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CLINICAL REPORT

Costello syndrome with special cutaneous manifestations and *HRAS* G12D mutation: A case report and literature review

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Abstract

Background: Costello syndrome (CS, OMIM 218040) is a rare congenital disorder caused by mutations in *HRAS*. Previous studies reported that approximately 80% of patients with CS share the same pathogenic variant in *HRAS* gene in c.34G> A (p.G12S). Here, we report a CS patient with c.34G> A (p.G12D) variant in *HRAS* gene and she presented with special manifestation.

Methods and Results: We describe a 31-year-old female patient who presented with distinctive facial appearance, intellectual disability, dental abnormalities, hyperkeratosis of palmer and planter, loose skin at birth, papillomata on the face and nipples. The whole-exome sequencing (WES) technology provided by Haotian Biotechnology (China) confirmed p.G12D variant in *HRAS* gene. To elucidate the typical features of CS with p.G12D variant, we further reviewed these previously reported cases and found that patients with G12D variant died within three months after birth due to multiple organ failure. They had the typical facial characteristics, failure to thrive, skin and cardiac abnormalities, and gene testing confirmed the diagnosis of CS.

Conclusion: To the best of our knowledge, this is the first article to report a patient with a p.G12D variant that had special but mild manifestation. Moreover, this report and literature review casts new light on the clinical features of p.G12D variant.

KEYWORDS

Costello syndrome, heterozygous variants, *HRAS* variant, p.G12D

1 | INTRODUCTION

Costello syndrome (CS) is a rare autosomal dominant genetic disease, which was first described by Costello in 1997 based on its distinctive phenotype. The characteristic symptoms of CS are as follows: growth delay, intellectual disability, dermatologic anomalies, cardiac problems, musculoskeletal abnormalities, special facial features, and a predisposition to developing neoplasia (Rauen, 2007). In most cases, Costello syndrome is caused by specific heterozygous, de novo variants in *HRAS* gene (Aoki et al., 2005; Gripp, Lin, et al., 2006; Kerr et al., 2006), which is the only diagnostic reference standard of CS (Rauen, 2007). This is the first article to report a patient with mottled skin pigmentation; the patient had been

Wen Qian, Meijie Zhang, and Hequn Huang contributed equally to this work.

diagnosed with CS by gene test. This patient had a p.G12D variant, which was identified for the first time in China. In this paper, we analyze the characteristics of multiple-system disorder of this disease by reviewing related literatures.

2 | SUBJECT

A 31-year-old female presented a 27-year history of rough and dark skin, which was accompanied by an increasing number of warts on the face. She was born at term with the following complications: skin laxity and rough, abnormal pigmentation, and thin and soft nails (toenails). One month after birth, she suffered from hair loss. Since then, a slight growth in vellus hair was observed. When she was a 2-year-old toddler, palmoplantar keratosis with clear boundaries began to appear; moreover, warty vegetations had arisen from the tip of the nose, and it gradually spread to the whole face. The enamel of her deciduous teeth showed corrosive damage at the age of four. Furthermore, the teeth were incomplete, easy to break, and fell off after teeth replacement. Moreover, her growth development and intelligence were later than that of ordinary people. Up to now, her weight and height were 59 kg and 150 cm. She had a sister without similar symptoms.

Before being admitted to this hospital, the patient had not been clearly diagnosed. Half a year ago, she was prescribed Acitentin 20 mg once a day for palmoplantar keratosis, and the dosage was reduced to 10 mg one month later. Liquid nitrogen freezing and laser were used to remove the vegetation on her face. She usually took cod liver oil and centrum as nutritional supplements. In recent years, the condition of the patient has improved slightly: the verrucous vegetation on the face has reduced; there has been thinning of the keratinized palm and plantar skin; and the rough and dark skin has improved in texture and appearance. Presently, most of the skin on her right leg basically became normal, and the skin also became smoother. There was no hereditary disease in her family, and her parents did not have a consanguineous marriage.

3 | PHYSICAL EXAMINATION AND LABORATORY TEST

Physical examination showed multiple small and large verrucous vegetation on the face and the bilateral papilla. Fine hair was rare on the patient's head, but mottled pigmentation following Blaschko's lines was scattered throughout her body. She had little hair and a tuft of vellus hair. Her teeth were maldeveloped. The deciduous teeth were retained, while the permanent teeth were lost. There were varying degrees of teeth atrophy. Her palms and some of the pads of her hands were keratinized and thickened, showing deformities at the fingers. The fingernails were hypoplastic (Figure 1).

An oral panoramic CT showed that the alveolar bone of the whole mouth was absorbed at different degrees, 13 was impacted, 12–22 absorbed into the root, 28 was retained, the residual roots 36, 37, 46, and 47 remained, while the roots of 38 and 48 were absorbed into the root tip; the root of 48 showed a low-density shadow (Figure 2). The histopathological examination of warts on the face revealed massive sebaceous hyperplasia in HE staining, so the patient was pathologically diagnosed with a sebaceous nevus. Moreover, HPV-6 and HPV-11 were positive in frozen skin tissues of the same site, with 2.52 × 10 ^ 3 copies.

The whole-exome sequencing (WES) technology, which was provided by Haotian Biotechnology (China), was used to select and purify the DNA for whole-exome hybridization. We found that *HRAS* gene had undergone non-synonymous variants: exon2: c.35G>A: p.G12D. It was a heterozygous variant, and the variant rate was less than 0.001 in human genomes. What's more, the whole-exome sequencing found that 27% of reads were the variant (117 normal reads, 31 variant reads), which indicated the possibility of mosaicism. However, the variant was not found in her parents and sister, who were analyzed from the dates provided by first-generation sequencing (Figure 3). Gene testing and histopathological examination were carried out after obtaining an informed consent from the participants.

4 | DISCUSSION

In view of the fact that the clinical manifestations of patients were mainly abnormalities of skin, teeth, hair, and nails, we used the whole-exome gene screening technology to searched for gene site variants related to ectoderm development. Then, we found *WNT10A* (NM_025216:exon3:c.G637A:p.G213S) and *HRAS* (NM_176795:exon2:c.G35A:p.G12D) gene variant from the patient's blood. Further serological results of the direct family members (including her father, mother, and sister) were obtained by performing the first-generation sequencing. The results indicate that the father and sister had the same *WNT10A* gene variant, while the *HRAS* gene variant was only found in the patient. In conclusion, combined with the clinical manifestations and gene testing, we confirmed the diagnosis of CS.

As reported in previous studies, the variant in *HRAS* gene: c.34G>A:p.G12S was most commonly seen in 80% of CS patients (Gripp & Rauen, 1993). Severe phenotypes were usually caused by uncommon genotypes, such as c.35G>T (p.G12V), c.35G>A (p.G12D), c.34G>C (p.G12A), c.34G>T (p.G12C). Recently, a number of studies have shown that there is a potential relationship between the different phenotype and genetic characteristics (Kuniba et al.,

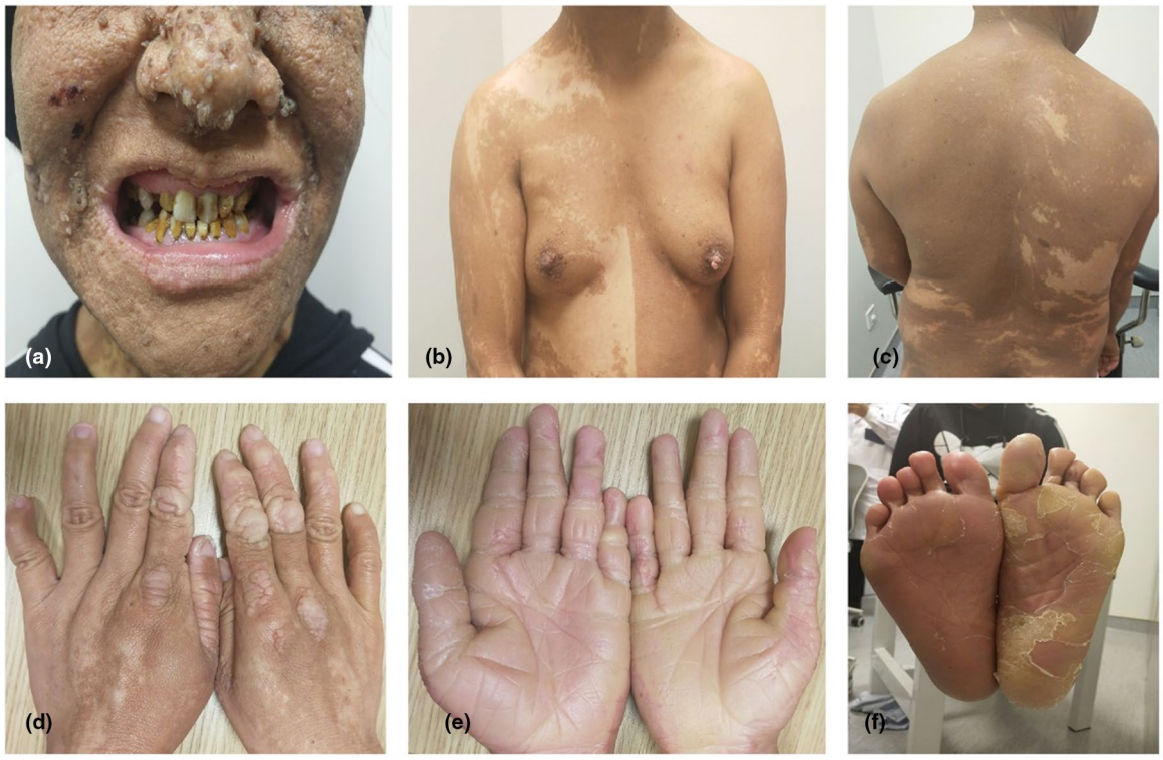

FIGURE 1 Clinical appearance of patient. (a) She had papillomata on the face and teeth dysplasia. (b,c) Mottled pigmentation was observed all over the body with clear boundaries. (d,e,f) Palmoplantar keratosis was also seen

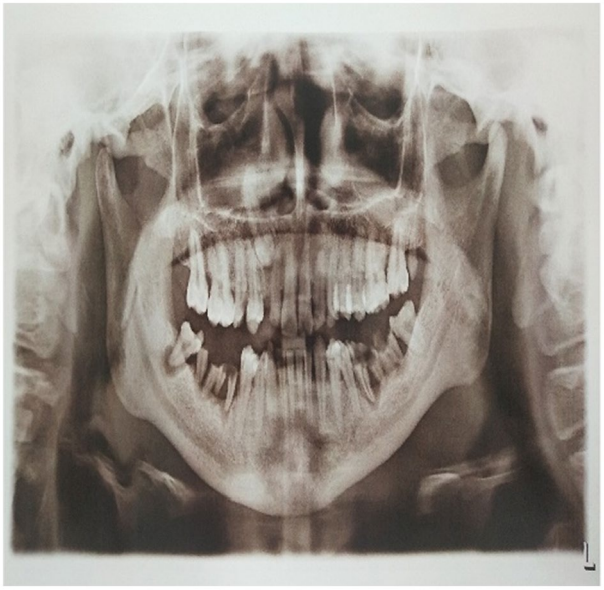

FIGURE 2 An oral panoramic CT showed that the alveolar bone was absorbed and damaged in different degrees

2009; Lin et al., 2011; Lo et al., 2008; Lorenz et al., 2012). To the best of our knowledge, the variant in p.G12V was reported in seven patients who died within the first postnatal week. Furthermore, the muscle reports of the patient biopsy revealed neuromuscular spindle excess (Quelin et al., 2017). In this patient, we found p.G12D variant in *HRAS* gene. Then, we reviewed recent articles about p.G12D variant, which is another rarer variant occurring in *HRAS*, and it may relate to several clinical phenotypes. To search articles published in the last 10 years, we used the keywords "Costello syndrome" and "*HRAS*" in the Pubmed and Web of Science databases. Thus, we finally got 103 papers. We found that all the five patients with G12D variant died within three months after birth due to multiple organ failure. They had the typical facial characteristics, failure to thrive, skin and cardiac abnormalities, and they were diagnosed with gene testing (Table 1). However, in our case, the patient had c.35G>A (p.G12D) heterozygous variant, which also alleviated the severity of the disease.

The RASopathies is a group of syndromes caused by variants in genes that encode the components of an RAS/mitogen-activated protein kinase (MAPK) pathway, including neurofibromatosis type 1 (NF1), capillary malformation-arteriovenous malformation syndrome (CMAM), Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), cardio-facio-cutaneous syndrome (CFC), Costello syndrome (CS), and Legius syndrome (LS) (Rauen, 2013). RAS/MAPK signaling pathway has the function of controlling cell behavior, including cell proliferation, differentiation, metabolism, and signal molecule conduction. It is difficult to distinguish CS syndrome from CFC and NS syndrome due to their overlapping features, such as distinct facial features, intellectual disability, cardiac abnormalities, and susceptibility to the tumor. Patients with CS and CFC can have characteristic clinical manifestations in the early

TABLE 1 Summary of patients with c.35G > A (p.G12D) mutation in *HRAS* gene

No	First author	Sex	Age	Clinical syndrome	Laboratory investigations	Diagnosis methods	Treatment and outcomes
1	Lo et al. (2008)	NA	3 months	Large fontanelles, widened sagittal suture, shortened limbs, loose skin over the hands and feet, hepatosplenomegaly, sparse hair, eyebrows, and eyelashes, hypoglycemia, severe jaundice, persistent respiratory distress	Paroxysmal multifocal atrial tachycardia, atrial septal defect and septal hypertrophy, dilated renal calyces	Mutation analysis	Died at 3 months of age due to respiratory distress
2	Lo et al. (2008)	Female	3 months	Distinctive facial appearance, hypoglycemia, atrial fibrillation, and cardiac failure, persistent hyponatremia	Radiographs confirmed ulnar deviation of the hands and probable dislocation of the left elbow. Shorten radius and ulna, hypertrophic cardiomyopathy, and dysplastic pulmonary valve	Mutation analysis	Died at 3 months of age from sepsis, and renal failure
3	Kuniba et al. (2009)	Male	NA	Distinctive facial appearance, respiratory failure, severe hypoglycemia, cardiac hypertrophy and renal failure	Hepatomegaly, laterally deviated wrists	three-dimensional (3D) ultrasonography and mutation analysis	Died soon after birth due to multiple organ failures.
4	Niihori et al. (2011)	Female	5 months	Failure to thrive, intellectual disability, coarse facial appearance, short neck, curly hair, loose skin	Premature ventricular contraction, laryngomalasia, hydrocephallus	NA	NA
5	Lorenz et al. (2012)	Female	2 weeks	Generalized skin edema, distinctive facial appearance, fine curly hair, broad and short neck with loose nuchal skin, insufficient respiratory efforts	Severe hypertrophic obstructive cardiomyopathy and a dysplastic thickened pulmonary valve, hepatomegaly, supraventricular tachycardia	Mutation analysis	Died at two weeks of age due to cardiocirculatory and respiratory failure

Abbreviation: NA, not available.

TABLE 2 Special clinical features of CS patients with the mosaic mutation

	Sex	Age	Special features	Genotype nucleotide substitution	% of mosaicism
Gripp, Stabley, etal. (2006)	Female	15 years	Irregular hypo- and hyperpigmentation	c.34G>A p.Gly12Ser	25%–30% (buccal cells)
Bertola et al. (2017)	Female	3 years 11 months	Irregular hypo- and hyperpigmentation; bifid uvul	c.38G>A p.Gly13Asp	<50% (blond hair)
Sol-Church et al. (2009)	Male	NA	Male-to-male transmission	c.34G>A p.Gly12Ser	7%–8% (buccal cells)
Girisha et al. (2010)	Male	13 months	Severe skin laxity (significantly reduction by age 13 months)	c.34G>A p.Gly12Ser	28.8% (blood)

Abbreviation: NA, not available.

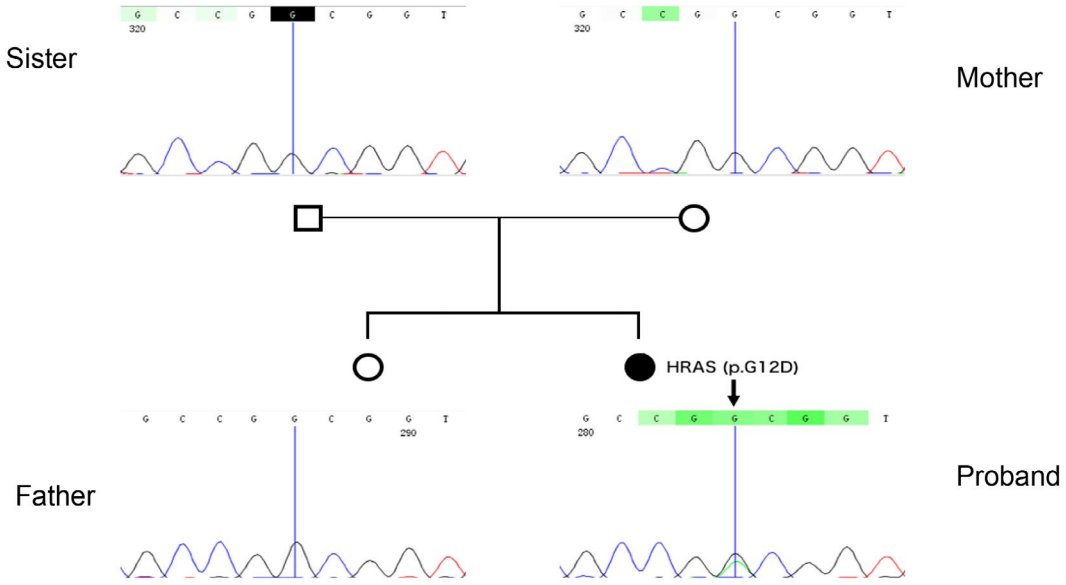

FIGURE 3 The results of the whole-exome sequencing. The whole-exome sequencing confirmed the variant of exon2: c.35G>A: p.G12D in the patient but not in her parents and sister, confirming the heterozygous mutation

phase, such as coarse facial features, deep palmer and planter crease, loose skin, abnormal hyperpigmentation, and failure to thrive. However, dental development abnormalities, especially class III malocclusion, soft tissue hyperplasia, and enamel hypo-mineralization, can be used to distinguish CS from CFC (Goodwin et al., 2014). Gene testing can help when it is necessary. In this case, growth retardation, intellectual disability, abnormal pigmentation, papillomata on the face and nipples, dental abnormalities, and keratosis of palms and planter were all in accordance with the characteristic clinical manifestations of CS. What's more, the discovery of *HRAS* gene variant further confirmed our conjecture. Almost half of the patients with CS will develop skin papillomata, regardless of their age. These patients are prone to benign or malignant tumors, especially the high risk of rhabdomyosarcoma, transitional cell carcinoma, and neuroblastoma (Gripp, 2005). Therefore, tumor screening is essential during the growth phase of the patient.

Pathogenic variant of *HRAS* was also found in Linear nevus sebaceous syndrome (LNSS; OMIM 163200), typically characterized by nevus sebaceous (NS), seizures, and mental retardation (Feuerstein & Mims, 1962; Levinsohn et al., 2013). Approximately 50% to 59% of them are complicated with ocular abnormalities (Park et al., 2009). Nevus sebaceous (NS) is a hallmark of LNSS, which is characterized by yellowish-orange to pink lesion, slightly raised, and sharply demarcated, and present as waxy or pebbly surfaces on the skin of the head, face, and neck. However, the main manifestation of our patient is irregular hypo- and hyperpigmentation. Despite features overlap between CS and LNSS, we still more prefer the diagnose of CS.

This patient had abnormal hyperpigmentation all over the body with clear boundaries, and the pigmentation was mottled locally in the four limbs, so the patient should be distinguished from linear and whorled nevoid hypermelanosis (LWNH; OMIM 614323). Kater first reported about

LWNH in 1988 (Kalter et al., 1988). It is a congenital disorder of pigment whereby individuals have swirled pigmentation, distributed along the Blaschko's line but without any skin and cardiac abnormalities, and growth retardation. At present, the irregular hypo-and hyperpigmentation on the patient's extremities and trunk had turned out to be better than before. We consider that there is a self-compensation of the body due to mosaic status for the *HRAS* variant, because mosaicism for the genetic disease may cause typical but much milder phenotype (Edwards et al., 1992). What's more, we reviewed five patients who were diagnosed as CS syndrome with mosaic variant by molecular biology technology. These patients have typical clinical manifestations, and mosaicism for variant resulted in some special phenotype, such as male to male transmission, unusually severe skin laxity, streaky hyperpigmentation. We report here on a patient with mild phenotype and unusually skin hypo-and hyperpigmentation, who carried the c.G35A (p.G12D) variant (Bertola et al., 2017; Girisha et al., 2010; Gripp et al., 2006; Sol-Church et al., 2009) (Table 2).

Palmoplantar keratoderma also presents in Odonto-onycho-dermal dysplasia (OODD; OMIM 257980). It is a subgroup of ectodermal dysplasia (EDs), which is a large group of diseases characterized by anomalies of ectodermal structures, such as teeth, nails, hair, skin, and sweat glands (Zirbel et al., 1995). Patients with OODD were reported to have erythematous atrophic patches on the face, sparse hair, hyperhidrosis, hyperkeratosis of the palms and soles, dystrophic nails, and oligodontia. Furthermore, the variant of *WNT10A* gene was associated with OODD (Kantaputra et al., 2014), which was also found in the blood of the patient and her father and sister. However, the possibility of OODD was excluded because these patients do not show intellectual disability, papillomata on the face, and coarse skin. Although the patient's father and sister had the same gene variant, they did not have any disease phenotype.

In conclusion, our patient was diagnosed with CS because she showed characteristic findings of CS, including distinctive facial appearance, intellectual disability, dental abnormalities, hyperkeratosis of palmer and planter, loose skin at birth, papillomata on the face and nipples, and typical variant of *HRAS* gene. Thus, there was no doubt about the clinical diagnosis of the patient. However, it is important to note that in recent years, all the five patients with p.G12D variant died within a few months after birth, while our patient was 31-year-old but without any severe life-threatening symptoms. We suppose that this novel existence of the patient can be attributed to heterozygous variants and mosaic status of *HRAS* gene: c.G35A:p.G12D, which can lead to distinctive symptoms and alleviate the severity. Moreover, it has been revealed that the keratinized palm and plantar skin, and rough and dark skin in the body were improved after treatment. By implanting artificial teeth, we can repair the missing and malformed teeth of the patient, and improve the quality of life. This gives us new inspiration in treatment.

It can be concluded that CS is one of the RASopathies due to the variant in genes that encode the RAS/MAPK pathway. Patients with CS are prone to the tumor, so it is important to regularly examine tumor indicators in these patients. There are no specific treatments for CS, so we should pay attention to patients with typical clinical manifestations and perform genetic testing if it is necessary to clarify the diagnosis and to prevent the severe progression of the disease.

5 | ETHICAL COMPLIANCE

All samples were collected after the patient and her family had given their written informed consent, and the study was approved by the research ethical committee of the First Affiliated Hospital of Nanjing Medical University.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Wen Qian drafted the versions of the manuscript. Wen Qian, Meijie Zhang, and Hequn Huang designed the project and assessed the clinical manifestation of the patient. Yihe Chen, Gajin Park reviewed related articles. Ni Zeng, Yueyue Li, Qian Lu contributed to data acquisition and interpretation. Dan Luo designed the project and reviewed the manuscript. All authors have read and approved the manuscript.

DATA AVAILABILITY STATEMENT

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

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