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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Navdeep Singh, MBBS, MS, Assistant Professor, Division of Transplantation, Department of Surgery, The Ohio State University, Columbus, OH 43210, United States. navdeep.singh@osumc.edu

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CASE REPORT

Novel compound heterozygous variants in the *TAF6* gene in a patient with Alazami-Yuan syndrome: A case report

Shuang-Zhu Lin, Jin-Hua Feng, Li-Ping Sun, Hong-Wei Ma, Wan-Qi Wang, Jia-Yi Li

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Shuang-Zhu Lin, Jin-Hua Feng, Li-Ping Sun, Diagnosis and Treatment Center for Children, The First Affiliated Hospital to Changchun University of Chinese Medicine, Changchun 130021, Jilin Province, China

Hong-Wei Ma, Department of Developmental Pediatrics, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Wan-Qi Wang, Jia-Yi Li, Changchun University of Chinese Medicine, Changchun 130021, Jilin Province, China

Corresponding author: Shuang-Zhu Lin, MD, Doctor, Diagnosis and Treatment Center for Children, First Affiliated Hospital to Changchun University of Chinese Medicine, No. 1478 Gongnong Road, Chaoyang District, Changchun 130021, Jilin Province, China.
61858@163.com

Abstract

BACKGROUND

This case report describes a novel genotypic and phenotypic presentation of Alazami-Yuan syndrome, and contributes to the current knowledge on the condition.

CASE SUMMARY

We report an 11-year-old boy with Alazami-Yuan syndrome. The main clinical manifestations were rapid development of puberty, typical facial features of Cornelia de Lange syndrome, and normal intelligence. Peripheral blood DNA samples obtained from the patient and his parents were sequenced using high-throughput whole-exosome sequencing, which was verified by Sanger sequencing. The results showed that there was a compound heterozygous mutation of c.1052delT and c.76A>T in the TATA-Box Binding Protein Associated Factor 6 (*TAF6*) gene. The mutation of c.1052delT was from his mother and the mutation of c.76A>T was from his father.

CONCLUSION

This study extends the mutation spectrum of the *TAF6* gene, and provides a molecular basis for the etiological diagnosis of Alazami-Yuan syndrome and genetic consultation for the family.

Key Words: Alazami-Yuan syndrome; *TAF6*; Children; Cornelia de Lange syndrome; Case

report

Core Tip: We report an 11-year-old boy with Alazami-Yuan syndrome. The main clinical manifestations were rapid development of puberty, typical facial features of Cornelia de Lange syndrome, and normal intelligence. DNA sequencing test showed that there was a compound heterozygous mutation of c.1052delT and c.76A>T in the TATA-Box Binding Protein Associated Factor 6 (*TAF6*) gene. This study extends the mutation spectrum of the *TAF6* gene, and provides a molecular basis for the etiological diagnosis of Alazami-Yuan syndrome and genetic consultation for the family.

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INTRODUCTION

Alazami-Yuan syndrome is an autosomal recessive genetic disease caused by mutation of the TATA-Box Binding Protein Associated Factor 6 (*TAF6*) gene. Its clinical features are similar to those of Cornelia de Lange syndrome (CdLS). Typical features include short stature, mental retardation, arched eyebrows, conjoined eyebrows, protruding bridge of the nose, nose tilted forward, and a thin upper lip[1,2]. There are differences in the gene mutation site and genetic mode between Alazami-Yuan syndrome and CdLS. CdLS is caused by mutations in Nipped-B-like protein (*NIPBL*), structural maintenance of chromosomes 1A (*SMC1A*), *SMC3*, *RAD21*, and histone deacetylase 8, and the genetic mode is autosomal dominant inheritance and X-linked dominant inheritance[3].

In this case study, two new mutations of the *TAF6* gene were found by high-throughput whole-exosome sequencing in an 11-year-old patient with rapid development of puberty and special facial features.

CASE PRESENTATION

Chief complaints

An 11-year-old male patient was referred to our clinic due to testicular enlargement and rapid growth in height.

History of present illness

The patient presented with testicular enlargement without obvious cause, no pubic hair, no spermatorrhea, and a small amount of beard hair for 6 mo. Peripheral blood DNA samples obtained from the patient and his parents were sequenced using high-throughput whole-exosome sequencing, which was verified by Sanger sequencing.

History of past illness

The patient was the 2.1 kg (< -3sd), 46 cm (< -1sd), and the product of a 36 wk pre-gnancy born by cesarean section to a gravida 1, para 0-1 mother without a history of asphyxiation and resuscitation. The patient exhibited catch-up growth after birth and no history of feeding difficulties. The physical and mental development of the child at 2-years-old was similar to that of children the same age.

Personal and family history

His non-consanguineous parents were clinically normal. His father and mother were 170 and 151 cm in height, respectively. There was no family history of genetic or infectious diseases.

Physical examination

On physical examination at his visit at 11 years of age, his weight was 52.5 kg and length was 146.1 cm. The patient had a clear mind, good spirit, normal hair, and no yellow coloring or bleeding spots on the skin. He had arched eyebrows, protruding bridge of the nose, forward leaning nostrils, a thin upper lip, a small amount of beard, normal jaw, and an inconspicuous laryngeal knot. Both pupils were equal in

size and were sensitive to light. Breath sounds in both lungs were clear, and dry and moist rales were not heard. Heart sounds were strong and regular, the heart rate was 90 bpm, and no pathological murmur was found in each valve area. The abdomen was soft, no tenderness and rebound pain was observed, the liver and spleen were unpalpable. The big toes on both feet were widened and the limbs were normal. Limb muscle tension was normal. Physiological reflexes were present, and pathological reflexes were not found. Bilateral testes were symmetrical, about 8-10 mL in size, without pubic hair.

Laboratory examinations

The patient's liver function, kidney function, electrolytes, blood glucose and blood lipids were normal. Insulin-like growth factor was normal. Karyotype analysis of cultured cells revealed a karyotype of 46XY. Sex hormone levels were as follows: estradiol 25 pg/mL, (adult male reference value: < 20-47 pg/mL), follicle-stimulating hormone 6.62 mIU/mL (adult male reference value: 1.27-19.26 mIU/mL), luteinizing hormone 3.20 mIU/mL (adult male reference value: 1.24-8.62 mIU/mL), and testosterone 1.75 ng/mL (adult male reference value: 1.75-7.81 ng/mL). Total 25 hydroxy vitamin D was 13.79 ng/mL (reference value < 20 ng/mL vitamin D deficiency). Fasting insulin was 23.1 mU/L (reference value: 2.3-11.8 mU/L). Thyroid function was evaluated as follows: Triiodothyronine 6.84 pmol/L (reference value: 2.63-5.71 pmol/L), thyroxine 12.10 pmol/L (reference value: 9.01-19.05 pmol/L), and thyroid-stimulating hormone 1.9145 μIU/mL (reference value: 0.30-4.80 μIU/mL).

Imaging examinations

The patient underwent a skeletal examination, and the results showed that the bone age was 13 years. Magnetic resonance imaging of the pituitary gland was normal. Slight lateral curvature of the thoracic spine was observed.

High throughput whole-exome sequencing and mitochondrial sequencing

Informed consent was obtained from the parents on behalf of the proband for whole-exome sequencing, mitochondrial sequencing, and the publication of photographs. DNA was obtained from peripheral blood samples from the patient and his parents. Sequencing and analyses were performed by the Beijing Mygenostics (Beijing, China), which is a high-tech biotechnology company providing life science instruments, reagents and technical services. The second generation sequencer Illumina NextSeq™500 (Illumina, San Diego, CA, United States) was used to sequence the captured region at two ends, with a reading length of 150 bp. After sequencing the target region, the splices and low-quality data in the sequencing data were removed. Using Burrows-Wheeler Aligner software to compare with the reference genome (hg19 version), the data on sequencing depth, homogeneity, and probe specificity were analyzed. Genome Analysis Toolkit software was used to detect the polymorphic sites in the comparison data of each sample, and statistical analyses of the data on single nucleotide polymorphisms (SNPs) and insertion deletion mutations (indels) were conducted. The SNPs and indels were screened using the database of SNPs, (http://www.ncbi.nlm.nih.gov/SNP), 1000 human genome (http://www.internationalgenome.org), and the Exome Aggregation Consortium database (http://exac.broadinstitute.org). Application of the human gene mutation database (HGMD, http://www.hgmd.cf.ac.uk) and the human Online Mendelian genetic database (OMIM, http://omim.org) confirmed the reported pathogenic gene locus. The effects of variation on protein structure and pathogenicity were predicted by Rev, Polyphen-2, and Sift. The American College of Medical Genetics and Genomics (ACMG) sequence variation interpretation standards and guidelines[4] were used for a comprehensive evaluation of the pathogenicity of mutation sites.

Gene detection results and pathogenicity analysis

Whole-exome sequencing showed that there was complex heterozygous variation of the *TAF6* gene in this patient, one of which was an unreported frameshift mutation c.1052delT (p.I351Tfs*40), which may lead to the loss of gene function; the frequency of the variation in the normal population database is unknown, and is a low-frequency variation; the results of protein function prediction are unknown, and are not reported in the HGMD database. According to Sanger sequencing, the variation originated from the child's mother, and the paternal gene was wild-type (Figure 1). According to ACMG guidelines, the mutation was suspected to be pathogenic.

The other was a missense mutation c.76A>T(p.M26L), which has not been reported. This missense mutation showed 76 nucleotide deficiency changes from adenine to thymine, resulting in the 26 amino acids changing from methionine to leucine. The frequency of the mutation in the normal population database is 0.0014, and is a low-frequency mutation; the results of protein function prediction are unknown, and are not reported in the HGMD database. According to Sanger sequencing, the variation originated from the child's father, and the maternal gene was wild-type (Figure 1). According to ACMG guidelines, the clinical significance of the variation is unknown.

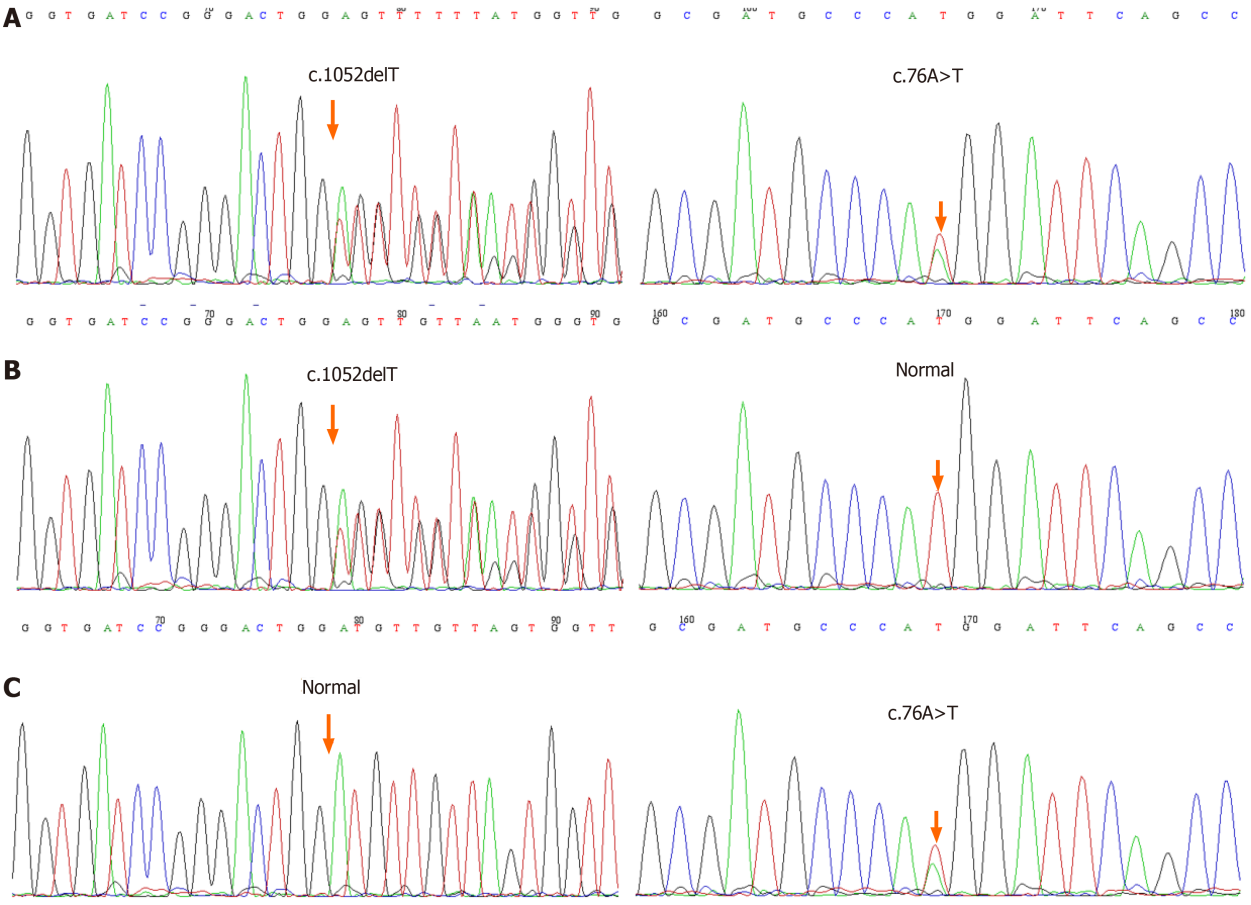

Figure 1 Sanger sequencing of the TATA-Box Binding Protein Associated Factor 6 gene in the patient and his parents. A: Compound heterozygote of c.1052delT and c.76A>T in the TATA-Box Binding Protein Associated Factor 6 gene in the patient; B: The mother of the patient is a c.1052delT mutation carrier; C: The father of the patient is a c.76A>T mutation carrier.

FINAL DIAGNOSIS

Sanger sequencing showed that there was a compound heterozygous mutation of c.1052delT and c.76A>T in the *TAF6* gene.

TREATMENT

According to the clinical manifestations, laboratory tests, and gene sequencing results, the clinical phenotype of the patient was Alazami-Yuan syndrome. The boy's weight was above the normal range, and he was given exercise and diet guidance. The patient's total 25 hydroxy vitamin D level was low, and vitamin D 2000 U was administered once a day for 3 mo, and calcium carbonate 500 mg once a day for 3 mo. To improve the final height of the child, 3.75 mg of diphereline was injected once every 28 d, and 10 U recombinant human growth hormone was injected sub-cutaneously every night.

OUTCOME AND FOLLOW-UP

After 4 mo of treatment, the child's height increased by 3.6 cm, his weight decreased by 0.7 kg, and the vitamin D level returned to normal. During treatment, skin at the injection site was good, fasting blood glucose and nail function were normal, and there was no eyelid edema, headache, or other adverse reactions.

DISCUSSION

The *TAF6* gene is located on chromosome 7q22.1, which is involved in the initiation and activation of

RNA transcription and is closely related to human cell viability[5]. The mutation of *TAF6* gene can lead to Alazami-Yuan syndrome. In published cases, 5 patients from two families have been reported. Their parents were consanguineous, and the mutation types were homozygous mutations, with mutation locations at c.136c>T and c.212t>C[1,2]. The clinical manifestations of these patients were similar, with short stature, mental retardation, and typical facial features of CdLS. We report a case of compound heterozygous mutation in which the parents were non-consanguineous and the mutation location was c.1052delT and c.76A>T. The main clinical manifestations were rapid puberty and special body surface characteristics, including arched eyebrows, protruding nose bridge, forward leaning nose, thin upper lip and widened big toes on both feet. The child had normal intelligence and was born small for gestational age, but had no history of feeding difficulties. Growth and development before puberty were basically normal.

CdLS (OMIM: 122470) is a type of multiple congenital dysplasia. Patients usually have physiological, cognitive and behavioral characteristics[6]. According to previous case reports, CdLS1 caused by gene mutation of *NIPBL* accounts for about 50% to 60% of CdLS cases[7]. A large number of individuals with typical CdLS carry a mosaic *NIPBL* variation[8]. Although individuals with typical CdLS phenotypes are likely to have mutations in *NIPBL*, individuals with one of the other pathogenic CdLS genes can also meet the standard for typical CdLS[9-14]. Typical CdLS has a unique craniofacial appearance and growth pattern, as well as limb deformities. However, not all CdLS patients show typical phenotypes, and there are differences in the manifestations of the disease itself, from mild to severe, and the degree of facial and limb involvement is also different[15]. In this report, although the patient had typical facial features of CdLS, he had a unique clinical phenotype and gene mutation sites, which has practical significance for in-depth research and clinical guidance.

The patient first attended hospital due to enlarged testicles for 6 mo. His bone age was 2 years older than his actual age, and puberty developed rapidly. In order to improve the final height of this patient, he was treated with the combination of diphereline and recombinant human growth hormone. The patient's special facial features were similar to those of CdLS which attracted our attention at his first visit, but the patient had no mental retardation or language deficiency. In order to determine the cause of the disease, we used high-throughput whole-exome sequencing and identified a compound heterozygous mutation of the *TAF6* gene. Most patients with CdLS have new mutations, and the risk of their parents having another CdLS child is low. In this case, the two mutated genes were from the father and mother, respectively. The probability of the parents having a child with Alazami-Yuan syndrome was 25%, and the probability of carrying the pathogenic gene in a subsequent child was 50%. It is suggested that prenatal consultation and diagnosis should be carried out if the child's mother has subsequent pregnancies.

CONCLUSION

Herein, the rapid development of puberty and older bone age were defined for the first time in the *TAF6* -related phenotype. We suggest that *TAF6* should be considered in individuals with rapid development of puberty and CdLS-overlapping features. Furthermore, our patient was found to be a compound heterozygote for two novel pathogenic variants in *TAF6*. Identification of a compound heterozygote should encourage clinicians to consider Alazami-Yuan syndrome in patients with similar clinical features and without a family history of consanguinity.

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FOOTNOTES

Author contributions: Lin SZ and Feng JH collected and analyzed all clinical data and wrote the manuscript; Sun LP participated in collation of the literature and the chart research; Ma HW was involved in the genetic diagnosis and treatment of the patients; Lin SZ, JF, Wang WQ, and Li JY substantially participated in drafting and revising the manuscript for important intellectual content; all authors involved have read and approved the final manuscript.

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ORCID number: Shuang-Zhu Lin 0000-0001-5333-2138; Jin-Hua Feng 0000-0002-2911-0022; Li-Ping Sun 0000-0002-3679-4469; Hong-Wei Ma 0000-0001-8678-5811; Wan-Qi Wang 0000-0002-8247-7616; Jia-Yi Li 0000-0002-7729-4479.

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