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CASE REPORT

Prenatal Phenotype Analysis of a Case with Cardiofaciocutaneous Syndrome Caused by BRAF Gene Mutation

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ABSTRACT

Background: **This study analyzed the prenatal clinical phenotype of a child with cardiocutaneous syndrome (CFCS) caused by BRAF gene mutation.**
Methods: **Chromosome microarray (CMA) and whole exome sequencing (WES) were used for the prenatal genetic diagnosis in a pregnant woman with fetal bone dysplasia (fetal macrocephaly, short femur) and polyhydramnios.**
Results: **CMA revealed no abnormalities, WES revealed BRAF de novo missense mutation (c.1406G > A, p.G469E), and the fetal parents showed no BRAF gene mutation.**
Conclusions: **Pathogenic variants in the BRAF gene leads to CFCS, which during pregnancy presents with signs of ultrasonographic abnormalities including macrocephaly, short femur, polyhydramnios.**
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KEYWORDS

BRAF gene, cardiofaciocutaneous syndrome (CFCS), whole exome sequencing (WES), prenatal diagnosis

CASE PRESENTATION

CFCS is a rare autosomal dominant genetic disease involving multiple systems of the body, caused by mutations in BRAF, MEK1, MEK2 and KRAS in the RAS-MAPK signaling pathway [1]. BRAF (gene mutation) causes about 75% of CFCS, with clinical manifestations such as cardiovascular defects, distinctive facial features, multiple lentigines, skeletal dysplasia, genital abnormalities, and sensorineural deafness [2]. At present, there are few reports on fetal CFCS. This paper investigated the strategies of prenatal diagnosis for fetuses with abnormal ultrasonographic phenotype, through analyzing the prenatal fetal phenotype of a case with CFCS mainly characterized by cranial and long bone dysplasia during pregnancy.

Research subjects and clinical information

The pregnant woman had regular menstrual periods. From 23 weeks of gestation, the biparietal diameter,



Figure 1. The distinctive facial features, shortness and webbing of neck, and short limbs of the neonate.

head circumference, and abdominal circumference of the fetus had increased progressively faster than those of the same age, while its femur length was shorter, accompanied by polyhydramnios. Invasive amniocentesis was performed at 30 weeks, and 30 ml of the amniotic fluid was collected for CMA and WES genetic testing. This study follows the STROBE statement.

MATERIALS AND METHODS

CMA test

Affymetrix SNP-array 750K chip detection was used, with parameters ranging from DNA copy repeats ≥ 50 kb and DNA copy deletions ≥ 25 kb.

WES test

Agilent SureSelectXT Human All Exon V6 kit was used to capture the genome and build the library. Double-terminal (150 bp × 2) sequencing was used for WES. The average depth of coverage was 100 times, with 96 per cent of the area having a depth of coverage of more than 10 times and 95 per cent of the area having a depth of coverage of more than 20 times. The data analysis was based on the GRCh37 (hg19) genome version. The gene mutation sites were consistent with the Sanger first-generation sequencing validation results.

RESULTS

Prenatal fetal development parameters and amniotic fluid status

From the 23 weeks of gestation, the biparietal diameter, head circumference, and abdominal circumference of the fetus grew progressively faster than those of the same age, approaching or exceeding the 90th percentile, whereas the femur length of the fetus was shorter, equal to or less than that of the same age in the 10th percentile, accompanied by polyhydramnios (Supplementary Table 1).

General status of the fetus after birth

The pregnant woman delivered a live-born male baby at G1P1G38 + 4 gestation (38 weeks + 4 days of gestation) with an Apgar score of 10 at 1 minute. The amniotic fluid volume during delivery was found to be about 9,100 mL, and the birth weight was 3,560 g, length 50 cm, and head circumference 37 cm. Physical examination showed large head, forehead with obvious protrusion, no eyebrows, wide eye distance, bridge collapse, lower ears, short neck, abnormal hand creases (Sydney line) and short limbs (Figure 1).

Neonatal screening results

Postnatal ultrasonographic cardiac screening revealed patent ductus arteriosus and atrial septal defect, hearing screening revealed failure of bilateral rapid brainstem evoked potential, and neonatal genetic metabolic disease examination showed no significant abnormality.

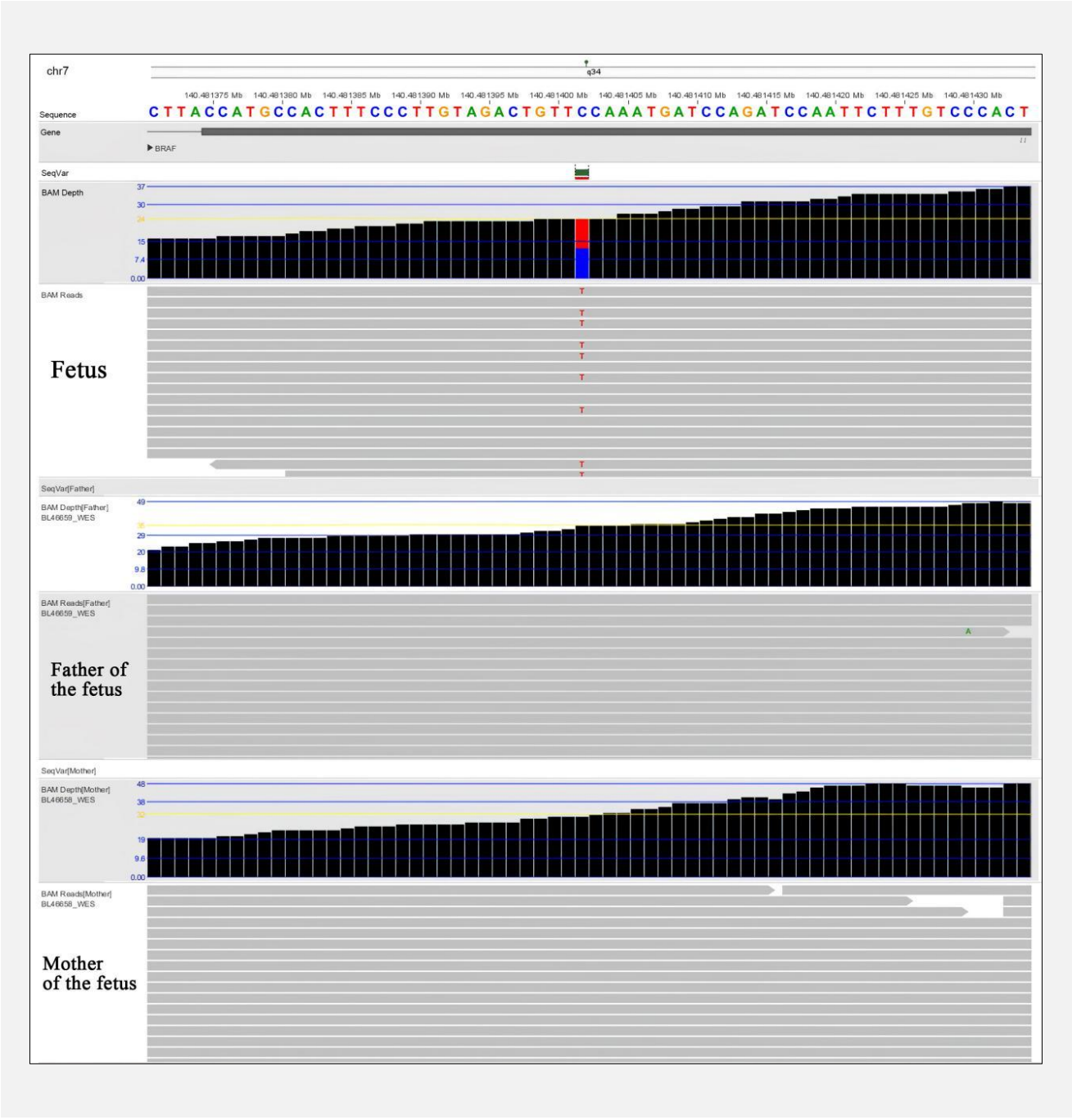


Figure 2. The presence of a de novo missense mutation, c.1406G > A, in the fetal BRAF gene suggested by WES.

Analysis of CMA test data

The results suggested no pathogenic microdeletions/duplications in the fetal chromosomal copy number.

Analysis of WES test data

Bioinformatics analysis suggested a de novo missense mutation, c.1406G > A (The base G (guanine) at position 1406 was replaced with A (adenine)), p.G469E (The amino acid at position 469 has changed from glycine G) to glutamic acid (E)), in exon 11 of the BRAF gene in the fetus (Figure 2). Sanger sequencing verified that this missense mutation was a de novo mutation, which was consistent with the WES results (Supplementary Figure 1). WES had better detection sensitivity compared to CMA.

DISCUSSION

Prenatal ultrasonography showed that the fetus had progressive and excessive increases in fetal biparietal diameter, head circumference and abdominal circumference from the second trimester of pregnancy, close to or exceeding the 90th percentile compared with fetuses of the same age. While the femur length had a progressive growth retardation, equal to or less than the 10^{th} percentile compared with fetuses of the same age, accompanied by polyhydramnios and overweight. At 38 weeks + 4 gestation when the neonate was born, the volume of amniotic fluid was 9,100 mL and the neonatal birth weight was 3,560 g, greater than the 90th percentile of the same-age neonates.

Postnatal physical examination of the proband revealed macrocephaly with a head circumference of 37 cm, greater than the 90th percentile of same-age neonates; distinctive facial characteristics including prominent forehead, no eyebrows, widely spaced eyes, collapsed nasal bridge and low ear position, short neck, short limbs and abnormal hand creases (Sydney line); ultrasonography revealed patent ductus arteriosus and atrial septal defect; hearing screening revealed failure of bilateral rapid brainstem evoked potential. These clinical manifestations were consistent with CFCS caused by BRAF (gene mutation).

Genetic testing suggested a de novo missense mutation, c.1406G > A, p.G469E, in exon 11 of the BRAF gene in the fetus. This is a variant with low frequency in the normal reference population gene database (allele frequency ExAC: 0.000008), and has not been reported in the 1000 Genomes and gnomAD databases. The p.G469E variant reduces the protein activity of B-Raf, resulting in diminished phosphorylation of MEK and ERK; a type of computer-aided analysis predicted that this variant has a high possibility of affecting protein structure/function; and in the ClinVar database, this variant is annotated as a pathogenic variant. According to the American College of Medical Genetics and Genomics (ACMG) genetic variant classification criteria and guidelines, this variant is considered as a pathogenic variant (PS2, PS3, PM1, PM2, PP3, PP5).

BRAF is involved in regulating the proliferation, survival, and differentiation of normal cells. Pathogenic mutations in the BRAF gene are inherited as an autosomal dominant trait, leading to CFCS, a genetic syndrome clinically characterized by distinctive facial features, heart defects, and intellectual disability [3,4]. Cases of CFCS are rare and most are sporadic de novo mutations. The incidence of the disease in Japan is 1:810,000 [5,6]. Goodwin et al. clinically found that the most common features included clinical manifestations such as macrocephaly, high forehead, convex facial profile, no eyebrows or sparse eyebrows, widely spaced eyes and increased medial canthal distance, and low ear position [7].

Fetuses suffering from CFC syndrome often have prenatal cardiac abnormalities, other characteristics including macrocephaly, macrosomia and urinary tract abnormalities, and polyhydramnios and preterm delivery are also common perinatal problems [3,8]. Templin et al. [9] studied the prenatal ultrasonographic data of 16 cases of CFCS and found that 81% of the pregnancies had abnormalities, 13% of the pregnant women had nuchal translucency thickening, 52% had polyhydramnios, and 67% of the patients had polyhydramnios with head circumference, biparietal diameter and abdominal circumference greater than the 90th percentile in percentages of 72%, 83%, and 81%, respectively. In contrast, 38% of the fetuses had femur lengths below the 10th percentile, and some cases also had urinary tract abnormalities.

Fetuses with CFCS often present with problems such as increased head circumference, biparietal diameter and abdominal circumference, polyhydramnios and relatively short femur length as well as cardiac abnormalities. Therefore, when the prenatal ultrasonography suggests this unusual pattern of growth parameters and accompanied by other abnormalities of the fetus, the possibility of monogenic genetic diseases such as CFCS must be considered. It is recommended that, in addition to CMA, whole exome sequencing needs to be selected for the screening and diagnosis of prenatal gene mutations. However, in the case of prenatal genetic diagnosis, due to the complexity and specialization of rare genetic diseases, possible information asymmetry between physicians and those tested may lead to ethical controversies as parents or pregnant women may make decisions without fully understanding the significance of the test, the risks, and subsequent management measures. In addition, the choice of parents to terminate a pregnancy after a fetus has been diagnosed with a rare genetic disease has become an ethical issue involving the right to life, choice and parental autonomy. Prenatal genetic diagnosis of rare genetic diseases, which relies on high-precision gene sequencing technology and specialized analysis software, is often accompanied by high testing costs, posing a financial burden to many families. Diagnosed fetuses also face long-term medical treatment and care costs, which vary by disease and treatment regimen, but are generally heavy. Although prenatal genetic screening for rare diseases is expensive, it is important for preventing hereditary diseases, reducing birth defects, alleviating the burden on families and society, promoting technological advances and cost reductions, and respecting the right to life and legal safeguards.

CONCLUSION

This report highlights BRAF gene mutations as potentially important genes leading to CFCS. Further sequencing by CMA and WES technologies is critical to understand the exact cause of the clinically observed phenotype.

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Declaration of Interest:
The authors have no conflicts of interest to declare.

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Additional material can be found online at:
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