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Discovery of Novel Desmoplakin Mutations in Carvajal Syndrome: Two Case Reports and Literature Review

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Keywords:

Carvajal syndrome; Woolly hair; Palmoplantar keratoderma; Dilated cardiomyopathy; Desmoplakin mutations

1. Abstract

1.1. Background: Carvajal syndrome(CS) is an autosomal dominant(AD) or autosomal recessive(AR) genetic cardiocutaneous syndrome that associates with mutations in desmoplakin (DSP) gene and characterized by woolly hair, palmoplantar keratoderma(PPK) as well as left ventricular dilated cardiomyopathy (DCM). Methods: In this report, whole exome sequencing(WES) was conducted to examine the mutations of patients and the Sanger sequencing was applied to identify suspicious variants in their parents. Results: A 7 years old female patient was admitted to our center due to heart failure. She had curly hair at birth, developed palmoplantar keratosis at the age of 4 years, and heart failure at the age of 6 years. WES result suggested she carried a novel homozygous variant c.4597C>T (p.Q1533X) in DSP gene, whereas her parents carried the same variant in heterozygous state. Patient 2 presented with similar symptoms and carried a de novo heterozygous variants c.1853A>C (p.H618P) in DSP gene. Conclusion: This report extended the spectrum of CS associated DSP gene mutations and provided important clinical references.

2. Introduction

Carvajal syndrome (CS) is a rare hereditary cardiocutaneous syndrome which mainly occurred in children and triggered by mutations in desmoplakin (DSP) gene [1] following either autosomal recessive or autosomal dominant inheritance pattern [1-2]. The presentations of CS are characterized by woolly hair, palmoplantar keratoderma(PPK) and left ventricular dilated cardiomyopathy (DCM) [1,3-4]. It can also be associated with other manifestations such as developmental delay, oligodontia, mucocutaneous blisters and heart failure, which has not been reported among Chinese [5-7]. Previous studies suggested that most DSP mutations are discovered to be located in exon 23 and exon 24 [Table 1] [2], although several unidentified genes remain. In this study, we presented two pediatric CS cases that presented with early on-set severe heart failure and associated with novel DSP mutations, in addition to a systemic literature review. To the best of our knowledge, this is the first report describing CS with severe heart failure in China.

Table 1: Desmoplakin mutations so far reported in association with Carvajal syndrome.

EO	AOP（y）	Sex	DCM	prognosis	FH	TA	Mutation	AR/AD	Reference
Finland	14	Female	+	SD	-	-	c.7964C>A,c.6310delA	AR	[8]
*	11	Female	+	HTX	-	-	c.C7960T、p.Q2654X	AR	[9]
*	14	Female	+	ICD,SD	+	+	c.7902delG	AD	[10]
Ecuador	6 patients		+	*	+	-	c.7901deIG	AR	[11]
Turkish	19	Female	+	HTX	-	-	c.7780delT	AR	[12]
*	11	Male	+	HTX	+	-	c.7123G>C, c.6986T>C	AR	[6]
*	5	Female	-	*	+	-	c.7123G>C、c.6986T>C	AR	[6]
Arab	16	Female	+	ICD	+	-	c.7123G>C	AR	[13]
Arab	21	Female	+	SD	+	-	c.7111C>A	AR	[14]
Arab	59	Female	+	ICD	+	-	c.7111C>A	AR	[14]
Ameirca	47	Male	+	ICD	-	-	c.6510_6511insCT (p.Asn2171Leufs*17)	AR	[3]
*	10	Male	+	HTX	+	-	c.5208-5209delAG	AR	[15]
China	3	Female	-	*	-	-	c.5152dupT、c.C6478T	AR	[16]
*	5	Female	+	HTX	+	-	c.4650-4651delTG	AR	[17]
*	8	Female	+	*	+	-	c.4650-4651delTG	AR	[17]
Arab	5	Male	+	ICD	-	-	c.3924delG	AR	[14]
Indian	11	Female	+	*	-	-	c.3901C>T	AR	[18]
Turkish	4	Male	+	lCD	-	-	c.3564T>A, c.4395T>A	AR	[19]
Lebanon	17	Male	+	*	-	+	c.1865T>C	AD	[20]
*	21	Male	+	HTX	+	+	c.1790C>T	AD	[21]
China	10	Male	+	*	-	+	c.1790C>T	AD	[22]
Caucasian	13	Female	+	ICD	-	-	c.1748T>C (p.Leu583Pro)	AR	[23]
Caucasian	29	Male	+	ICD	+	+	c.1691C>T (p.Thr564Ile)	AD	[24]
Caucasian	10	Male	+	*	+	+	c.1691C>T	AD	[24]
Caucasian	22	Female	+	ICD	-	+	c.1691C>T	AD	[23]
Caucasian	43	Female	+	ICD	+	+	c.1678A>T	AD	[1]
Caucasian	41	Male	+	SD	+	+	c.1678A>T	AD	[1]
*	3	Female	+	HTX	-		p.R1400X、p.R2284X	AR	[24]
Turkish	3.5	Male	+	SD	-		R1267X	AR	[25]
*	37	Female	+	*	+	+	c.878A>T	AD	[26]
*	3	Female	+	ICD,SD	+	+	c.608 ins	AD	[10]

AOP: age of patient, EO: ethnic origin, FH: family history, TA:tooth agenesis, DCM:dilated cardiomyopathy, SCD: sudden cardiac death, HTX: heart transplantation.

3. Case Reports

3.1. Patient 1

A 7-year-old girl complaining dyspnea and chest distress for 2 days was admitted to our hospital due to heart failure. She was born naturally at term with woolly hair and developed keratoderma at the age of 4. The patient was otherwise asymptomatic until a year ago when she developed intermittent dyspnea and chest distress with no identified cause. The patient has not been systemically reviewed and treated before. Her parents were non-consanguineous and no family history was identified. Physical examination showed that the patient was delayed in development with 110cm tall (less than the 3rd percentile of the same age) and a weight of approximately 17kg (less than the 3rd percentile of the same age). Further examination revealed heart failure presentations including jugular venous distension, hepatomegaly and an elevated plasma NT-proBNP level of 18883pg/mL (reference 0-450pg/ml). Electrocardiography (ECG) identified right-axis deviation with decreased voltage and sporadic premature ventricular complex. Echocardiogram showed a severely dilated heart with biventricular dysfunction and moderate mitral regurgitation. The systolic function was also impaired with an EF of 26%. As shown in figure 3A, whole exome sequencing (WES) was conducted and the results showed that the patient carried a homozygous nonsense variant on exon 23 of the DSP gene (c. 4597C > T, p. Q1533X). Function analysis indicated that this point mutation associated with a truncation of the desmosomal areolar protein at glutamine position 1533, and may induce disease by degradation of the mutant protein due to nonsense mediated mRNA degradation (NMD). Further Sanger sequencing tests confirmed heterozygous variation at this locus in both of her parents. (Figure 3B and C). To the best of our knowledge, the Q1533X was a novel variant that has not been reported previously. However, according to the recommendations of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) [27], this variant was qualified to be classified as culprit gene mutation. Based on above clinical presentations and evidence, the patient was eventually diagnosed as CS. The patient's heart failure was corrected and successfully discharged after receiving diuresis, heart rate reduction, ventricular remodeling inhibition and other supporting treatments.

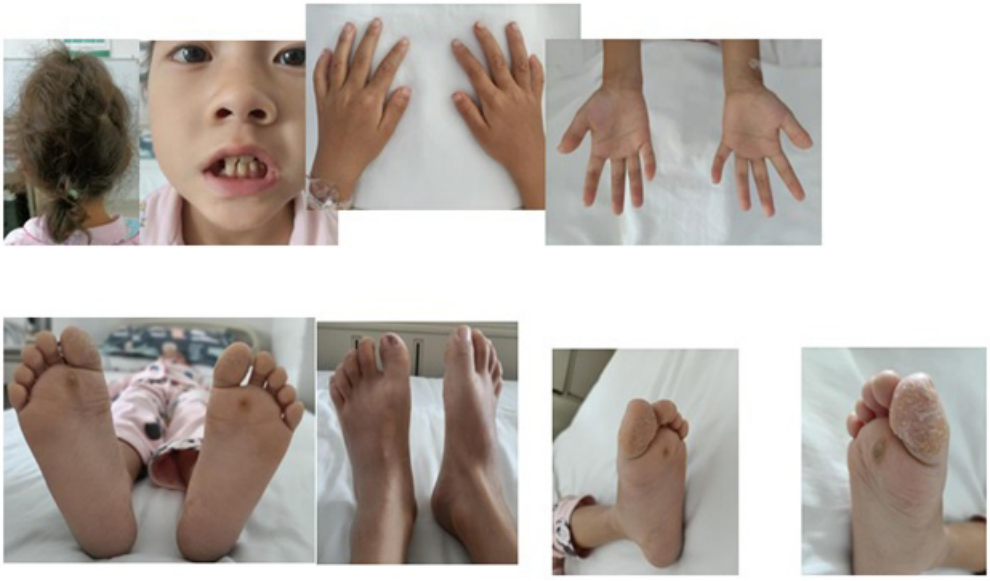


Figure 1: clinical features of patient 1: A: Woolly, curly, rough hair; B: Malaligned dentition; C-D: Rough, keratinized, thickened skin of both hands E-H: diffuse skin thickening of both feet and focal plantar keratoderma.

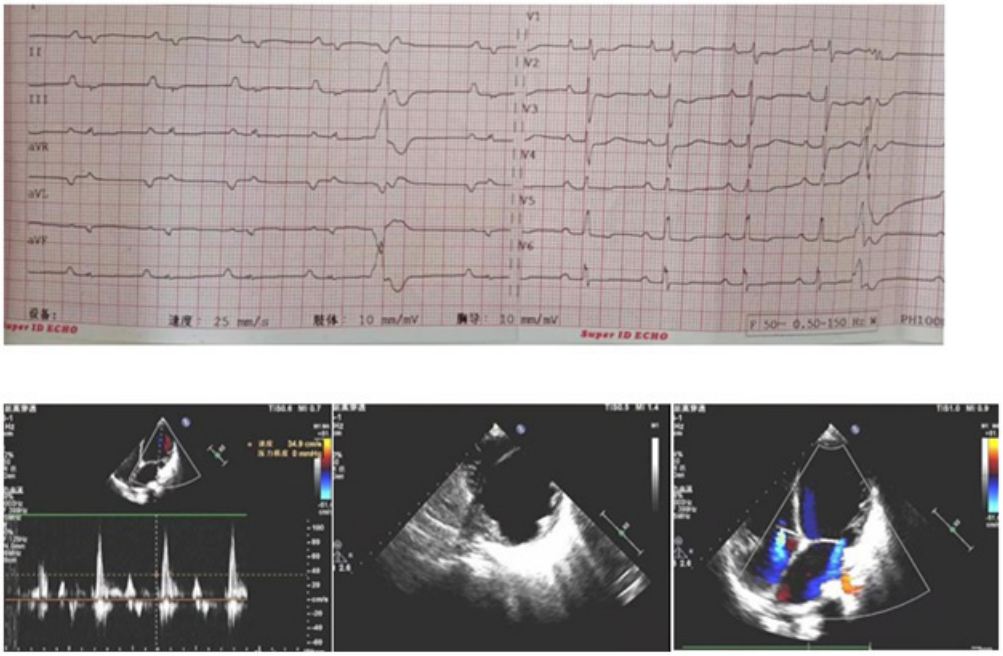


Figure 2. Abnormal cardiac manifestations of patient 1：A: ECG showed sinus rhythm and a premature ventricular complex. B-D: Echocardiogram ；LA30*36*55mm，LV56mm，RAd28mm，RVd31mm（transverse diameter, EF26%.

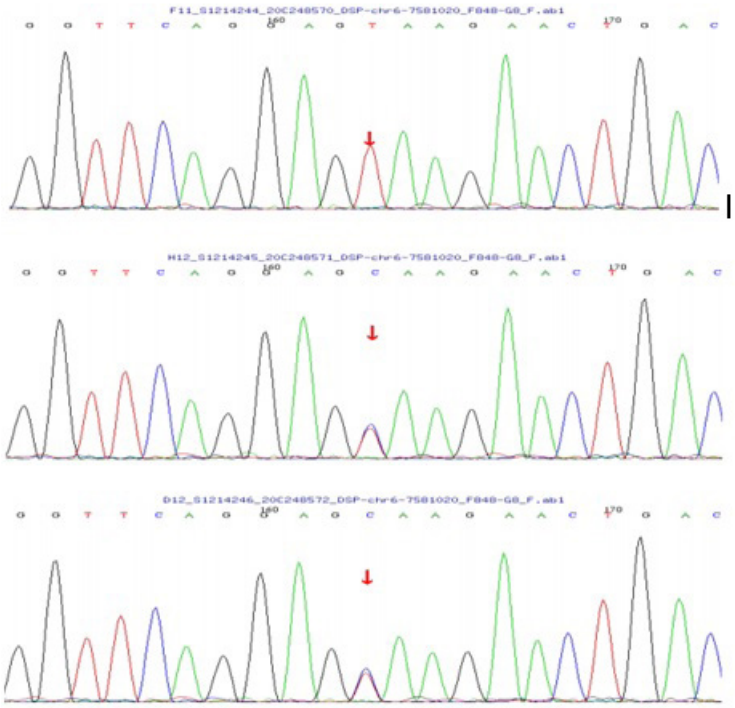


Figure 3. Electropherograms of sanger sequencing showing homozygous and heterozygous *DSP* c.4597C>T (p.Q1533X) identified in patient 1 (A) and her parents (B, father; C, mother).

2.2 Patient 2

A 9-year-old boy complaining of dyspnea and edema was admitted to our hospital due to heart failure (HF). Similar to patient 1, patient 2 was born naturally at term with woolly hair and presented with keratoderma at the age of 4. The patient was otherwise asymptotic until 3 months ago when he developed intermittent cough, dyspnea and activity restriction. No Family history was identified. Physical examination showed the patient also suffered from development delay and presented with signs of heart failure including jugular venous distension and hepatomegaly as well as an increased plasma NT-proBNP level of 12919.8pg/ml (reference 0-450pg/ml). ECG showed multiple abnormalities including positive ptfv1 sign and frequent polymorphic premature ventricular contractions (Figure 5 A-D). Echocardiogram showed a severely dilated heart with biventricular dysfunction and moderate mitral regurgitation, pulmonary hypertension as well as severe tricuspid

regurgitation. The systolic function was severely impaired with an EF of 18%. Cardiac MRI confirmed dilatation of both ventricles with reduced systolic function (Figure 5 H, I). Contrast-enhanced cardiac MRI indicated myocardial injury in the ventricular wall of the central segment to apical segment of the inferior wall of the left ventricle (Figure 5 J, K). Next, WES identified a de novo heterozygous DSP variants c.1853A>C (p.H618P) in Exon 14 in patient 2, which was absent from neither of his parents examined by sanger sequencing (Figure 6). This variant was recorded in the OMIM database in association with symptoms resemble CS including dilated cardiomyopathy with woolly hair, palmoplantar keratoderma, and tooth agenesis (DCWHKTA)(OMIM#615821). Multiple in silico algorithms supported a deleterious effect of the mutation gene. Moreover, in vitro expression analysis in primary human keratinocytes demonstrated a reduction of H618P mutant Cx43 membrane intensity to less than 80% compared to wildtype DSP (PMID: 26604139). In summary, this mutation was highly possible a driver mutation for autosomal dominant DCWHKTA according to ACMG recommendations。

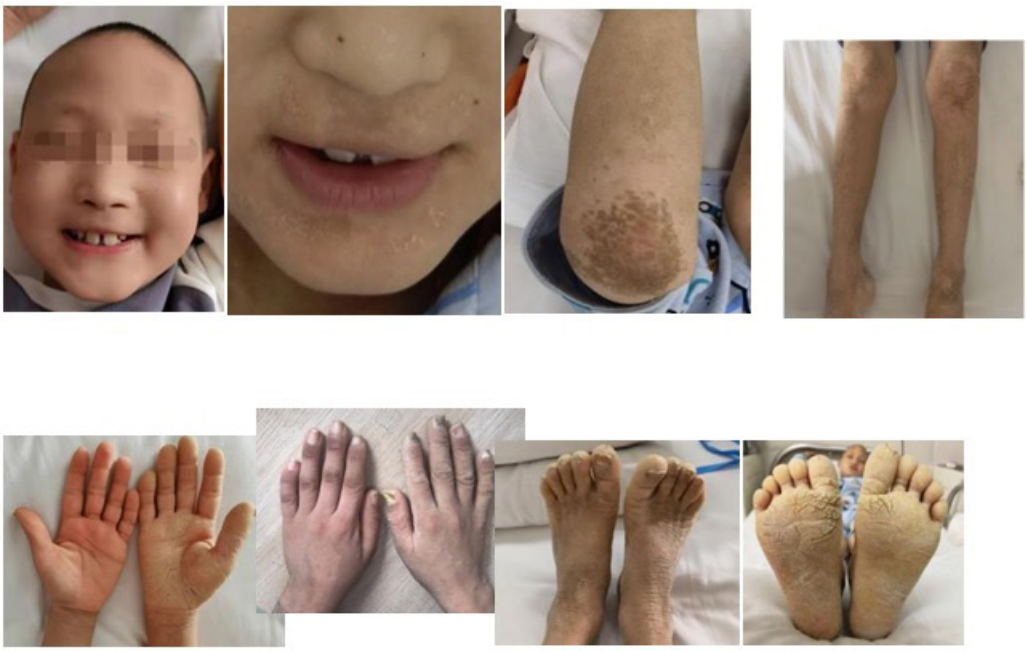
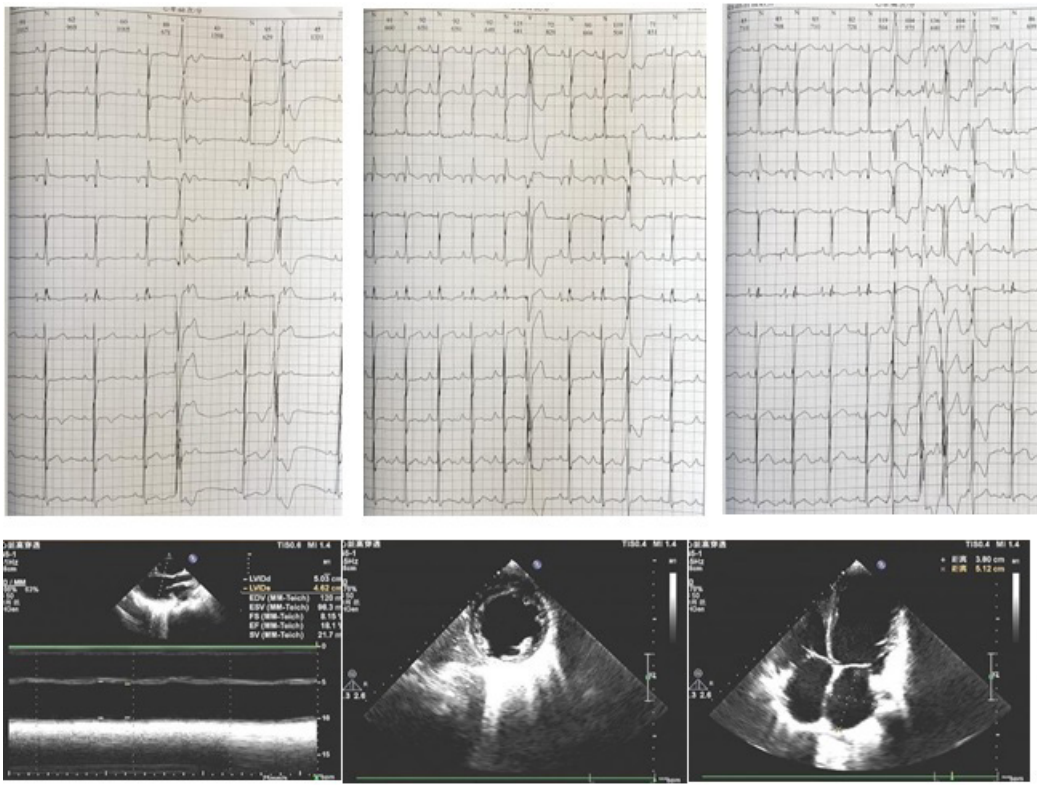


Figure 4. clinical features of proband 2 ： A: sparse eyebrows; B: affected dentition; C:-D: skin thickening, hyperplastic plaque; E and F: keratosis of the palms; G and H: thick, white, and dystrophic finger nails, palmoplantar hyperkeratosis.



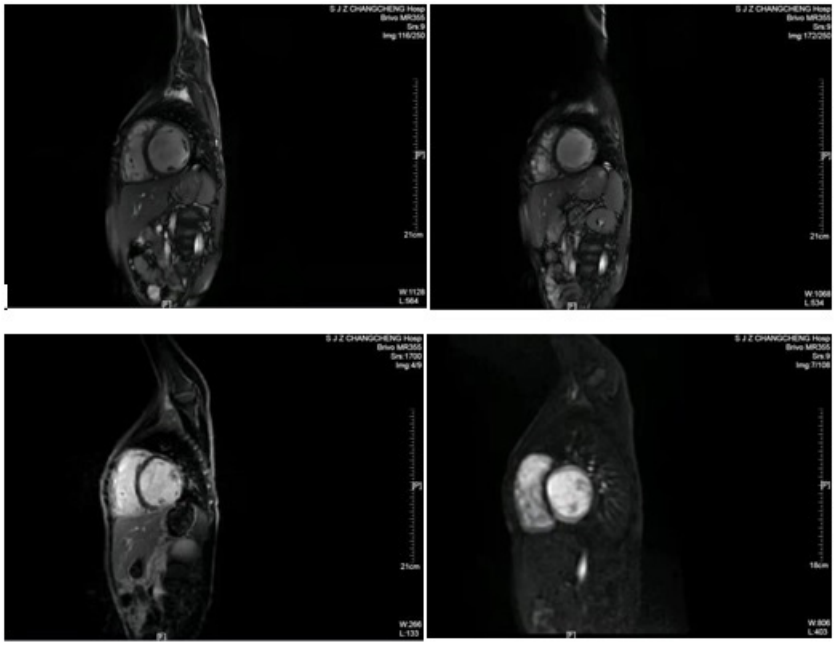


Figure 5. Abnormal cardiac manifestations in patient 2: A: ECG: B-D: 24 hours Holter electrocardiography: polymorphic premature ventricular beats; E-G: Echocardiogram: LA37*38*51mm, LV50mm, RA35*51mm, RV37mm (transverse diameter)EF18%; H-K hypertrabeculation of the LV myocardium. circumferential/ring-like pattern of epicardial or midmyocardial delayed enhancement pattern.

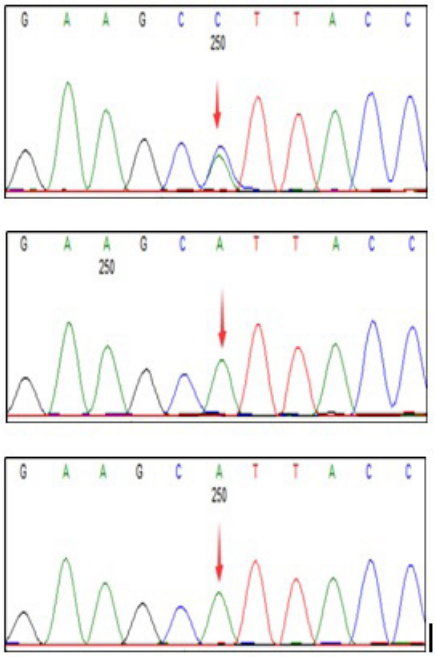


Figure 6. Electropherograms of sanger sequencing showing *de novo* heterozygous *DSP* variants c.1853A>C (p.H618P) identified in proband 2 (A), which was absent from both of his healthy non-consanguinous parents (B, father; C, mother) without relevant family history.

In addition, patient 2 also carried another mutation of uncertain significance c.8044C>G (p. Q2682E) in Exon 24 of DSP which was also identified in his healthy father. We proposed that this might be a nonsense mutation due to its maximum minor allele frequency of 0.0003009 in east Asian gnomAD database and negative findings suggested by in silico algorithms. However, further functional study was needed to better examine the role of Q2682E mutation in CS pathogenesis.

Patient 2 was diagnosed as CS and was successfully discharged after receiving similar treatments as introduced in case 1.

3. Discussion

Carvajal syndrome is a rare disease that was first described in 1996 [28]. Since then, multiple reports have been published suggesting that this disease is driven by DSP gene mutations [29]. The two cases introduced above both not only presented with characteristic woolly hair at birth, followed by palmoplantar keratoderma but also developed heart failure in a relatively young age. In addition, to the best of our knowledge, the p. Q1533X, p.H618P and p.Q2682E mutations identified in this report were first described in association with CS. To better understand this rare disease, we searched related studies in databases “Pubmed” and “Sciencedirect” for articles including keywords of "wooly hair", "dilated cardiomyopathy", "palmoplantarkeratosis", "Carvajal syndrome", and "desmoplakin gene", pubslihed from January 2000 to November 2021 and conducted a systemic literature review. We discovered a total of 51 CS cases. In 37/39 cases who received gene sequencing, DSP gene mutations were identified. The CS associated DSP mutations were summarized and presented in Table 1. It is well accepted that even with the same gene mutation, disease phenotypes can vary depends on the nature and location of mutations. DSP protein has a tripartite structure consisting of six spectrin repeats (SRs) at the N-terminus, a central rod domain with a variable region, and three plakin repeat regions at the C-terminus [2]. Previous studies indicated that mutations occurred in the SR6 region often resulted in autosomal dominant inheritance of the disease while mutations occur within SR4, SR8, the variable region of the rod domain, and the C-terminal plakin repeats often resulted in autosomal recessive

inheritance of the disease [1-2,6]. In addition, truncating mutations located in exons 23 and 24 are often associated with cardiac symptoms [2]. Currently, no study has been designed to investigate why different mutations in DSP gene result in different disease phenotype and inheritance pattern. One hypothesis is that only mutations disrupting the scaffold structure of desmosomes by integrating abnormal desmoplakin molecules would result in dominant mutation. However, this hypothesis needs to be further examined in in vitro studies. Interestingly, the c.1853A>C（p.H618P）mutation in patient 2 is identical to what has been identified in a previous case who was diagnosed as erythrokeratodermia cardiomyopathy syndrome（EKA）with presentations of severe erythrokeratodermia, alopecia and visual impairment [30]. This discovery may challenge the current differentiation between these two rare diseases. In addition, symptoms presented by patient 2 including woolly hair, PPK and tachyarrhythmia need to be differentiated from another cardiocutaneous syndrome named NAXOS disease which associated with mutation in the plakoglobin gene and characterized by arrhythmogenic right ventricular cardiomyopathy, hypokinesis, and tachyarrhythmia [31]. The dermatology presentations between these two disease are similar but unlike NAXOS, CS predominantly involves the left ventricle and often presents as dilated cardiomyopathy. However, this differential diagnosis angle based on which ventricle is involved has been challenged as recent studies suggest that either of left and/or right ventricle can be involved with mutations in DSP gene [5]. Even though the culprit role of DSP mutation has been identified in the pathogenesis of CS, no targeted treatment has been developed and patients often associate premature death. Based on our experience, patients often associate with better outcomes if they were correctly diagnosed early in the disease course. Therefore, early gene sequencing in suspected patients is recommended.

4. Conclusion

In this report, we described two cases of CS syndrome with early onset heart failure for the first time in Chinese and discovered novel mutations in the DSP gene. This study not only extended the spectrum of CS associated DSP gene mutations but also shed light upon the importance of early gene sequencing in suspected patients.

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