Clinical Case Report

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Novel chromosomal microduplications associated with dolichocephaly craniosynostosis

A case report

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Abstract

Instruction: Craniosynostosis is a human disorder characterized by the premature fusing of the cranial sutures in infants. Point mutations in hotspot genes such as *FGFRs* are the well-recognized causes of syndromic craniosynostosis, but chromosomal abbreviations may also play an important role in developing this disease. Here, we report the case in China of a 2-year-boy dolichocephaly craniosynostosis. Karyotyping by both G-bind staining and array-based DNA hybridization identified microduplications on Chromosomes 8p11.22 q12.1 and 16q11.2 q21, but none of the known pathogenic mutations was detected.

Conclusions: This finding not only expands knowledge on the genetic mechanism of craniosynostosis but also provides a new target for the early diagnosis of this rare disease.

Abbreviations: OMIM = Online Mendelian Inheritance in Man, SNV = single nucleotide variant.

Keywords: chromosomal microduplication, dolichocephaly craniosynostosis, *FGFR*

1. Introduction

Three to five out of 10,000 births develop an abnormally shaped skull when the cranial bones fuse prematurely. This condition is known as craniosynostosis, which results in cosmetic problems and insufficient cranial interior space associated with neurological complications.[1] In general, sagittal craniosynostosis accounts for approximately 60% of the frequencies of varies type of craniosynostosis.[2] At least 57 genes, including *FGFRs*, *TWIST1*, *MSX2*, *EFNB1*, *ERF*, and *TCF12*, are reported to be associated with craniosynostosis.[3–6] Besides single nucleotide variants (SNVs), a few chromosomal abnormalities have also been reported as being linked with craniosynostosis.[7–9] However, these correlations were predominantly defined based on sporadic American or European cases, which can explain merely a small fraction of affected individuals.[9,10] Given its highly heterogeneous and complex etiology, genetic investigations on much more cases are urgently required for grasping the entire spectrum of craniosynostosis' disease mechanism. Here, we detail the case of a Chinese infant with dolichocephaly craniosynostosis carrying novel chromosomal microduplications.

2. Case report

A 2-year-old boy was born by caesarean section to non-consanguineous, healthy parents with no family history of abnormal head shape. The child was born at 40 weeks through a normal pregnancy procedure, and exhibited a birth weight of 3.2 kg. He was first admitted to the Qingdao Women and Children's Hospital when he was 10 months old, manifesting clinical skull abnormalities (dolichocephaly, defined as cranial index ratio lower than 76) and weak acoustic and visual responses, although papilledema was not observed in this patient with fundus examination. He was 9.9 kg (50–60 percentiles) in weight, 72.0 cm (30–40 percentiles) in height, and 46.5 cm (50–60 percentiles) in occipitofrontal circumference. At 27 months of age, an abnormal skull formation and weak responses continued to be observed, in addition to widely spaced eyes (hypertelorism), a small lower jaw (micrognathia), protruding chest (pectus carinatum), weak muscle tone (hypotonia), and enlarged toes as well as partial syndactyly (Fig. 1).

To explore the genetic mechanisms of this disease, karyotyping on peripheral blood was performed by 2 methods: G-band staining via CytoVision GSL120 Platform and DNA hybridization via Affymetrix CytoScan 750K Array. Both methods revealed the same de novo microduplications at 8p11.22 q12.1 (39,489,479–57,610,327 bp) and 16q11.2 q21 (46,489,514–64,515,400 bp) in the chromosomes of this patient.

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The research (case no. QDWCH728) was approved by the Ethics Committee of Qingdao Women and Children's Hospital.

All analyzed individuals provided informed consent and explicitly agree to public dissemination of their variation data.

DY treated the patient, coordinated, and supervised data collection, and reviewed and revised the manuscript. SL provided the pathology images and carried out the analyses, and reviewed and revised the manuscript. QL and KZ performed the karyotyping and exome sequencing experiments, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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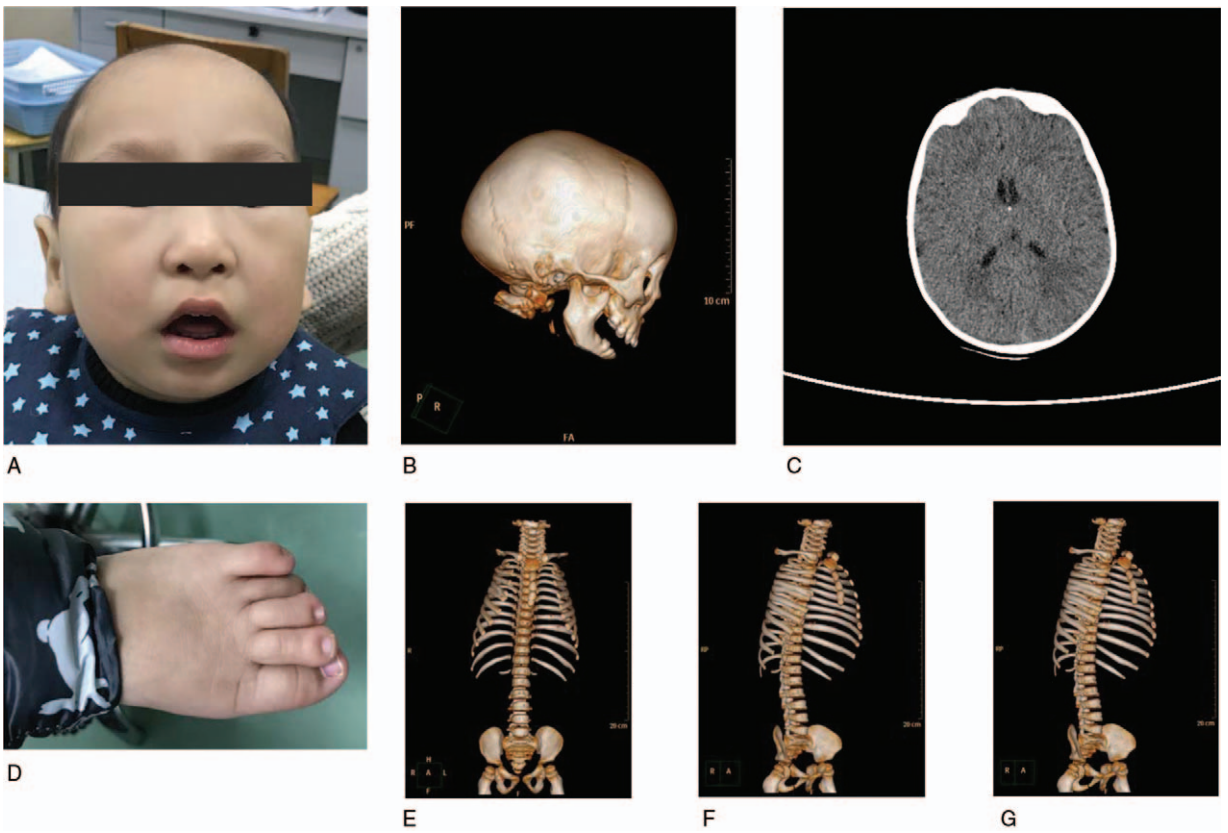

Figure 1. The diagnostic features of a patient. (A) Facial photograph showing big ear and fish-shaped lips. (B) Foot anomaly. (C and D) Dolichocephaly craniosynostosis (cephalic index below 76). (E–G) Breast bone skeletal deformation (chest protrusion).

The former microduplication was homozygous, while the latter showed a 70% rate of mosaicism. Both of them were not detected in the patient's parents.

Whole exome sequencing was also performed by enriching the exonic DNA via the Agilent SureSelect Human All Exome V6 kit, and then sequencing it via the Illumina Hiseq 2500 platform with an average 75× coverage. After filtering those benign SNVs by comparing against OMIM, NCBI ClinVar, and dbSNP database, a dozen homozygous nonsynonymous SNVs were identified in this patient (Table 1), which were likely pathogenic or of uncertain significance. However, none of these SNVs was located in the known genes responsible for craniosynostosis disorders, or was associated with diseases in the existing OMIM database.

3. Discussion

Rare diseases have attracted increasingly more attention from the research community, not only in regard to seeking better patient management tools such as prenatal diagnosis, but also

Table 1

Homozygous nonsynonymous single nucleotide variants identified in this patient.

Cytoband	Gene	Accession number	Exon	Nucleotide change	Amino acid change
1p36.21	PRAMEF14	NM_001024661	exon4	c.G1276A	p.D426N
1p36.21	PRAMEF19	NM_001099790	exon3	c.C1280T	p.S427L
1q44	OR2T34	NM_001001821	exon1	c.G800C	p.R267P
10q11.22	FRMPD2	NM_001018071	exon21	c.A2620G	p.S874G
12p13.31	ZNF705A	NM_001004328	exon5	c.A376G	p.T126A
12p13.31	ZNF705A	NM_001004328H	exon5	c.G557A	p.R186H
15q24.3	PEAK1	NM_024776	exon8	c.C4223A	p.P1408Q
15q24.3	PEAK1	NM_024776	exon5	c.T1318C	p.S440P
2q12.2	RGPD3	NM_001144013	exon20	c.A3851G	p.H1284R
2q12.2	RGPD3	NM_001144013	exon4	c.G331A	p.D111N
2q13	RGPD5	NM_001164463	exon20	c.T4622G	p.V1541G
7q22.1	MUC12	NM_001164462	exon2	c.A11681C	p.K3894T
9p12	ANKRD20A2	NM_001012419	exon15	c.T2279C	p.I760T
9p12	ANKRD20A2	NM_001012419	exon15	c.T2357C	p.M786T
9p11.2	CNTNAP3B	NM_001201380	exon23	c.G3741C	p.M1247I

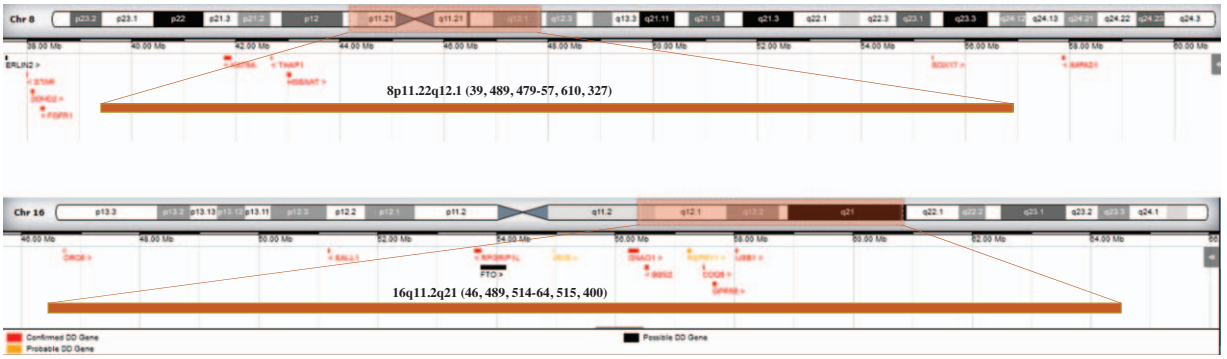

Figure 2. Developmental disorder-related genes involved in the 2 microduplications in the patient.

for expanding understanding of the underlying mechanisms. It is important that craniosynostosis be recognized and treated because of its potential link with malfunctional sensory, respirator, and/or neurological functions. A surgical treatment is available to improve the situation for severe craniosynostosis, although some attempts of gene therapy on craniosynostosis are explored in mouse model.[11] Thus the elucidation of molecular mechanism of various craniosynostosis is crucial to guide and advance these treatments. Previous studies have identified many SNVs and a few chromosomal abnormalities which cause craniosynostosis, but the entire spectrum of craniosynostosis' disease mechanism is far from being disclosed. Here, we have ruled out the possibilities that the known hotspot mutations resulted through deep exome sequencing in craniosynostosis. Particularly, pathogenic FGFR2 mutants (Ala344Pro, Cys342Trp, Ille617Phe, Glu731Lys, and Cys278-Phe) which were reported in other Chinese craniosynostosis patients were not detected in this patient.[12–17] Moreover, we observed novel copy number variations on this patient's chromosomes 8 and 16 through G-bind staining and array-based DNA hybridization. These results have led us to deduce that these chromosomal variations were responsible for the subject's phenotype, and in particular the characteristics of craniosynostosis.

A close examination of these 2 regions revealed a number of development disorder-related genes (Fig. 2). First, triple dosage of these genes may have contributed to the phenotypic characteristics of this patient. It was further noted that 8p11.22 q12.1 is merely 1 Mb downstream of *FGFR1*. We speculate that duplication of this region might regulate the expression of FGFR1, thereby causing development of dolichocephaly craniosynostosis. Second, no literature evidence available to support the association between duplication of 16q11.2 q21 with craniosynstosis. However, BBS2 (OMIM 606151, Ch-Band: 16q21, DNA position: 56.52–56.55 Mb), SALL1 (OMIM 602218, Ch-Band: 16q12.1, DNA position: 51.17–51.18 Mb), and CDH8 gene (OMIM 603008, Ch-Band: 16q22.1, DNA position: 61.69–62.07 Mb) are plausible candidates for contributing to the patient's phenotype: syndactyly, cognitive impairment, and hearing impairment, which was also proposed in a case study on a 5.5-year-old girl with a duplication of about 22.5 Mb spanning over 16q11.2-q22.1 region.[18] It is recommended that extensive research should be carried out in the near future to verify this hypothesis.

4. Conclusions

We have outlined the case of a patient exhibiting dolichocephaly craniosynostosis but without the reported pathogenic gene mutations. Our findings suggest that atypical mosaic duplications in the region of chromosomes 8p11.22 q12.1 (39,489,479–57,610,327 bp) and 16q11.2 q21 (46,489,514–64,515,400 bp) could be responsible for the subject's development of craniosynostosis. These novel chromosomal variations not only provide fresh impetus for exploring the molecular etiology of this rare disease but also pave the way for a novel prenatal diagnosis of craniosynostosis.

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