A NOVEL CEP57 MUTATION OF MOSAIC VARIEGATED ANEUPLOIDY SYNDROME IN A CHINESE GIRL : A CASE REPORT AND REVIEW OF LITERATURE

Biyun Feng[1], Qianwen Zhang[1], Guoying Chang[1], Xiumin Wang[1]

1. Department of Endocrinology and Metabolism, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

ESPE 2021
The 59th Annual Meeting Online
22-26 September 2021

INTRODUCTION

Mosaic aneuploidy syndrome (MVA) is a rare autosomal recessive disorder characterized by chimeric aneuploidy in different chromosomes and tissues, with trisomy and monosomy. The clinical manifestations of MVA are intrauterine growth restriction, developmental delay, microcephaly, special facies, and mental retardation. In addition, it also has tumor susceptibility, especially leukemia, Wilms tumor, and rhabdomyosarcoma.

Mutations in BUB1B, CEP57, and TRIP13 genes cause MVA1, MVA2, and MVA3 respectively. The CEP57 gene locates in chromosome 11q21, contains 11 exons, encodes a 500 amino acid protein, and plays a role in stabilizing microtubules. It has been reported that CEP57 gene is closely associated with skeletal development and tumor suppression. Mutations in the CEP57 gene cause MVA2, which show specific manifestations such as hypothyroidism, short limb ends, and congenital heart disease in addition to the common phenotype of MVA. After searching the literature, there have been only 10 cases reported to date.

In this paper, we present a case of homozygous mutation of CEP57 gene diagnosed by karyotype analysis and whole exome sequencing, and analyze its phenotype and the therapeutic effect after application of growth hormone.

AIM

Mosaic variegated 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 tumor. We retrospectively analyzed the clinical data of a 9-year-old girl, genetic and karyotype analysis were performed.This study hereby helps deeper understanding the CEP57 gene mutation, and promote further study on corelation among CEP57 gene, aneuploidy and cancer.

METHOD

- Patient

A careful counseling has been offered to proband and her parents to obtain an informed consent. The study was approved by the ethics committee of Shanghai Children's Medical Center.

- Chromosome analysis

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

- Whole-exome sequencing

Informed consent was obtained from the parents and approved by the hospital's review board prior to molecular analysis, then 2 mL peripheral blood of the girl and her parents was collected respectively. The blood was placed in ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes for examination. Exons were captured using the Agilent Sureselect method, high-throughput sequencing was performed using the Illumina sequencing platform, sequencing data were matched and analyzed by NextGENe ® software, and variation filtering and interpretation were performed with the Ingenuity online software system.

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 2500 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 (<-3SD). She presented with dysmorphic features including long face, large forehead, facial asymmetry, 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 (NM014679.4) 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.*

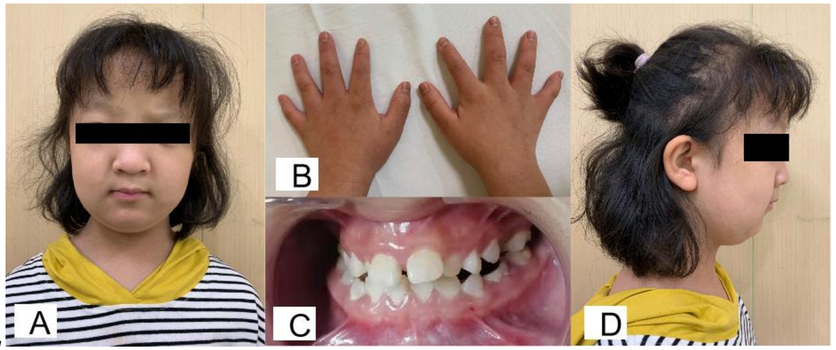

Fig. 1 Image of the patient. **a,d.** Facial abnormalities included long face, large forehead, facial asymmetry, low set ears, wide nasal bridge and nasal tip, small mandible and retrognathia. **b.** Short fingers. **c.** Small and sparse teeth

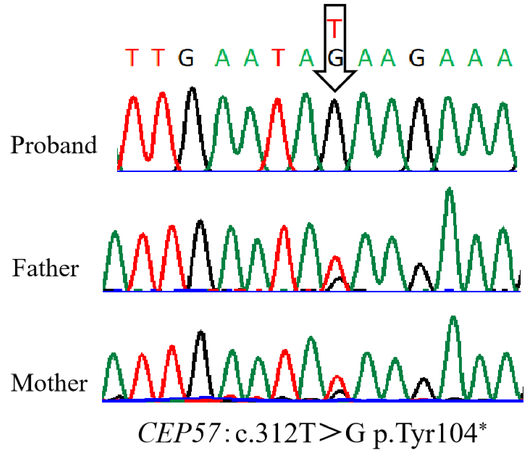

Fig 2. Sanger sequencing indicated a novel homozygous nonsense mutation (c.312T＞G, p.Tyr104* in exon 3) in the patient. Both the parents carried heterozygous variants at this locus. Black arrow shows mutant base

CONCLUSIONS

We present the first case of MVA in a patient 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

Aziz K et al 2018. Mosaic-variegated aneuploidy syndrome mutation or haploinsufficiency in Cep57 impairs tumor suppression. J Clin Invest 2018; 128:3517-3534.

Brightman DS et al. 2018. Mosaic variegated aneuploidy syndrome caused by a CEP57 mutation diagnosed by whole exome sequencing. Clin Case Rep 2018; 6:1531-1534.

Callier P et al. Microcephaly is not mandatory for the diagnosis of mosaic variegated aneuploidy syndrome. Am J Med Genet A 2005; 137:204-207.

Dery T et al. Follow-up of two adult brothers with homozygous CEP57 pathogenic variants expands the phenotype of Mosaic Variegated Aneuploidy Syndrome. Eur J Med Genet 2020; 63:104044.

Hanks S et al. Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. Nat Genet 36:1159-1161.

Lukinavicius G, Lavogina D, Orpinell M, Umezawa K, Reymond L, Garin N, Gonczy P, Johnsson K. 2013. Selective chemical crosslinking reveals a Cep57-Cep63-Cep152 centrosomal complex. Curr Biol 2004; 23:265-270.

Meunier S et al. Pivotal role of translokin/CEP57 in the unconventional secretion versus nuclear translocation of FGF2. Traffic 2009; 10:1765-1772.

Ph.D. TRF et al. Homozygous BUB1B Mutation and Susceptibility to Gastrointestinal Neoplasia. New England Journal of Medicine 2010;363.

Pinson L et al. CEP57 mutation in a girl with mosaic variegated aneuploidy syndrome. Am J Med Genet A 2014;164A:177-181.

Snape K et al. Mutations in CEP57 cause mosaic variegated aneuploidy syndrome. Nat Genet 2011;43:527-529.

Wu Q et al. Cep57, a NEDD1-binding pericentriolar material component, is essential for spindle pole integrity. Cell Res 2012;22:1390-1401.

Yost S et al. Biallelic TRIP13 mutations predispose to Wilms tumor and chromosome missegregation. Nat Genet 2017;49:1148-1151.

Zhou H et al. Cep57 is a Mis12-interacting kinetochore protein involved in kinetochore targeting of Mad1-Mad2. Nat Commun 2016;7:10151.

ACKNOWLEDGEMENTS

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

CONTACT INFORMATION

Corresponding Author:

wangxiumin1019@126.com