

Alstrom Syndrome with Novel ALMS1 Mutations: A Case Report



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ABSTRACT

Objective To report novel mutations of ALMS1 and evaluate clinical characteristics in the Chinese Child with Alstrom syndrome (ALMS).

Methods The Child and his parents were examined clinically and venous blood was collected. ALMS1 gene analysis was carried out using DNA Sanger sequencing. Using polymerase chain reaction (PCR) amplified ALMS1 gene exons and splice sequence. The objective products were directly sequenced and analyzed. Pathogenic gene mutations were identified by contrast with the transcript (GRCh37/hg19).

Results The Child had typical clinical features of Alstrom syndrome. Sequencing the ALMS1 gene confirmed 2 novel heterozygous non-sense mutations in exon8, c.4600C > T (p.Q1534X) and in exon16, c.11410C > T (p.R3804X), respectively, resulting in premature protein truncation.

Conclusions 2 novel heterozygous non-sense mutations were identified in the Chinese Child with Alstrom syndrome, expanding the ALMS1 gene mutations causing Alstrom syndrome.

Introduction

Alstrom Syndrome is a kind of recessive and single gene (monogenic) ciliopathy, caused by ALMS1 gene mutations, typical characteristics affecting multiple systems, including early retinal dystrophy, Progressive blindness, sensorineural hearing impairment, childhood obesity, insulin resistance, type 2 diabetes mellitus, cardiomyopathy, multiple organ fibrosis and failure [1]. In 1959, this condition was reported for first time by Alstrom [2]. ALMS1 gene located in the basal parts and centrosomes of ciliated cells, widely expressed in various infected organs or tissues and led to the pathological changes in flagella transport and cell cycle regulation [3, 4]. Recent studies had show that ALMS1 played an important role in cell migration, extracellular matrix production [4, 5], and in the endosomal trafficking of transferrin, GLUT4, and Notch1 [6, 7]. The precise molecular pathogenic mechanisms have not been clarified so far. The literatures reported 239 ALMS1 gene mutations [1]. The population prevalence of ALMS is about one case per 1,000,000 persons. 700 cases had been reported worldwide nearly [8]. The reports of the Alstrom syndrome were less in China, especially about the pathogen-

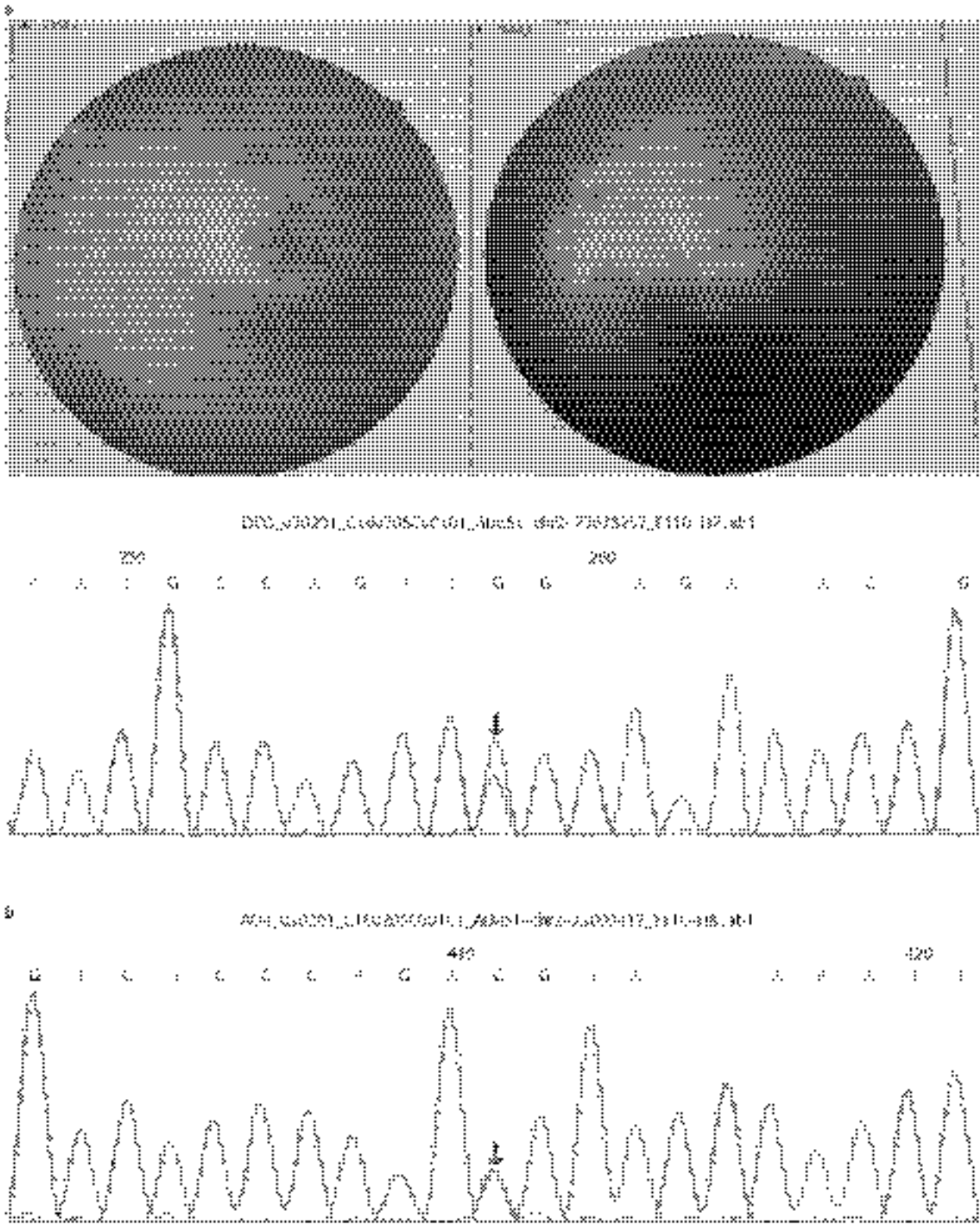
ic gene. We aimed to evaluate clinical characteristics and identify the pathogenic gene in the Chinese Child with Alstrom syndrome.

Material and Methods

Case report

The 11-year-old Chinese boy presented with poor vision, nystagmus, photophobia and hearing disorder for 8 years, more Drinks and polyuria for 2 years, but intelligence was normal. His prior disease history included poor vision along with binaural hearing loss at the age of 2. His vision continued to deteriorate and he just had perception of light by the age of 6. He was also previously considered to have typical symptoms of diabetes (more drinks, polyuria, polyphagia and weight loss) at the age of 9 and suffered from acute pancreatitis Once. His Parents were not close relative. His brother and sister were normal. The boy had no family history of similar disorders.

Fundus examination showed pigment retinal degeneration, pale optic discs and vessels anomaly (► Fig. 1). Pure tone audiograms



► **Fig. 1** Bilateral fundus features (retinitis pigmentosa, vessels anomaly, and optic atrophy) of the boy. **a** Sequence (sense strand) showing a heterozygous nonsense mutation in exon 8, c.4600C>T (p.Q1534X). **b** Sequence (sense strand) showing a heterozygous nonsense mutation in exon 16, c.11410C>T (p.R3804X). Figure **a, b** ALSM1 gene sequencing results in the boy

(PTA) showed bilateral high tone (90 decibels) sensorineural hearing loss. Physical examinations showed the patient was not obese (BMI 19.8 kg/m²), short stature, skin pigmentation and acanthosis nigricans. The examinations of the thyroid gland, lung, heart, abdomen were normal. External genital organs showed the bilateral testicular volume were 4 ml, penis about 3.5 cm and Tanner stage was 1. Spine and limbs were not seen deformity. There were no evidences of poly/syndactyly.

Laboratory testing results suggested that the urinalysis and blood count analysis were normal. Levels of blood creatinine, urea nitrogen, Insulin-like growth factor 1, growth hormone, adrenocorticotrophic hormone, cortisol were normal. The Sex hormone results were Luteinizing hormone (0.39 IU/L, range, 0.2–4.9), progesterone (0.34 nmol/L, range, <0.32–1.05), follicle-stimulating hormone (7.10 IU/L, range, 1.8–3.2), prolactin (226.81 mIU/L, range, 63.3–254.5), testosterone (1.36 nmol/L, range, 0.62–5.20), estradiol (<43.31 pmol/L, range, 18–59). The experimental result of parathyroid hormone was 12.90 pg/ml. The levels of fasting plasma glucose (9.43 mmol/l, range, 3.9–6.1), glycosylated hemoglobin (6.5%), fasting c-peptide (1596.73 pmol/l, range, 270–1280) and fasting insulin (108.63 uIU/ml, range, 5–25), aspartate aminotransferase (63.01 U/l, range, 13–35), alanine aminotransferase (68.21 U/l, range, 7–40), uric acid (504.51 umol/l, range, 155.00–357.00), triglycerides (7.56 mmol/l; range, 0.56–1.7), total cholesterol (7.33 mmol/l, range, 2.8–5.2) were elevated. The pancreas and thyroid related antibodies were negative. The thyroid stimulating hormone (TSH 133.710 mIU/L, range, 0.70–6.40) was elevated, thyroid hormones (FT3 4.53 pmol/L, range, 3.5–10.0; FT4 9.57 pmol/L, range, 10.0–28.0) were reduced. Thyroid ultrasound showed that the shape and size were normal and the blood velocity of thyroid artery significantly reduced. Karyotype analysis was normal structure with chromosomes 46 xy. The X-ray of hand showed bone developed in advance, conforming to skeletal age of 11 to 12 years old. Cardiac ultrasound showed that cardiac structure was normal.

Methods

We signed the consent form and were approved by the hospital ethics committee. Venous blood was collected from the child and his parents. Using Magbind Blood DNA Kit (CWBIO, JiangSu) extracted genomic DNA according to the kit instruction. Designed the primer according to the sequence of ALMS1 gene, then amplified using PCR. The PCR reaction conditions as follows: 95 °C pre degeneration 10 min, modified 30 s, 58 °C–64 °C, annealing 30 s, 72 °C chain extension 45 s, amplification 25 cycles, 72 °C added chain extension 5 min in the last. PCR system volume were 100 ul. Then conducted high-throughput sequencing and analysis for PCR amplification products of ALMS1 gene single point using sequencing machine (illumina HiSeq 2500) and found the sequence containing the insertion/deletion (InDel) using GATK software. Interpreted InDel and determined the gene mutations using the consensus coding Sequence project (CCDS), human genome database (HG19) and dbSNP (v138) information. The above gene amplifications and gene sequence analysis were completed by Beijing Mai Keno Gene Technology Company.

Results

The clinical features of the object

The object who did not come from a close relative family suffered from eyes lesions (progressive vision loss, nystagmus, photophobia and retinitis pigmentosa), hearing loss, hyperinsulinemia, type 2 diabetes mellitus, liver function damaged, dyslipidaemia, hypothyroidism and high uric acid disease.

The genetic detection results

By direct sequencing of the ALMS1 gene, we identified 2 novel heterozygous nonsense mutations in exon 8, c.4600C>T (p.Q1534X) and in exon 16, c.11410C>T (p.R3804X) in the boy (Figure A and B) and caused premature protein truncation leading to disease. The 2 mutations were not reported in the literature. The boy's father carried the heterozygous p.R3804X change. The boy's mother carried the heterozygous p.Q1534X change.

Discussion

ALMS is a rare autosomal recessive hereditary disease, which is caused by gene mutations in ALMS1 located in 2 p13, containing 23 exons and encoding a protein comprised of 4,169 amino acids[9].

The majority mutations were nonsense and frameshift variations (96%), leading to translation early termination [1]. Marshall, et al. identified there was a strong pathogenic clustering gathered in ALMS1 gene exons 8 (49%), 10 (17%) and 16 (19%), known as the mutational hotspots for ALMS1. Marshall, et al. also identified novel mutations in ALMS1 in exons 3, 5, 8, 9, 10, 12, 14, 15, 16, 17, 18, 19 and 21[1]. ALMS1 gene mutations had reported rarely in China. First reported mutation was homozygous nonsense mutation, c.8335 c>T (Q2471X), located in exon 10 [10]. We found the child with 2 novel heterozygous nonsense mutations, c.4600C>T (p.Q1534X), in exon 8 and c.11410C>T (p.R3804X), in exon 16. Our finding expanded the ALMS1 pathogenic genes causing Alstrom syndrome.

Alstrom syndrome belonged to a kind of ciliopathy. There were overlapping phenotypes with other ciliopathies, for instance, Bardet-Biedl syndrome (BBS) and Senior-Loken syndrome, particularly with BBS [11]. Alstrom syndrome had relative normal intelligence and no polydactyly. Because of the clinical overlapping phenotypes and delayed appearing of the disease symptoms, the diagnosis was very difficult. However, diagnostic criteria had been established to help precise diagnosis of the disease[12]. The boy had the clinical features of Alstrom syndrome and was short of polydactyly and mental retardation. Gene tests diagnosed the disease clearly.

Recently, some experiments of the ciliopathies had been carried out, mainly concentrated in the restore of kidney or liver function, such as delaying retinal degeneration progression in BBS [13], as well as on polycystic kidney disease (PKD) [14, 15]. But its efficacy in other affected organs was limited. Up to now, no specific therapy exists for the patients. Symptomatic treatment can be given only. We must continue to study molecular pathogenic mechanism of the disease and clear targets for gene therapy.

Conclusions

We reported 2 novel mutations in the patient with ALMS. Our findings expanded pathogenic genes of ALMS1.

Acknowledgment

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Informed Consent

Written informed consent was obtained from the patient for publication of this report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Conflicts of Interest

No conflict of interest was declared.

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