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Case Report

Whole Exome Sequencing of *ALMS1* gene Identified a Novel Pathogenic Homozygous Mutation (c.3132_3133delAC/p.Gln1045ValfsTer2) in a Turkish Family

O ***Kilicaslan***, R ***Eroz***

Abstract ***Backgroud:*** Alstrom syndrome (AS) is a rare autosomal recessive disorder caused by pathogenic mutation in *ALMS1* (ALMS1 centrosome and basal body associated protein) gene. ***Case Presentation:*** A 13.5-year-old male patient, who was born from consanguineous parents of Turkish descent, applied due to the complaint of obesity and non palpable testes. He had optic atrophy and hearing loss. His weight and body mass index were over 97th percentile. The fasting blood glucose level of the patient was 111 mg/dl and the patient had high level of insulin. Because AS was considered, genetic analysis of the *ALMS1* gene was performed and a homozygous pathogenic (Class-II) mutation c.3132_3133delAC/p.Gln1045ValfsTer2 was detected in the exon 8 region of the *ALMS1* gene. His mother was heterozygous carrier of the same mutation. ***Conclusion:*** A novel c.3132_3133delAC mutation in *ALMS1* gene cause clinical findings of AS such as obesity, reduced visual acuity, hearing loss and other systems manifestations.

Key words *ALMS1 gene; Alstrom syndrome; Hearing loss; Obesity; Reduced visual acuity*

Introduction

Alstrom syndrome (AS) (OMIM 203800) is a rare autosomal recessive genetic disorder which demonstrates manifestations of the multisystem involvement. Its worldwide prevalence is known as 1 per 1 million in the general population. It has been first described by Swedish Carl-Henry Alstrom in 1959.[1]

This disorder involves the complications associated with multiple organ systems. Major problems include sensorineural loss (particularly visual and audial loss), endocrine and metabolic disorders (particularly hormonal), cardiac, varying grades of pulmonary and urological complications, organ failures (hepatic, cardiac and renal failure), developmental retardations (particularly in motor functions) and having recurrent lower and upper respiratory tract infections.[1]

AS is caused by the pathogenic alterations in the *ALMS1* gene, which is located on the short arm of Chromosome 2, comprised of 23 exons and encoding a protein of 4169 amino acids length. Each parent is a heterozygous carrier of recessively inherited pathogenic mutation for the occurrence of AS. Male and female subjects are equally affected and no ethnical difference has been reported with respect to mutation carriage in the responsible gene.[1,2]

We have presented a case with pathogenic novel homozygous mutation c.3132_3133delAC/p.Gln1045ValfsTer2 in the exon 8 of *ALMS1* gene.

Pediatrics Department of Medical Faculty, University of Duzce, Duzce, Turkey
O **Kilicaslan** *MD*

Medical Genetics Department of Medical Faculty, University of Aksaray, Aksaray, Turkey
R **Eroz** *PhD*

Correspondence to: Asst.Prof. O **Kilicaslan**
Email: dronderklcsln@gmail.com

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Case Presentation

A 13.5-year-old male patient applied to our clinic due to the complaint of obesity and non palpable testes. He was born at term with a birth weight of 4.200 gr. He was diagnosed with optic atrophy at the optical examination performed due to the complaint of reduced vision and had recurrent ear infections that cause subsequent hearing loss. The patient had long-term obesity, while his aunt and grandfather were diagnosed with type 1 Diabetes Mellitus.

Body weight, height and mass index (BMI) values of the patient were over 97th percentile (81 kg), 26th percentile (156 cm) and over 95th percentile (33.3 kg/m^2), respectively. His physical examination revealed stable findings including blood pressure. The whole blood test results were shown in Table 1. Whole urinalysis test of the patient revealed no pathology. While other system examinations were normal, testes were nonpalpable and seen that located in the bilateral inguinal canals by the scrotal ultrasonography. After the informed consent was taken from the patient's parents, whole exome sequence analysis of the *ALMS1* gene was performed and a pathogenic novel homozygous mutation (c.3132_3133delAC/p.Gln1045ValfsTer2) was detected in the exon 8 of *ALMS1* gene (Figure 1 b). The hereditary characteristics of the disorder was taken into consideration, whole exome sequence analysis of the related gene was also ordered for the mother and heterozygous c.3132_3133delAC/p.Gln1045ValfsTer2 mutation also was detected, too (Figure 1 c). Since the father of the proband was abroad and did not come to give blood, genetic analysis could not be done for the father. Considering that the proband had homozygous mutation, it can be said that the father of the proband is also a heterozygous carrier for the same mutation. There was a consanguineous marriage between the parents (Figure 1 a).

Discussion

AS is a rare genetic disorder that demonstrates a multisystemic, complex and progressive course. The *ALMS1* gene is responsible for the disease. Although, biological function of this gene is not exactly clarified, available evidence suggests that it plays a role in the ciliary function and/or ciliogenesis. It is suggested that ALMS1 protein plays a role in the regulation of cell cycle. As a consequence, it may cause a wide range of clinical complications by leading to damage in many organs. Even though, clinical progression of the disorder may vary between the patients, its progressive process usually begins in the childhood age.[3]

The major effects of the disease in the eyes are known as degeneration in the rod and cone cells, nystagmus, visual field defects, cataract and blindness.[2] In the first stage, subnormal vision, photophobia and nystagmus are determined in the infancy. As the age increase, decreased function of initially cone and subsequently rod cells are detected. Varying degrees of visual loss start concurrently with retinal dystrophy. Complete visual loss usually occurs after 20s of the patient.[4] Unfortunately, the treatment of the progressive visual loss have not found yet.[5] Our patient was prediagnosed with optic atrophy after ophthalmological evaluation performed due to his complaint of reduced visual loss started at about 10 year of age and he was taken to follow-up by the ophthalmologists.

While slowly progressive, mild-moderate bilateral sensorineural hearing loss develops in many patients, severe deafness is determined in a small number of patients. Impaired speech is not expected since deafness develops slowly and these patients usually do not have defects at the age of mouth-ear coordination was achieved.[1] Because the our patient was received recurrent treatments for otitis media since infancy, he diagnosed with chronic otisis media and subsequently under follow-up for hearing loss subsequent to chronic otitis media.

Obesity is an important finding observed in almost all the children with AS. Birth weight and increasing fatty mass, not monitored in the first year of age, increase after that age and become a life-restricting medical complication for the children.[5] Insulin resistance and diabetes mellitus develop before the 20th-year of age as well as obesity in majority of the patients. Hypertriglyceridemia and hypothyroidism are the other metabolic complications of AS.[6,7] Because BMI and body weight values of our patient were over respectively 95th and 97th percentile, he was obese. Insulin level was high (116.2 uIU/mL) and fasting blood glucose level (111 mg/dl) was considered as impaired in the patient. Cholesterol values were not high. However, thyroid stimulating hormone level was found higher (6.62 uIU/mL) than normal range (N=0.7-4.61 uIU/mL), whereas free T4 level (1.01 ng/dL) was detected within normal range. The patient was taken to follow-up for both hypothyroidism and potential metabolic complications.

Hypogonadism, expected findings in AS, is more frequently seen in particularly males, whereas females

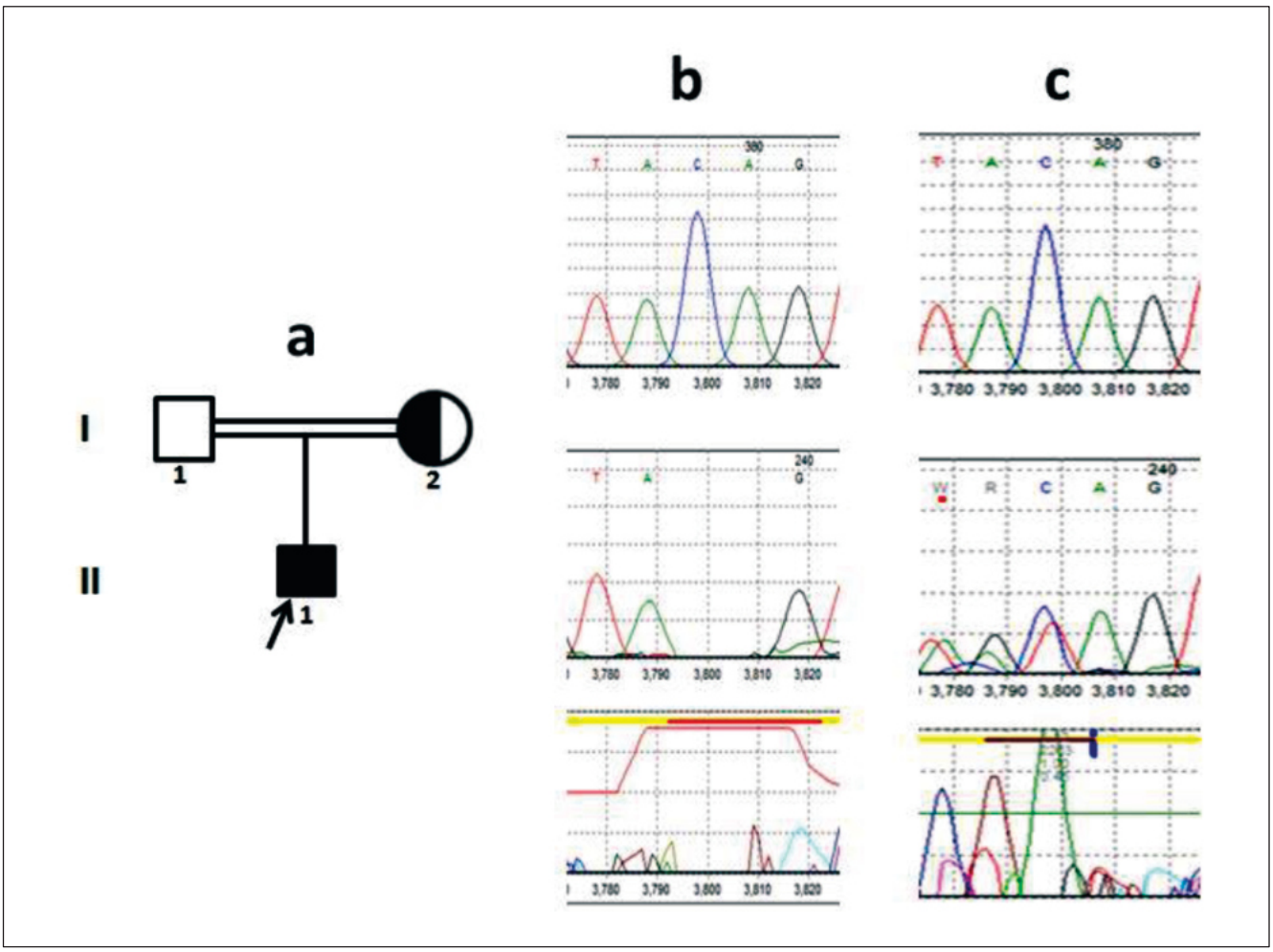

Figure 1 (a) Family pedigree of patient, (b) sanger sequencing traces of the family showing the presence of the pathogenic homozygous class 2 mutation c.3132_3133delAC/p.Gln1045ValfsTer2 in the exon 8 of *ALMS1* gene and (c) a heterozygous c.3132_3133delAC/p.Gln1045ValfsTer2 mutation state in mother.

Table 1 Whole blood count results of the patient

Fasting blood glucose	111 mg/dl	Thyroid Stimulating Hormone	6.62 uIU/mL
Urea	24.7 mg/dL	Free T4	1.01 ng/dL
Creatinine	0.66 mg/dL	Follicle Stimulating Hormone	11.99 mIU/mL
Alanine aminotransferase	57.8 U/mL	Luteinizing Hormone	6.49 mIU/mL
Aspartate aminotransferase	30.2 IU/L	Estradiol (E2)	42.79 pg/mL
Cholesterol	188 mg/dL	Total Testesterone	214 ng/dL
HDL Cholesterol	40 mg/dL	Haemoglobulin	12.3 gr/dl
LDL Cholesterol	122 mg/dL	Leukocyte	8900 uL
Triglycerides	126 mg/dL	Lymphocyte	2520 uL
HbA1c	5.7%	Neutrophils	5320 uL
Insulin	116.2 uIU/mL	Platelets	273000 uL

HDL: High-density lipoprotein; LDL: Low-density lipoprotein

more commonly indicate high levels of androgens.[1] Because the testes of our patient were nonpalpable in the physical examination, the ultrasonography was performed and the testes were found located in the inguinal canal. Testosterone level was low, whereas the levels of Follicle Stimulating Hormone and Luteinizing Hormone were within normal ranges. The operation was planned for the patient and he was taken into follow-up.

The other complications of the children with AS include cardiac, pulmonary, hepatic and renal dysfunction. It is known that it cause dilated cardiomyopathy by leading to myocardial fibrosis with an unknown action mechanism.[8] Recurrent acute lower and upper respiratory tract infections, hronic obstructive pulmonary disease and persistent coughing are the apparent pulmonary pathologies.[9] Elevated asymptomatic hepatic transaminases, hepatosplenomegaly, steatosis, fibrosis, cirrhosis and portal hypertension may be detected in liver.[5] Renal diseases are prominent as a component of accompanied with other ciliopathies. On the other hand, onset and progression of renal dysfunction are not clarified yet in AS. It was mentioned that renal damage starts early and progresses fast in the children with AS and consequently a high prevalence of advanced chronic renal disease in the young ages will be encountered. It has been suggested that AS should be classified as a rare genetic kidney disease like other inherited renal ciliopathies.[10] Our patient had no cardiac or pulmonary complaint. The results of whole urinalysis test, blood count, renal and liver function tests were found within normal ranges. The patient was planned to be referred to the Department of Pediatric Cardiology for cardiological evaluation.

AS should be considered in unexplained early-onset obesity with another factor, hormonal and metabolic disorders, reduced visual acuity, hearing loss and hypogonadism in the children and the sequence analysis of the *ALMS1* gene should be performed. We have reported a case with a novel pathogenic mutation identified in the *ALMS1* gene together with his clinical and laboratory findings to provide a contribution to the literature.

Conflict of Interest

The authors have no financial or competing interests in relation to this work.

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