cardiac death; SD, sudden death; SM, spontaneous mutation; VT, ventricular tachycardia; VVP, valvulopathy; WH, wooly hair; y, years.

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and presents with woolly hair and palmokeratosis. However, SFWHS is often accompanied by increased skin fragility and recurrent blisters at birth.[41,42] TDOS is a rare autosomal-dominant ectodermal dysplasia, with woolly hair at birth, caused by variants in the *DLX3* gene. However, as patients with TDOS age, their hair becomes thicker and straighter. Besides, almost all TDOS patients exhibit dental abnormalities.[43,44] It is worth noting that neither SFWHS nor TDOS will present with cardiac disease, which can be as the basis for distinguishing them from Carvajal syndrome.[41–44]

Our study has several limitations. First, apart from the proband and her parents, we have been unable to trace the genotypes of other family members. Second, due to the limited information available, we could not further explore the function of the mutated exon. Third, more cases need to be collected to obtain the epidemiological data.

Conclusion

In this study, we presented a case of Carvajal syndrome performed as global dilated cardiomyopathy sparse woolly hair, striate palmoplantar keratoderma on both palms and soles, leukonychia, and dental dysplasia. A novel heterozygous variant c.4597C > T (p.Q1533X), never reported before, was found in exon 6 in *DSP* gene in our patient); there is moderate evidence for this variant to be considered pathogenic (MutationTaster, http://www.mutationtaster.org).[45] The parents were both heterozygous for the identified nonsense variant without the phenotype of Carvajal syndrome, implying that the novel variant in *DSP* caused the disease in an autosomal recessive manner. As more cases are reported, more clinical phenotypes of Carvajal syndrome are emerging. Thus, future studies need to pay more attention to the correlation between genotype and phenotype.

Abbreviations

ARVC, arrhythmogenic right ventricular cardiomyopathy; *DSP, desmoplakin*; MD, Menkes disease; MRI, magnetic resonance imaging; SFWHS, skin fragility/woolly hair syndrome; TDOS, tricho-dento-osseus syndrome.

Ethics Approval and Informed Consent

All procedures performed in this study involving human participants were approved by the Ethics Committee of the Shijiazhuang Great Wall Cardiovascular Hospital. Publication of the case details was also approved by the Shijiazhuang Great Wall Cardiovascular Hospital.

Consent for Publication

Written informed consent was obtained from the patient's father for publication of this Case report and any accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no conflicts of interest in this work.

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