Case Report

Identification of a Novel Mutation in ALMS1 in a Chinese Patient with Monogenic Diabetic Syndrome by Whole-Exome Sequencing

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Received: 13-Aug-2022;
Revision: 12-Sep-2022;
Accepted: 22-Sep-2022;
Published: 20-Dec-2022

Abstract

Alstrom syndrome (AS) is one type of monogenic diabetic syndromes caused by mutation in the *ALMS1*. Due to rare prevalence and overlaps of clinical symptoms, monogenic diabetes is often misdiagnosed. Here, we report a Chinese diabetes patient with poor blood glucose control and insulin resistance. With whole-exome sequencing (WES), this patient was classified into monogenic diabetes and diagnosed as AS with one novel gene mutation identified. This study highlights the clinical application of WES in the diagnosis of monogenic diabetes.

Keywords: *Alstrom syndrome, diabetes mellitus, monogenic diabetes, whole-exome sequencing*

Introduction

Diabetes mellitus is a metabolic disease and classification is needed after the diagnosis of diabetes for determining therapy.[1] There is one rare type called monogenic diabetes. It is caused by genetic mutations. Due to the clinical overlaps and complexity, monogenic diabetes is often misdiagnosed.[2,3] Here, we report a clinical application of whole-exome sequencing (WES) in assisting the identification of Alstrom syndrome (AS).

Case Report

A 30-year-old Han Chinese female with diabetes for over 20 years was admitted to this hospital because of poor glycemic control (glycosylated hemoglobin 13.0%). High-dose insulin therapy was needed (84 IU/day). Her height was 142 cm (<third centile), her weight 57 kg, and her waist-to-height ratio 0.62 with sparse hair [Figure 1a]. She has no polydactyly [Figure 1b and c].

On admission, the results of 0 and 2-hour oral glucose tolerance test about C-peptide were 2.72 nmol/L and 2.65 nmol/L. More than 20 years ago, her vision gradually decreased. Nystagmus and blindness occurred at the age of 12. Pattern visual-evoked potential indicated P100 wave amplitude of both eyes decreased, suggesting optic nerve damage. Flash electroretinography suggested abnormal cone-rod cells. She has evidence of renal failure secondary to diabetic nephropathy. One year before her most recent admission, her estimated GFR was 66.92 mL/min consistent with grade 2 renal failure. On admission, eGFR was 14.61 mL/min consistent with end-stage renal failure. Kidney biopsy revealed diabetic nodular glomerulosclerosis. Twenty years ago, she was diagnosed with chronic otitis media following which she developed sensorineural deafness for which she was prescribed hearing aids. Peripheral blood chromosome analysis was 46, XX karyotype. She had hypertension and hypertriglyceridemia for 6 years. Menstruation began at the age of 15 and was irregular. Her parents are not a related marriage. Her parents, grandmother,

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Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_544_22

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How to cite this article: Zhong M, Huang LN, Zhang SJ, Yan SJ. Identification of a novel mutation in ALMS1 in a Chinese patient with monogenic diabetic syndrome by whole-exome sequencing. Niger J Clin Pract 2022;25:2077-80.

and her uncle were diagnosed with type 2 diabetes. This patient has a younger brother with normal glucose tolerance.

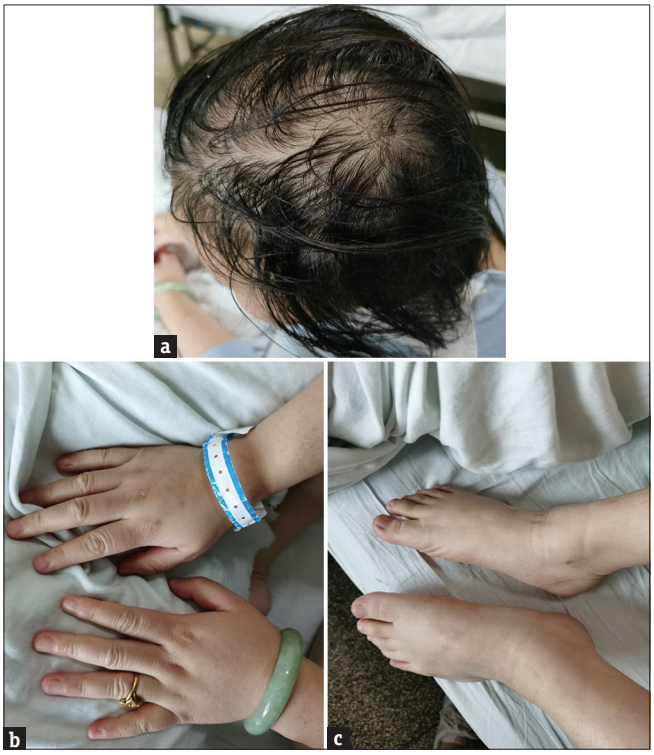

Figure 1: Clinical features of the patient: (a) the hair of the patient, (b) normal fingers, and (c) normal toes

Gene test was done in Precisiongenes Technology, Inc. (Haimen, China). All sequencing was performed on the Nova seq 6000 platform (Illumina). Variants with minor allele frequency less than 0.05 in population databases and expected to occur in the coding/splicing region were selected.[4] Sanger sequencing was performed to confirm the mutation. The summary of sequencing parameters can be found in Table 1.

The patient had two nonsense pathological variants in exon 8 of *ALMS1*: c.3896C>A: p.Ser1299 * (chr2: 73677553) and c.6673C>T: p.Gln2225 * (chr2: 73680330) [Figure 2a]. The result was confirmed by Sanger sequencing [Figure 3]. The gene regions c.3896C>A and c.6673C>T involved are highly conserved in human [Figure 2b]. c.3896C>A is a rare variant, with a population frequency of 0.0001 in East Asian backgrounds according to VarCards. The population frequency of c.6673C>T is not found in VarCards. According to the guideline,[5] the two mutations are pathogenic. Sanger sequencing showed that her father was heterozygous for c.3896C>A mutation. Her mother was heterozygous for c.6673C>T mutation. The proband was a heterozygous complex mutation [Figure 3].

Modification of lifestyle, diets, exercise, and follow-up were administered. Due to renal insufficiency, insulin was

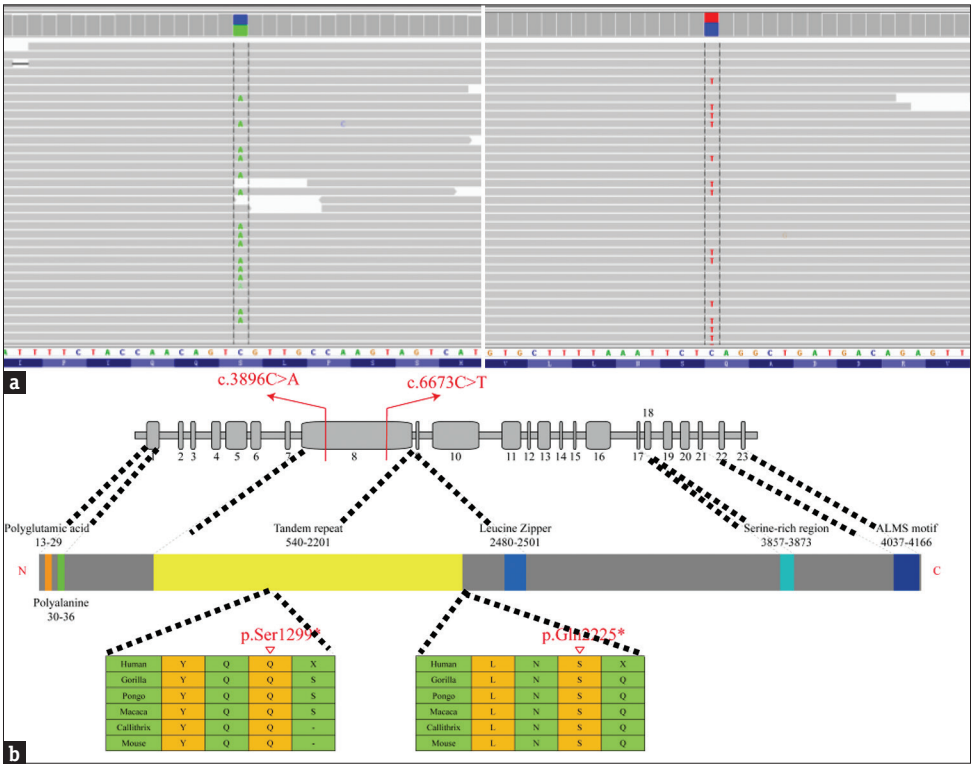

Figure 2: The mutations in exon and the affected structure in protein: (a) the alignment of sequences indicated two substitutions in exon 8 of ALMS1 and (b) amino acid sequence conservation analysis in human and some species

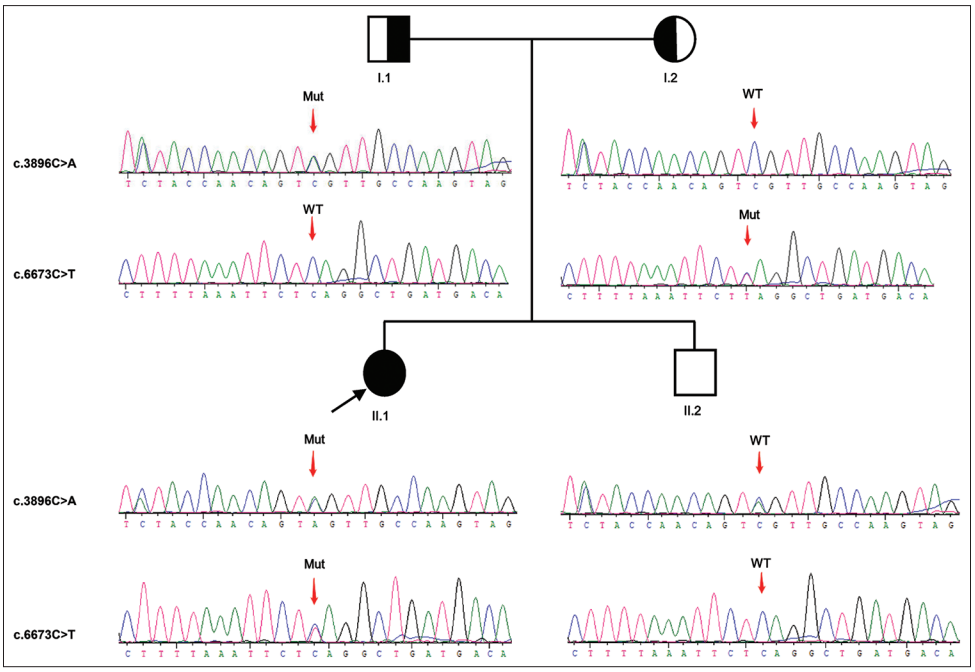

Figure 3: The family pedigree and Sanger sequence analysis. Proband was indicated by a black arrow; mutation was indicated by a red arrow. Her father was heterozygous for c.3896C>A mutation and her mother was heterozygous for c.6673C>T mutation. The proband was heterozygous complex mutations

Table 1: High-throughput sequencing parameters

Sequencing parameters	Values
Total size	48,541,962
Size of alignments to reference genes	48,521,225 (99.96%)
20×coverage degree of the targeted area	97.74
Average coverage of the target area	203.3×
Total length of target area (BP)	18,737,841
Effective data in the target area (MBP)	3809.46

used to control blood glucose (68 IU/day). Liraglutide was performed to maintain her body weight. For other systemic complications, we treated symptomatically.

Discussion

Diabetes with particular clinical manifestations needs to be considered monogenic diabetes. Compared to conventional genetic analysis, WES is more effective and efficient.[6] Here, we report a young diabetes patient with poor blood glucose control. With WES, the patient was diagnosed as AS.

The patient's diabetes history has been clear for more than 20 years. It could be easily misdiagnosed as common type of diabetes. However, features of young age onset diabetes, long duration but reserved islet function and insulin resistance, are different from type 1 diabetes, type 2 diabetes, and latent autoimmune diabetes of adults. It was required to consider monogenic diabetes. The clinical manifestations of AS are extremely diverse.[3] In childhood, it is often characterized by cone-rod dystrophy, blindness, and neurosensorial deafness. Adolescents and adults often present with metabolic syndrome, progressive fibrosis, and sexual dysfunction.[7] Bardet–Biedl syndrome also needs to be ruled out though this patient did not present mental retardation or polydactyly (toe) deformity. We used WES to screen for possible mutations and found the patient had two mutations in the *ALMS1* gene.

AS is an autosomal-recessive disease caused by mutations in the exons of *ALMS1* gene. ALMS1 protein contains a tandem repeat sequence domain, leucine Zipper, serine-rich region, and an ALMS motif.[8] ALMS1 is widely expressed in tissues and is an intracellular protein related to cell cilia function. Most of mutations in *ALMS1* related with AS are nonsense mutations or frameshift mutations. Nonsense mutations often result in premature termination codons and truncated proteins. The most common pathogenic mutations at the DNA level are substitution and at the protein-level frameshifts.[9] The most common type of mutation is compound heterozygous mutation, which is consistent with our patient.

This patient has two AS-related pathogenic mutations in *ALMS1* including c.3896C>A and c.6673C>T. c.3896C>A had been reported previously[10] and c.6673C>T is a novel mutation. Mutation in c.3896C>A originated from her father; c.6673C>T mutation originated from her mother. The proband was a heterozygous complex mutation in

ALMS1 gene. Two mutations are nonsense mutations and located at conserved regions, resulting in *ALMS1* mRNA premature degradation or truncated protein occurred. Patients with exon 8 mutations usually have normal or mild abnormal renal function. Surprisingly, our patient has severe renal impairment, which may be due to her long course of the disease.

Patients and families should be followed up in a multidisciplinary center. For patients with diabetes and obesity, modification of lifestyle, exercise, and diet are recommended. In addition to insulin, insulin-sensitizing agents can also be used to control blood glucose. GLP-1 receptor agonists can be performed on obese patients. Corresponding treatment is also required if patients are complicated with other syndromes.[3,8]

Conclusion

We diagnosed a long-term diabetes patient as AS by WES and identified one novel *ALMS1* gene pathogenic mutation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Author contributions

Ming Zhong contributed to the acquisition of data and wrote the manuscript; Sun-Jie Yan revised the manuscript critically for important intellectual content and conducted the design of the study; and Ling-Ning Huang and Song-Jing Zhang contributed to discussion and the data analysis.

Acknowledgments

The authors would like to thank the patient and her family. The authors also want to express their gratitude to Dr. Yi-Hua Yao from the Department of Ophthalmology, the First Affiliated Hospital of Fujian Medical University.

Financial support and sponsorship

This study was supported by Joint Funds for the Innovation of Science and Technology, Fujian province (grant number: 2020Y9114).

Conflicts of interest

There are no conflicts of interest.

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