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ORIGINAL ARTICLE

Phenotypic variability of syndromic craniosynostosis caused by c.833G > T in *FGFR2*: Clinical and genetic evaluation of eight patients from a five-generation family

Xianda Wei[1,2] | **Guori Huang**[2,3] | **Baoheng Gui**[1,2] | **Bobo Xie**[1,2] | **Shaoke Chen**[2,3] | **Xin Fan**[2,3] | **Yujun Chen**[2,3]

[1]Center for Medical Genetics and Genomics, The Second Affiliated Hospital of Guangxi Medical University, Nanning, China

[2]The Guangxi Health Commission Key Laboratory of Medical Genetics and Genomics, The Second Affiliated Hospital of Guangxi Medical University, Nanning, China

[3]Department of Pediatrics, The Second Affiliated Hospital of Guangxi Medical University, Nanning, China

Correspondence
Xin Fan and Yujun Chen, Department of Pediatrics, The Second Affiliated Hospital of Guangxi Medical University, No. 166 Daxuedong Road, Nanning, Guangxi, China.
Email: fanxin602@163.com and chenyujun1006@163.com

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Abstract

Objective: Craniosynostosis is the result of the early fusion of cranial sutures. Syndromic craniosynostosis includes but not limited by Crouzon syndrome and Pfeiffer syndrome. Considerable phenotypic overlap exists among these syndromes and mutations in *FGFR2* may cause different syndromes. This study aims to investigate the explanation of the phenotypic variability via clinical and genetic evaluation for eight patients in a large pedigree.

Methods: For each patient, comprehensive physical examination, cranial plain CT scan with three-dimensional CT reconstruction (3D-CT), and eye examinations were conducted. Whole exome sequencing was applied for genetic diagnosis of the proband. Variants were analyzed and interpreted following the ACMG/AMP guidelines. Sanger sequencing was performed to reveal genotypes of all the family members.

Results: A pathogenic variant in the *FGFR2* gene, c.833G > T (p.C278F), was identified and proved to be co-segregate with the disease. Some symptoms of head, hearing, vision, mouth, teeth expressed differently by affected individuals. Nonetheless, all the eight patients manifested core symptoms of Crouzon syndrome without abnormality in the limbs, which could exclude diagnosis of Pfeiffer syndrome.

Conclusion: We have established clinical and genetic diagnosis of Crouzon syndrome for eight patients in a five-generation Chinese family. Variability of clinical features among these familial patients was slighter than that in previously reported sporadic cases.

KEYWORDS
craniosynostosis, Crouzon syndrome, *FGFR2*

Xianda Wei and Guori Huang contributed equally.

1 | INTRODUCTION

Craniosynostosis is the result of the early fusion of cranial sutures, which can classify as syndromic and non-syndromic with an isolated finding (Johnson & Wilkie, 2011). The prevalence of craniosynostosis is 1 per 2000 to 1 per 2500 live births (Kajdic et al., 2018). Non-syndromic craniosynostosis occurs in 75% of cases, and 25% account for syndromic craniosynostosis, which includes but not limited by Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, Jackson–Weiss syndrome, and Beare–Stevenson cutis gyrata syndrome (Kajdic et al., 2018). To date, 57 genes have been related with craniosynostosis, the most common ones being FGF receptor genes, including *FGFR2, FGFR3*, and transcription factors *TWIST, MSX2* (Agochukwu et al., 2012; Senarath-Yapa et al., 2012). *FGFR2* at chromosome 10q25–26, are responsible for 100% individuals affected with Crouzon syndrome or Apert syndrome, and for over 95% individuals with Pfeiffer syndrome (Wenger et al., 1998). Considerable phenotypic overlap exists among these syndromes, as well as discriminating features that can aid in the specific diagnosis. For example, limb abnormalities occur occasionally in patients with Pfeiffer syndrome and Apert syndrome, but rarely in those with Crouzon syndrome (Wenger et al., 1998). Nonetheless, the heterogeneity of clinical phenotypes of the various associated syndromes poses challenge to clinical diagnosis and classification of the disease.

In this study, we performed clinical evaluations and genetic testing for eight patients in a five-generation Chinese pedigree. In order to reflect phenotypic variability of syndromic craniosynostosis caused by a certain mutation, we also present a review of previously reported sporadic patients sharing the same disease-causing mutation.

2 | METHODS

2.1 | Clinical assessment and informed consent

The pedigree was from Qinzhou City, Guangxi Zhuang Autonomous Region, China. For affected individuals, detailed enquiry about medical history, as well as comprehensive physical examination were performed. Cranial plain CT scan with three-dimensional CT reconstruction (3D-CT), and eye examinations were conducted. All protocols were in accordance with the standard guidelines and approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University (Nanning, China). Written informed consent for participation in the present study and the publication of images was obtained from all participating subjects in accordance with the Declaration of Helsinki.

2.2 | Genetic testing

Genomic DNA extraction (Lab-Aid DNA kit, Zeesan Biotech Co., Ltd. China), target capturing for whole exome sequencing (Human All Exon V5 Kit, Agilent Technologies, CA) and library sequencing (Hiseq 2500 platform, Illumina, USA) were conducted following

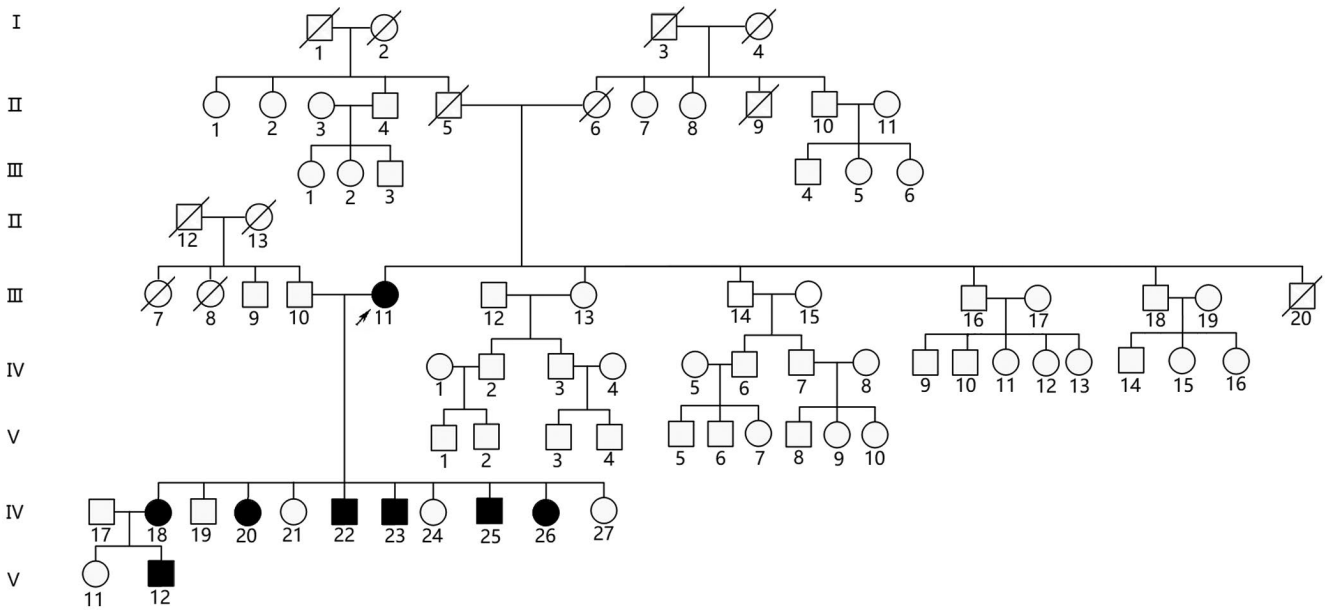

FIGURE 1 Family tree of the five-generation pedigree

TABLE 1 Clinical features of the eight patients

Patient	III-11	IV-18	IV-20	IV-22	IV-23	IV-25	IV-26	V-12
Gender	Female	Female	Female	Male	Male	Male	Female	Male
Age (year)	48	26	9	16	11	18	22	1
Head								
Craniosynostosis	+	+	+	+	+	+	+	+
Hydrocephalus	+	−	−	−	−	−	−	−
Face								
Midface hypoplasia	+	+	+	+	+	+	+	+
Ears								
hearing impairment	L: Sensorineural hearing loss R: Mixed hearing loss	Mixed hearing loss	L: normal. R:Unilateral conductive hearing loss	Bilateral conductive hearing loss	Bilateral conductive hearing loss	Bilateral conductive hearing loss	Mild hearing impairment	Unknown
Eyes								
Ocular proptosis	+ (R: 2.23/2.23 L: 2.23/2.23)	+ (R: 2.30/2.30 L: 2.30/2.30)	+ (R: 2.16/2.43 L: 2.14/2.37)	+ (R: 1.97/2.23 L: 1.86/2.25)	+ (R: 1.99/2.11 L: 1.93/2.25)	+ (R: 2.38/2.38 L: 2.29/2.29)	UNKNOWN	+ (R:1.76/2.26 L:1.78/2.22)
Hypertelorism	+	+	+	+	+	+	+	+
Uncorrected visual acuity (left)	0.9 (myopia)	0.05 (myopia)	0.6 (myopia)	0 (myopia)	0.9 (myopia)	1.5 (normal)	Unknown	Unknown
Uncorrected visual acuity (right)	0.8 (myopia)	0.05 (myopia)	0.7 (myopia)	0.5 (myopia)	0.9 (myopia)	1.5 (normal)	Unknown	Unknown
Axial length (left)	21.77 mm (normal)	21.64 mm (normal)	22.14 mm (increased)	22.03 mm (normal)	21.71 mm (normal)	23.97 mm (normal)	Unknown	Unknown
Axial length (right)	21.39 mm (normal)	21.43 mm (normal)	22.31 mm (increased)	21.71 mm (normal)	21.18 mm (normal)	23.78 mm (normal)	Unknown	Unknown
Nose								
Parrot-like nose	+	+	+	+	+	+	+	+
Deviation of Unknown nasal septum	+	+	+	+	+	+	+	+
Mouth								
High-arched palate	−	+	+	+	+	+	+	+
Teeth								
Dental crowding	+	−	+	+	+	+	+	+
Skull								
Empty sella	+	+	+	+	+	+	Unknown	+
Finger impression of inner skull plate	+	+	+	+	+	+	Unknown	+
Fingers	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Toes	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Intelligence	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

standard protocols of kits and instruments. Data analysis and annotation were performed utilizing the Genome Analysis Toolkit. Variants were identified and filtered on the TGex™ platform. For candidate variants, the inclusion criteria were: (1) heterozygous variant in an established causative gene of dominant Mendelian disorder with likely association with the patient's phenotype; (2) variant with frequencies in the East Asian population in the databases of Gnomad, ESP, or 1000G and our in-house database were all below 0.5%; (3) computational evidence supported a deleterious effect. Candidate variants were verified by Sanger sequencing and true variants were curated following the ACMG/AMP guideline (Richards et al., 2015).

FIGURE 2 Faces and heads of the eight patients

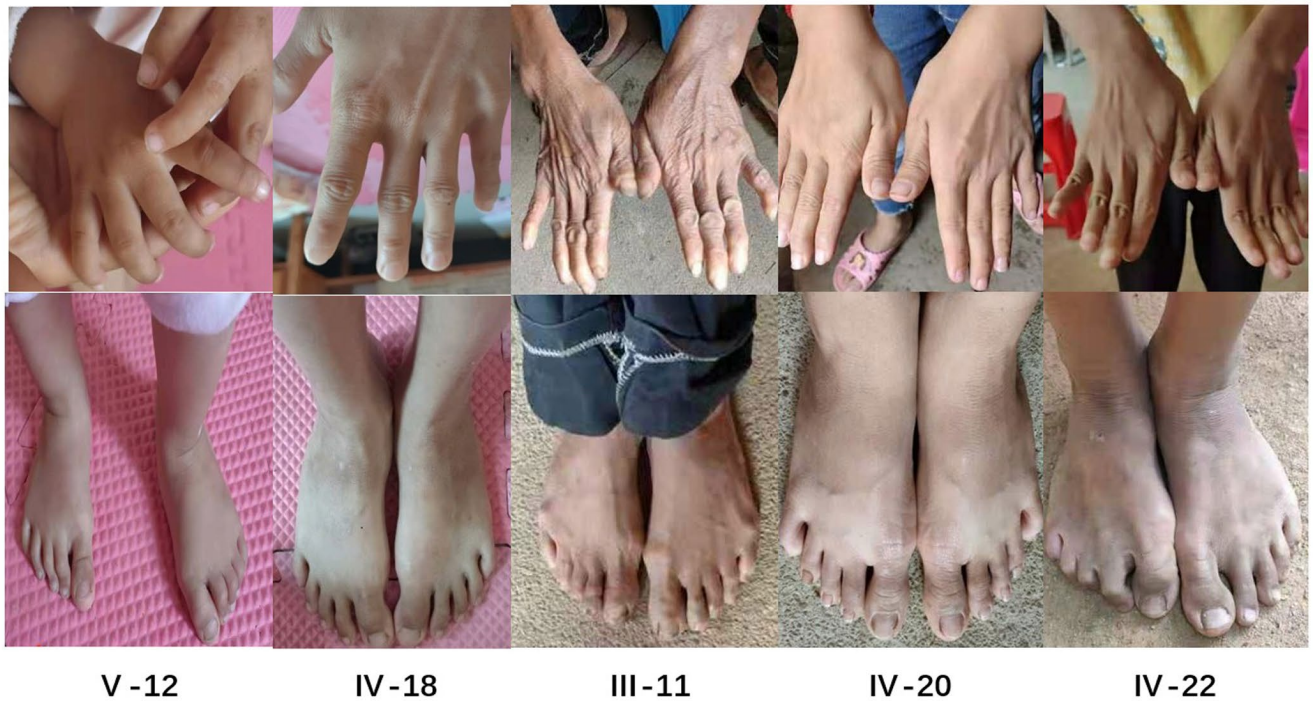

FIGURE 3 Hands and foot of five patients

3 | RESULTS

3.1 | Clinical presentation

After comprehensive enquiry about family history, we collected basic information of 76 individuals in the five-generation pedigree. A total of eight affected family members from three generations were identified and provided with clinical assessment (Figure 1). Results of physical examination and CT scanning are listed in Table 1. The patients showed common dysmorphism including craniosynostosis, midface hypoplasia, hypertelorism parrot-like nose, and deviation of nasal septum (Figure 2). Varying degrees of hearing impairment were found in seven patients except V-12 (1-year-old), of whom the risk for later occurrence of hearing loss cannot be excluded. Neither of the eight patients had abnormalities in limbs, fingers, toes, or intelligence. In particular, there was no significant broadening of the thumbs or big toes. We have collected photos of hand and feet of five patients (Figure 3). Eye

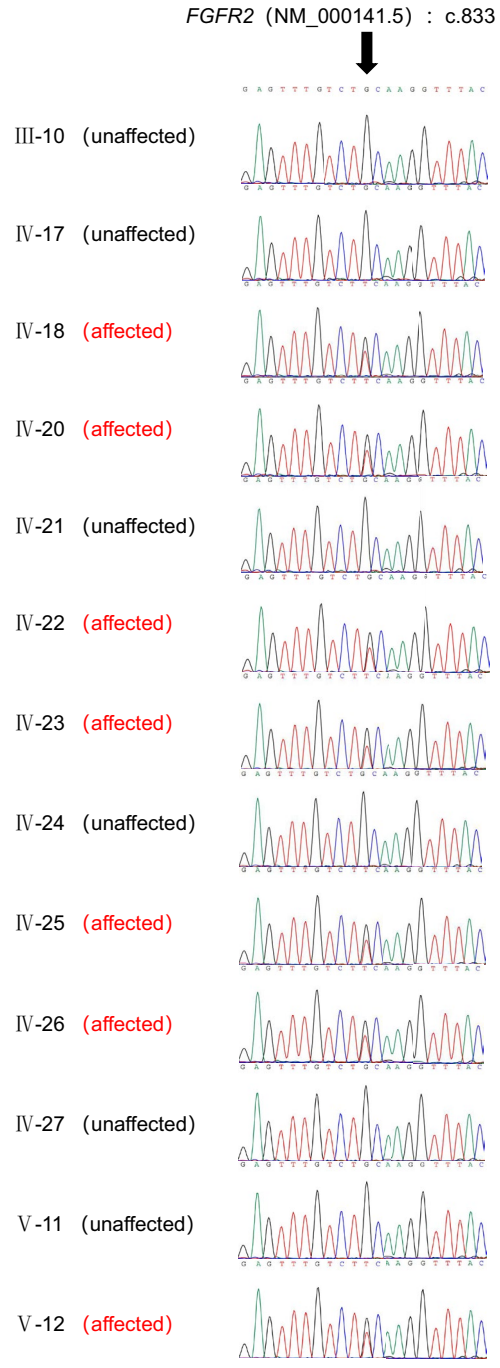

FIGURE 4 Co-segregation of the disease with *FGFR2* c.833G > T in seven patients and six unaffected family members

examinations found abnormalities including binocular protrusion, retraction of upper, and lower eyelids, deep anterior chamber in eight patients. Detailed inspection of vision were conducted for six patients except V-12 (too young) and IV-26 (missed examination). Increased axial length was found in IV-20 but not in the others. Five patients except IV-25 were diagnosed with myopia by bilateral uncorrected visual acuity. Cranial plain CT scan with three-dimensional CT reconstruction (3D-CT) has revealed a "finger pressure" change in the inner plate of the skull, increased angle between the lateral walls of the orbits, shallow orbits, sphenoid body dysplasia, and gathered carotid tubes on both sides, for all of the six patients except IV-26 (missed examination).

3.2 | Genetic analysis

Whole exome sequencing was performed and 18.1 Gb clean data were generated covering 95.5% of exome target regions at minimum depth of 20. A total of 135,155 functional variants were called. Through filtering, we identified five variants as candidates (supplemental table). After initial genetic assessment, a heterozygous variant (VAF% = 51.64%) in *FGFR2* gene, NM_000141.5: c.833G > T (p.Cys278Phe), was considered as a potential disease-causing variant, which was then verified by Sanger sequencing. The variant was present in all of the other seven patients and absent in six unaffected family members, showing co-segregation with the disease (Figure 4). The altered amino acid, Cys 278, is a part of the disulfide bridge that stabilizes the IgIII loop in all FGFR proteins and is the most conserved amino acid of the extracellular domains in the Ig superfamily. The change of Cys278 would destroy the disulfide bond in the Ig-III domain, leaving the other cysteine at position 342 potentially unpaired to participate in intermolecular disulfide bonding, which potentially results in a ligand-independent dimerization of receptor molecules and constitutive activation. With all of the evidences shown in Table 2, we determined *FGFR2* c.833G > T as a pathogenic variant and the common cause of disease in the pedigree.

4 | DISCUSSION AND CONCLUSIONS

In this study, we identified a variant in the *FGFR2* gene: NM_000141.5: c.833G > T (p.Cys278Phe) in eight familial patients. This locus is a mutational hotspot, which has been reported in other ethnic groups. In fact, pathogenic variants in *FGFR2* may cause variable phenotypes and severity of disease, as c.833G > T in *FGFR2* can lead to both Crouzon syndrome and Pfeiffer syndrome.

Previously published literatures reported patients diagnosed with different syndromes caused by *FGFR2* c.833G > T, which have been reviewed and summarized in Table 3. Pooled data show that Crouzon syndrome accounted for about 85% of clinical diagnosis of sporadic patients, and Pfeiffer syndrome accounted for almost all of the remaining. As reported, core clinical symptoms caused

TABLE 2 Evidences for classification of *FGFR2* c.833G > T

Code	Evidence	Reference
PS3	Mutated MC3T3 osteoblastic cells display adhesion defects when cultured on plastic	Santos-Ruiz et al. (2007)
	Functional studies suggest that the C278F variant results in a gain of function of the receptor resulting in negative autoregulation and advanced fetal cranial ossification	Britto et al. (2001)
	In vivo functional studies in chicken embryos also showed the variant is gain of function and produced midface hypoplasia and hypertelorism during the early stages of facial morphogenesis.	Li et al. (2013)
PM1	This variant is one of the most common causes of Crouzon syndrome and has been reported in many affected individuals	Clinvar SCV000659621.4
PM6_Very Strong	This variant has been previously reported as an assumed de novo heterozygous variant in at least seven individuals with typical features of craniosynostosis.	Oldridge et al. (1995) Steinberger et al. (1999)
PP1	Co-segregation with disease in multiple affected family members.	This study Sagong et al. (2014)
PP3	Multiple lines of computational evidence support a deleterious effect.	REVEL: 0.976 CADD:29.4 Polyphen: possibly_damaging SIFT: deleterious

TABLE 3 Clinical diagnosis and symptoms of reviewed cases with *FGFR2* c.833G > T

Reference	Number of cases		Symptoms
	Crouzon syndrome	Pfeiffer syndrome	
Oldridge et al. (1995)	6	0	craniosynostosis, associated proptosis, and midface hypoplasia.
Passos-Bueno et al. (1998)	1	1	enlargement of toes, clinodactyly of the 5th finger
Kan et al. (2002)	5	1	Not specified
Chun et al. (2003)	0	1	Not specified
Shotelersuk et al. (2003)	1	0	psychomotor retardation (IQ = 53), moderate mixed hearing loss
Hoefkens et al. (2004)	1	0	craniosynostosis, hypertelorism, midface hypoplasia pupils dislocated morphological anomaly of the external acoustic duct
Chang et al. (2006)	2	0	acrocephaly, exophthalmos, maxillary hypoplasia with "parrot-like" nose, short upper lip, high narrow palate, narrowly spaced teeth, prognathism
Lajeunie et al. (2006)	5	0	Not specified
Stenirri et al. (2007)	1	0	Not specified
Yu et al. (2009)	1	0	brachycephaly, abnormal head shape, small midface, proptosis and fused sutures, proptosis
Chokdeemboon et al. (2013)	0	2	craniosynostosis, ocular proptosis, midface hypoplasia, broad and medially deviated thumbs, great toes , Cutaneous syndactyly
Roscioli et al. (2013)	12	1	Not specified
Nur et al. (2014)	6	0	typical craniofacial features, high palate, anomaly heart defect
Sagong et al. (2014)	1	0	hearing impairment, absence of an external auditory canal hypoplastic maxilla, protruded mandible, mild hypertelorism, exophthalmos, and aural atresia
Suh et al. (2014)	1	0	Not specified
Júnior et al. (2015)	0	2	brachycephaly, midface hypoplasia, dysmorphic facies, prominent forehead, exophthalmos strabismus high-arched palate broad medially deviated/great toes, broad radially deviated thumbs
Lin et al. (2017)	1	0	craniosynostosis, shallow orbits, and ocular proptosis, midface hypoplasia
Topa et al. (2020)	2	0	Not specified
Total	46	8	

by *FGFR2* c.833G > T are craniosynostosis, ocular proptosis, and midface hypoplasia. Less-common symptoms include hypertelorism, low-set ears , broad and medially deviated thumbs, and great toes with variable degree of cutaneous syndactyly, maxillary hypoplasia with parrot-like nose, short upper lip, high narrow palate, narrowly spaced teeth, prognathism, heart defect, moderate faciostenosis, moderate mixed hearing loss, and absence of an external auditory canal. Only a few patients were affected with mental retardation. Nonetheless, clinical diagnosis depending solely on symptoms and physical signs is subjective and superficial. For example, misdiagnosis could occur when patients had not developed some late-onset symptoms or symptoms with incomplete penetrance. Genetic testing helps to investigate potential disease-causing mutations and to determine the molecular basis of the syndrome.

In spite of some difference in symptoms of head/ hearing/ vision/ mouth/ teeth, all the eight patients should be diagnosed of Crouzon syndrome without abnormality in the limbs, which could exclude diagnosis of Pfeiffer syndrome. Our findings indicates that members in a family affected with syndromic craniosynostosis caused by FGFR2 c.833G > T would manifest slight phenotypic variability, which may be generated from diverse environmental factors during development, as well as differences in when or where the mutant allele was expressed. This variability confined to Crouzon syndrome would not be as significant as that of sporadic cases, a minority of which be diagnosed with other syndromes. Genetic background, which is similar for familial patients but not sporadic patients, is a reasonable explanation of this phenomenon.

In conclusion, we have established clinical and genetic diagnosis of Crouzon syndrome for eight patients in a five-generation Chinese family. Variability of clinical features among these familial patients was slighter than that in previously reported sporadic cases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Funding acquisition: Xin Fan. Resources: Yujun Chen, Baoheng Gui, and Shaoke Chen. Clinical Investigation: Guori Huang, Xin Fan, and Shaoke Chen. Genetic Curation: Xianda Wei, BoBo Xie, and Baoheng Gui. Writing: Xianda Wei and Xin Fan.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Yujun Chen https://orcid.org/0000-0002-5981-9411

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SUPPORTING INFORMATION

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