Mosaic aneuploidy syndrome (MVA) is a rare autosomal recessive disorder characterized by clusters of mosaic aneuploidy in different chromosomes and tissues, with symptoms like intellectual disability, dysmorphism, hypotonia, developmental delay, microcephaly, special facial features, and mental retardation. In addition, it also has tumor susceptibility, especially Wilms tumor and thyroid carcinoma.

Mutations in BUB1B, CEP57, and TRIP13 genes cause MVA1, MVA2, and MVA3 respectively. The CEP57 gene located in chromosome 11q21, contains 11 exons, encodes a 500 amino acid protein, and plays a role in stabilizing microtubules. It has been shown to be closely associated with skeletal development and tumor suppression. Mutations in the CEP57 gene cause MVA2, which show specific manifestations such as hypothyroidism, short fourth finger, and congenital heart disease in addition to the common phenotypes of MVA. After searching the literature, there have been reports of cases in which patients showed a variety of clinical features, with some patients showing the phenotype of MVA, while others showed characteristics of CEP57-related diseases.

In this paper, we present a case of homozygous mutation of CEP57 gene diagnosed by whole exome sequencing, and analyze its phenotype and the mechanism of the disease.

AIM

Mosaic aneuploidy syndrome (MVA) is a rare genetic disease characterized by mosaic aneuploidies, intrauterine growth restriction, developmental delay, microcephaly, facial dysmorphism, mental retardation, and susceptibility to tumors. We retrospectively analyzed the clinical data of a 9-year-old girl, genetic and cytogenetic analysis were performed. This study helps us understand the disease more deeply and propose further study on correlation among CEP57 gene, aneuploidy, and cancer.

METHOD

Lymphocytes were isolated from the patient's peripheral blood for culture, hypotonic shock treatment and fixation. Appropriate specimen were selected for slide preparation, roasting, Geimsa staining and chromosome banding.

Whole-exome sequencing

Sanger sequencing indicated a novel homozygous nonsense mutation (c.312T>G) in CEP57 gene (NM_144679.4) at the termination of protein translation (p.Tyr104*). The mutations in CEP57 have been reported to cause MVA. Sanger sequencing indicated both the parents of the child carried heterozygous variants at this locus, and no other causative genes were found. Chromosome analysis suggested that 79 of 100 cells were 46,XX, while 21 cells showed aneuploidies.

RESULTS

The proband, a 9-year-old Chinese girl is the second child of non-consanguinity parents. She underwent cesarean section (37 weeks) with a birth length of 45 cm and a birth weight of 2900 g. Her psychomotor development is normal. All her family members are healthy. Her father's height was 172 cm, her mother was 155 cm, and her 15 years old sister was 164 cm tall.

Growth retardation was observed after two years of her birth. At the age of 5, echocardiogram showed she had patent ductus arteriosus. Last examination, at the age of 9, showed severe growth retardation with microcephaly. Her height was 121 cm (2.35SD), her weight was 27.35 kg (0.26SD) and her head circumference was 46cm (<2SD). She presented with dysmorphic features including long face, large forehead, low set ears, wide nasal bridge and nasal tip, small mandible and retrognathia. Her teeth was small and fingers was short.

WES revealed c.312T>G of CEP57 gene (NM_144679.4) a novel homozygous mutation, leading to the termination of protein translation (p.Tyr104*). The mutations in CEP57 have been reported to cause MVA. Sanger sequencing indicated both the parents of the child carried heterozygous variants at this locus, and no other causative genes were found. Chromosome analysis suggested that 79 of 100 cells were 46,XX, while 21 cells showed aneuploidies, confirmed the diagnosis of MVA.

CONCLUSIONS

We present the first case of MVA with CEP57 mutation in China, identifying a novel homozygous nonsense mutation in CEP57 gene (p.Tyr104*). The phenotypes were mildly different from those described in the literatures.

REFERENCES


CONCLUSION

We present the first case of MVA with CEP57 mutation in China, identifying a novel homozygous nonsense mutation in CEP57 gene (p.Tyr104*). The phenotypes were mildly different from those described in the literatures.

ACKNOWLEDGEMENTS

Thanks to all the members of the Department of Endocrinology and Metabolism at Shanghai Children’s Medical Center, Shanghai Jiaotong University School of Medicine.

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