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

Wen Qian | Meijie Zhang | Hequn Huang | Yihe Chen | Gajin Park | Ni Zeng | Yueye Li | Qian Lu | Dan Luo

1Department of Dermatology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China
2Department of Dermatology, No. 1 Hospital and Key Laboratory of Dermatology, Ministry of Education, Anhui Medical University, Hefei, China
3Department of Mycology, Institute of Dermatology, Chinese Academy of Medical Science and Peking Union Medical College, Nanjing, China

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
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 $2.52 \times 10^3$ 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.,...
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 \textit{HRAS} gene. Then, we reviewed recent articles about p.G12D variant, which is another rarer variant occurring in \textit{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 “\textit{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

\textbf{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.

\textbf{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 \textit{HRAS} gene. Then, we reviewed recent articles about p.G12D variant, which is another rarer variant occurring in \textit{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 “\textit{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
| 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, hydrocephalus                          | 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.
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

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

| Sex  | Age       | Special features                                      | Genotype nucleotide substitution | % of mosaicism          |
|------|-----------|-------------------------------------------------------|----------------------------------|-------------------------|
| Gripp, Stablye, et al. (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 uvula | 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) |

**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.

Abbreviation: NA, not available.
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 palm 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.

ACKNOWLEDGMENTS
We would like to thank the patient and her family for their participation. We thank the patient and her family members for their contribution to this study. This work was supported by grants from the China National Natural Science Foundation (grant number 81771512, 81371757, and 81171518).

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.

ORCID
Wen Qian https://orcid.org/0000-0001-6600-8249

REFERENCES
Aoki, Y., Niihori, T., Kawame, H., Kurosawa, K., Ohashi, H., Tanaka, Y., Filocamo, M., Kato, K., Suzuki, Y., Kure, S., & Matsubara, Y. (2005). Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nature Genetics, 37(10), 1038–1040. https://doi.org/10.1038/ng1641
Bertola, D., Buscarilli, M., Stabile, D. L., Baker, L., Doyle, D., Bartholomew, D. W., Sol-Church, K., & Gripp, K. W. (2017). Phenotypic spectrum of Costello syndrome individuals harboring the rare HRAS mutation.
p.Gly13Asp. American Journal of Medical Genetics: Part A, 173(5), 1309–1318. https://doi.org/10.1002/ajmg.a.38178

Edwards, M. J., Wenstrup, R. J., Byers, P. H., & Cohn, D. H. (1992). Recurrence of lethal osteogenesis imperfecta due to parental mosaicism for a mutation in the COL1A2 gene of type I collagen. The mosaic parent exhibits phenotypic features of a mild form of the disease. Human Mutation, 1(1), 47–54. https://doi.org/10.1002/humu.1380010108

Feuerstein, R. C., & Mims, L. C. (1962). Linear nevus sebaceous with convulsions and mental retardation. American Journal of Diseases of Children, 104, 675–679.

Girisha, K. M., Lewis, L. E., Phadke, S. R., & Kutsche, K. (2010). Costello syndrome with severe cutis laxa and mosaic HRAS G12S mutation. American Journal of Medical Genetics: Part A, 152A(11), 2861–2864. https://doi.org/10.1002/ajmg.a.33687

Goodwin, A. F., Oberoi, S., Landan, M., Charles, C., Massie, J. C., Fairley, C., Rauen, K. A., & Klein, O. D. (2014). Craniofacial and dental development in Costello syndrome. American Journal of Medical Genetics: Part A, 164A(6), 1425–1430. https://doi.org/10.1002/ajmg.a.36475

Gripp, K. W. (2005). Tumor predisposition in Costello syndrome. American Journal of Medical Genetics Part C: Seminars in Genetic Medicine, 137C(1), 72–77. https://doi.org/10.1002/ajmg.c.30065

Gripp, K. W., Lin, A. E., Stabley, D. L., Nicholson, L., Scott, C. I., Doyle, D., Aoki, Y., Matsubara, Y., Zackai, E. H., Lapunzina, P., Gonzalez-Meneses, A., Holbrook, J., Agresta, C. A., Gonzalez, I. L., & Sol-Church, K. (2006). HRAS mutation analysis in Costello syndrome: Genotype and phenotype correlation. American Journal of Medical Genetics: Part A, 140(1), 1–7. https://doi.org/10.1002/ajmg.a.31047

Gripp, K. W., & Rauen, K. A. (1993). Costello syndrome. Encyclopedia of Cancer, 33, 497–498.

Gripp, K. W., Stabley, D. L., Nicholson, L., Hoffman, J. D., & Sol-Church, K. (2006). Somatic mosaicism for an HRAS mutation causes Costello syndrome. American Journal of Medical Genetics: Part A, 140(20), 2163–2169. https://doi.org/10.1002/ajmg.a.313456

Kalter, D. C., Griffiths, W. A., & Atherton, D. J. (1988). Linear and whorled nevoid hypermelanosis. Journal of the American Academy of Dermatology, 19(6), 1037–1044. https://doi.org/10.1016/s0190-9622(88)70269-8

Kantaputra, P., Kaewugha, M., Jotikasthira, D., & Kantaputra, W. (2014). Tricho-odonto-onycho-dermal dysplasia and WNT10A mutations. American Journal of Medical Genetics: Part A, 164A(4), 1041–1048. https://doi.org/10.1002/ajmg.a.36388

Kerr, B., Delrue, M. A., Sigaudy, S., Perveen, R., Marche, M., Burgelin, I., Stef, M., Tang, B., Eden, O. B., O’Sullivan, J., De Sandre-Giovannoli, A., Reardon, W., Brewer, C., Bennett, C., Quarel, O., McCan, E., Donnai, D., Stewart, F., & Hennekam, R., … Black, G. (2006). Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. Journal of Medical Genetics, 43(5), 401–405. https://doi.org/10.1136/jmg.2005.040352

Kuniba, H., Pool, R. K., Sasaki, K., Shimokawa, O., Harada, N., Kondoh, T., Egashira, M., Moriuchi, H., Yoshiura, K.-I., & Niikawa, N. (2009). Prenatal diagnosis of Costello syndrome using 3D ultrasonography amniocentesis confirmation of the rare HRAS mutation G12D. American Journal of Medical Genetics: Part A, 149A(4), 785–787. https://doi.org/10.1002/ajmg.a.32335

Levinsohn, J. L., Tian, L. C., Boyden, L. M., McNiff, J. M., Narayan, D., Loring, E. S., Yun, D., Sugarman, J. L., Overton, J. D., Mane, S. S., Lifton, R. P., Puller, A. S., Wagner, A. M., Antaya, R. J., & Choate, K. A. (2013). Whole-exome sequencing reveals somatic mutations in HRAS and KRAS, which cause nevus sebaceous. Journal of Investigative Dermatology, 133(3), 827–830.

Lin, A. E., Alexander, M. E., Colan, S. D., Kerr, B., Rauen, K. A., Noonan, J., Baffa, J., Hopkins, E., Sol-Church, K., Limongelli, G., Digilio, M. C., Marino, B., Innes, A. M., Aoki, Y., Silberbach, M., Delrue, M.-A., White, S. M., Hamilton, R. M., O’Connor, W., … Gripp, K. W. (2011). Clinical, pathological, and molecular analyses of cardiovascular abnormalities in Costello syndrome: A Ras/MAPK pathway syndrome. American Journal of Medical Genetics: Part A, 155A(3), 486–507. https://doi.org/10.1002/ajmg.a.33857

Lo, I. F. M., Brewer, C., Shannon, N., Shorto, J., Tang, B., Black, G., Søo, M. T., Ng, D. K. K., Lam, S. T. S., & Kerr, B. (2008). Severe neonatal manifestations of Costello syndrome. Journal of Medical Genetics, 45(3), 167–171. https://doi.org/10.1136/jmg.2007.054411

Lorenz, S., Petersen, C., Kordass, U., Seidel, H., Zenger, K., & Kutsche, K. (2012). Two cases with severe lethal course of Costello syndrome associated with HRAS p.G12C and p.G12D. European Journal of Medical Genetics, 55(11), 615–619. https://doi.org/10.1016/j.ejmg.2012.07.007

Niibori, T., Aoki, Y., Okamoto, N., Kuwosawa, K., Ohashi, H., Mizuno, S., Kawame, H., Inazawa, J., Ohura, T., Arai, H., Nabatame, S., Kikuchi, K., Kuroki, Y., Miura, M., Tanaka, T., Ohtake, A., Omori, I., Ihara, K., Mabe, H., … Matsubara, Y. (2011). HRAS mutations identified in Costello syndrome patients can induce cellular senescence: Possible implications for the pathogenesis of Costello syndrome. Journal of Human Genetics, 56(10), 707–715. https://doi.org/10.1038/jhg.2011.85

Park, J. M., Kim, D. S., Kim, J., Lee, M. G., & Oh, S. H. (2009). Epibulbar complex choristoma and hemimeligenecphaly in linear nevus sebaceous naevus syndrome. Clinical and Experimental Dermatology, 34(8), e686–e689.

Quélin, C., Loget, P., Rozel, C., D’Hervé, D., Fradin, M., Demurger, F., Odent, S., Pasquier, L., Cavé, H., & Marcourelles, P. (2017). Fetal costello syndrome with neuromuscular spindles excess and p.Gly12Val HRAS mutation. European Journal of Medical Genetics, 60(7), 395–398. https://doi.org/10.1016/j.ejmg.2017.03.014

Rauen, K. A. (2007). HRAS and the Costello syndrome. Clinical Genetics, 71(2), 101–108. https://doi.org/10.1111/j.1399-0004.2007.00743.x

Rauen, K. A. (2013). The RASopathies. Annual Review of Genomics and Human Genetics, 14, 355–369. https://doi.org/10.1146/annurev-genom-091212-153523

Sol-Church, K., Stabley, D. L., Demmer, L. A., Agbulos, A., Lin, A. E., Smoot, L., Nicholson, L. I., & Gripp, K. W. (2009). Male-to-male transmission of Costello syndrome: G12S HRAS germline mutation inherited from a father with somatic mosaicism. American Journal of Medical Genetics: Part A, 149A(3), 315–321. https://doi.org/10.1002/ajmg.a.32639

Zirbel, G. M., Ruttum, M. S., Post, A. C., & Esterly, N. B. (1995). Odonto-onycho-dermal dysplasia. British Journal of Dermatology, 133, 797–800.

How to cite this article: Qian W, Zhang M, Huang H, et al. Costello syndrome with special cutaneous manifestations and HRAS G12D mutation: A case report and literature review. Mol Genet Genomic Med. 2021;9:e1690. https://doi.org/10.1002/mgg3.1690