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CLINICAL REPORT

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Extremely severe scoliosis, heterotopic ossification, and osteoarthritis in a three-generation family with Crouzon syndrome carrying a mutant c.799T>C *FGFR2*

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Abstract

Background: Crouzon syndrome is a rare and complex autosomal dominant craniosynostosis syndrome with a prevalence of approximately 1 in 60,000 births. The typical features are craniosynostosis, proptosis, midfacial hypoplasia, and noncranial manifestations, including deformities in the cervical spine, elbow, and fingers. Crouzon syndrome is usually caused by pathogenic variants in the fibroblast growth factor receptor 2 (*FGFR2*) gene.

Methods: We reported a three-generation family with Crouzon syndrome; the proband showed extremely severe limb abnormalities. The clinical features were obtained by physical examination and radiographic examination. Sanger sequencing of all 18 exons of *FGFR2* was conducted to identify the disease-causing mutation.

Results: The proband was a 44-year-old man who showed characteristics of Crouzon syndrome, including craniofacial dysostosis, shallow orbits, proptosis, midface hypoplasia, beaked nose, strabismus, short superior lip, short stature, and neck injection. In addition to these typical characteristics, radiographic examination showed severe scoliosis, heterotopic ossification of the elbows, knee osteoarthritis, metacarpophalangeal joint valgus, collapse of the articular surface of the thumb metacarpal, knuckle ossification and fusion. Sanger sequencing identified a heterozygous pathogenic variant c.799T>C, p.(Ser267Pro) in exon 7 of *FGFR2* in affected individuals.

Conclusion: Crouzon syndrome in this three-generation family was caused by c.799T>C *FGFR2*, and the patient showed a different phenotypic appearance from other Crouzon patients with c.799T>C *FGFR2*.

KEYWORDS

c.799T > C *FGFR2*, Crouzon syndrome, heterotopic ossification, osteoarthritis, severe scoliosis

1 | INTRODUCTION

Crouzon syndrome (CS, [OMIM #123500]) is a rare and complex autosomal dominant craniosynostosis with a highly variable phenotypic appearance and variable penetrance. The prevalence of CS is approximately 1 in 60,000 births (Yeh et al., 2013). The typical features are craniosynostosis, proptosis, midfacial hypoplasia, and in some cases, a beaked nose, prominent mandible, strabismus, and intellectual disability. Noncranial manifestations of CS were also reported, including deformities in the cervical spine, elbow, and fingers (Kjaer, Hansen, Kjaer, & Skovby, 2000; Proudman, Moore, Abbott, & David, 1994), aorta (Meng & Zhang, 2018), and lymphatic vessels (Bourgeois & Moniotte, 2009). CS is usually caused by pathogenic variants in the fibroblast growth factor receptor 2 (*FGFR2*, [OMIM *176943]) gene, which is located at 10q26 and encodes a signal-transduction transmembrane protein FGFR2. The FGFR2 protein contains three extracellular immunoglobulin-like domains (IgI, IgII, IgIII), a single transmembrane domain and a split tyrosine kinase domain (TK1 and TK2) (Traynis, Bernstein, Gardner, & Schrijver, 2012). The FGFR2 protein increases the tyrosine phosphorylation of several intracellular proteins by binding to FGF and autophosphorylation. Most pathogenic variants related to CS were in the IgII domain. Here, we report a different clinical phenotype of CS caused by a verified pathogenic variant described several times previously in *FGFR2*.

2 | CASE REPORT

In this study, we reported a three-generation family of CS with extremely severe limb abnormalities (Figure 1A). The 44-year-old proband showed typical characteristics of CS, including craniofacial dysostosis, shallow orbits, proptosis, midfacial hypoplasia, beaked nose, strabismus, short superior lip, short stature, and neck injection (Figure 1C a-b). In addition, scoliosis (Figure 1C b), stiff elbows that could not be straightened (Figure 1C c), swollen knees and arthrogryposis of knuckles (Figure 1C d,e) were also observed, and the movement of both sides was affected. Radiographic examination showed severe scoliosis of the thoracic segment (Figure 1D a), heterotopic ossification surrounding the elbow joint on both sides (Figure 1D b), articular stenosis and thinning of the cartilage, which indicates knee joint osteoarthritis (Figure 1D d), metacarpophalangeal joint valgus, collapse of the articular surface of the thumb metacarpal, knuckle ossification, and fusion of fingers (Figure 1D c). The clinical phenotype of other family members was less severe, the proband's sister showed craniofacial dysostosis, downslanting palpebral fissures, and dental malposition (Figure 1C f,g), and the proband's nephew showed ptosis of the right upper eyelid, strabismus and, slightly short fingers (Figure 1C h-j). No severe limb abnormality was observed.

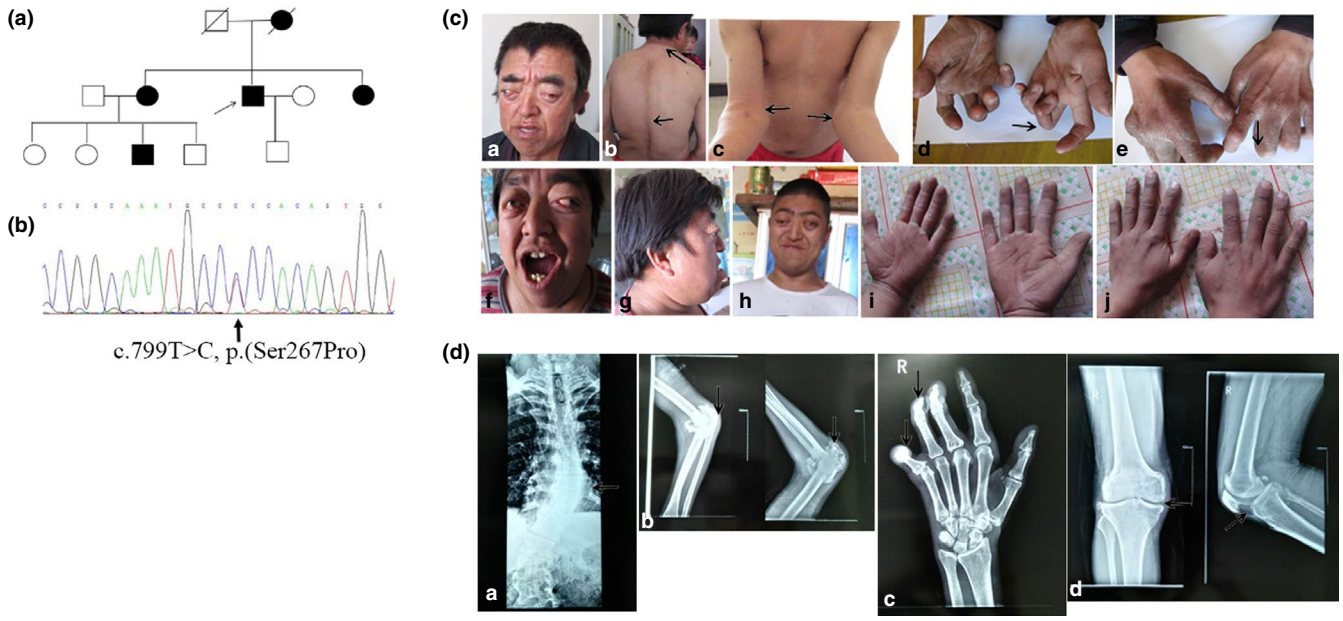

FIGURE 1 (A) Pedigree of the family, black symbols represent the affected individuals, arrow indicates the proband. (B) Sanger sequencing showing a heterozygous change c.799T>C in *FGFR2*, (C) Craniofacial and limb features of the family members. a–e: the proband, f–g: the sister of the proband, h–j: the nephew of the proband. (D) Radiographic studies of the proband, a: severe scoliosis, b: heterotopic ossification of elbow, c: metacarpoparthrosis, collapse of the articular surface of the thumb metacarpal, knuckle ossification and fusion, d: knee joint osteoarthritis

3 | MOLECULAR ANALYSIS

This study was approved by the Ethics Committee of Reproductive Health of the Liaoning Province, with informed consent from the patient's family. Blood samples from the family members were collected, and genomic DNA was extracted.

Sanger sequencing of all 18 exons of *FGFR2* (NM_000141.4) was performed according to standard methods. A heterozygous pathogenic variant c.799T>C in exon 7 was identified in three affected individuals, and the pathogenic variant resulted in replacement of serine (TCC) by proline (CCC), p.(Ser267Pro) (Figure 1b). The variant was not found in the ExAC(the Exome Aggregation Consortium) or 1000G(1,000 Genomes) databases, and the prediction was performed by SIFT, Polyphen2, Mutationtaster, and LRT. The scores were 0.001, 0.99, 1, and 0.0000, respectively, suggesting that this mutation was "damaging", so the variant was considered a disease-causing pathogenic variant.

4 | DISCUSSION

CS, Pfeiffer syndrome and Apert syndrome are typical craniosynostosis syndromes that share similar facial phenotypes, including craniosynostosis, proptosis, and midfacial dysplasia. Unlike Pfeiffer syndrome, which can present wide and deviated thumbs, and Apert syndrome, which can present severe syndactyly, CS usually does not present limb abnormalities. However, radiographically recognizable abnormalities in the hands were first reported in 1982 (Kaler, Bixler, & Yu, 1982), and then some other limb abnormalities were reported, such as carpal fusions (Anderson, Hall, Evans, Jones, & Hayward, 1997), clinodactyly, delay of hand ossification (Kjaer et al., 2000), olecranon dysplasia, radius dislocation (Ke, Yang, Tianyi, et al., 2015), and severe kyphoscoliosis (Umezu et al., 2017). In this family, the proband showed more severe limb abnormalities than previously reported CS patients, whereas wide and deviated thumbs and severe syndactyly were absent, which are typical phenotypes of Pfeiffer syndrome and Apert syndrome, respectively, so this family was diagnosed with CS.

FGFR2 gene pathogenic variants were responsible for CS, Pfeiffer syndrome and Apert syndrome. In total, 134 mutations in *FGFR2* have been reported according to HGMD professional 2018.4(http://www.hgmd.cf.ac.uk/ac/gene.php?gene=FGFR2), 51 in CS, 27 in Pfeiffer syndrome, nine in Apert syndrome, and 57 in other syndromes. In this study, c.799T>C was confirmed as the disease-causing mutation, which had been reported five times previously (Table S1). This pathogenic variant was first reported in a sporadic CS patient (Oldridge et al., 1995), and the clinical phenotype was proptosis and midfacial hypoplasia. Subsequently, three sporadic CS cases with this pathogenic variant were reported, all of which were typical CS without limb abnormalities (Lajeunie et al., 2006) (Roscioli et al., 2013) (Ke, Yang, Ge, et al., 2015). Recently, c.799T>C in a CS patient with slightly broad thumbs, prominent umbilical stump, broad halluces, and cutis gyrata was reported by LeBlanc (LeBlanc et al., 2018). In this study, a three-generation CS family with c.799T>C *FGFR2* was first described. In total, three affected individuals were reported. Additionally, the proband showed severe limb abnormalities that were not observed in other CS patients with the same mutation.

All pathogenic variants of *FGFR2* related to CS were reviewed, and the limb phenotypes are listed (Table S2). Of the 112 studies, only eight studies reported that the CS also exhibited slight limb deformities, including one patient with a c.799T>C pathogenic variant that showed slightly broad thumbs. In our study, severe limb deformities were observed in the proband, while the other two patients had no limb deformity, which may be ascribed to the poor living conditions, age and long-term physical labor of the proband; in addition, epigenetic regulation may play an important role in the different phenotypes caused by the same pathogenic variant.

In summary, this study identified c.799T>C *FGFR2* in a three-generation Chinese family with CS. This finding extends the phenotype spectrum of CS related to *FGFR2* pathogenic variants and is of great value for genetic counseling and prenatal diagnosis in families with syndromic craniosynostosis.

CONFLICT OF INTEREST

We would like to submit the manuscript, which we wish to be considered for publication in "Molecular Genetics & Genomic Medicine". No conflict of interest exits in the submission of this manuscript, and the manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described was the original research that has not been published previously, and not under consideration for publication elsewhere. We deeply appreciate your consideration of our manuscript and we look forward to receiving comments from the reviewers.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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