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Atypical Presentation and a Novel Mutation in ALMS1: Implications for Clinical and Molecular Diagnostic Strategies for Alström Syndrome

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To the Editor

Alström Syndrome (ALMS;MIM 203800), characterized by progressive phenotypes affects nearly all organs. Approximately 100 different *ALMS1* mutations cluster primarily in exons 8, 10 or 16 (1,2). *ALMS1* localizes to centrosomes and basal bodies of ciliated cells and is ubiquitously expressed, suggesting roles in ciliary function and/or intraflagellar transport (2).

Clinical presentation begins with vision loss in the first year leading to childhood blindness. Dilated cardiomyopathy (DCM) can occur in infancy or adulthood. Obesity, begins early and persists into adulthood. In childhood, sensorineural hearing loss, and insulin-resistant type 2 diabetes mellitus (T2DM) develop. Multiple organ failure progresses gradually in the second to third decade. Males have small genitalia and infertility, typified by disordered basal testosterone and baseline LH/FSH levels. Fibrotic seminiferous tubules and an absence of Leydig cells have been documented (1). Normal intelligence serves as a differential diagnosis to Bardet Biedl Syndrome (BBS), a phenotypically similar ciliopathy (3).

We report an 18y old male, born to first-cousin consanguineous parents from a small, remote village in central Turkey, who presented febrile convulsions at one week of age. Deteriorating retinal and optic disc pathology led to blindness by the age of 8y and initial hearing deficits progressed. Hepatomegaly was discovered by ultrasonography, but transaminases were only mildly elevated. There was no portal hypertension.

At 16y, he manifested DCM with dilated atria and ventricles, grade-3 tricuspid insufficiency and grade-2 mitral insufficiency, grade-2 mitral and tricuspid regurgitation, and mitral valve prolapse (Fig. 1a). At 18.75y, he was again hospitalized with CHF. Echocardiography showed restrictive and DCM, pericardial effusion, grade III/IV tricuspid insufficiency and

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grade-II/III mitral insufficiency. Ascites, probably due to CHF, was documented. Atrial fibrillation developed and the patient died due to cardiac arrest.

The patient's haplotype was homozygous within a <2Mb region surrounding *ALMS1* (Fig 1d). Sequencing of all *ALMS1* exons and splice sites revealed a novel homozygous mutation, 9749C>A (Ser3250X) in exon 11 (Fig. 1e). We identified a heterozygous intronic polymorphism, IVS19 -8 del T, present only in the maternal lineage, suggesting that the variation was a recent event arising after the common ancestor from either the mother or maternal grandparent.

There were several deviations from the classical presentation. Although BMI was not documented in childhood, his parents state that he was always underdeveloped and was never obese. At 18y, his BMI (kg/m²) was 22 (146.5 cm/47.5 kg (both <3rd centile). OGGT showed that he lacked IR, or T2DM. Growth hormone IGF-1, bone age, HbA1C, lipids, thyroid and renal function were normal. Further, he did not show genital anomalies, but his testosterone was 52 ng/dl (134–625), LH (13.9 ng/dl – (0.8–7.6) and FSH (32.4 ng/dl (0.7–11.1).

The patient had additional features not been previously described in ALMS. Ultrasound showed an abnormal thickening of the gallbladder wall, a condition common in individuals with BBS (3). It is unclear whether this thickening could be attributed to the massive fibrosis of multiple organs of patients with ALMS (2) or to dysfunction in the motile cilia in the gallbladder.

Neuroanatomical brain abnormalities and profound cognitive impairments are reported in BBS, but not ALMS (3). Structural magnetic resonance imaging (MRI) revealed prominent cerebellar hemisphere folium due to atrophy, and a mildly thin brain stalk in conventional sagittal T1-weighted and axial T2-weighted flair brain images. Prominent peripheral and central cerebrospinal fluid distance secondary to cortical atrophy, and thin corpus callosum infundibulum were noted. Fourth ventricle at infratentorial sections, basal ganglia and thalamus were normal in examination of the supratentorial sections (Fig. 1c). These changes are unlikely to be due to vision loss, which is frequent in ALMS patients without MRI abnormalities. Electroencephalography was normal. He had significant cognitive impairment with social developmental delays, and was unable to perform aspects of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) intelligence test at age 18 y, resulting in a score of <40 (normal range 80–120).

Several hypotheses could explain the presence of such unusual characteristics in this patient. It is plausible to consider that the location of the mutation in *ALMS1* exon 11 may affect splice variants producing different isoforms.

The variability seen in this patient may also be due to genetic modifiers that could impact neurodevelopment, obesity, and hypogonadism.

The full range of clinical heterogeneity in individuals harboring *ALMS1* mutations is still unknown. Genetic confirmation of ALMS in this patient expands the phenotypic spectrum and suggests that, in patients with milder features or unusual phenotypes, should not rule out seeking a genetic diagnosis of ALMS.

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Fig. 1.

Fig. 1a. Echocardiography in M mode showing ejection fraction; 36%, LVDd (left ventricular diastolic diameter); 5.57cm, LVSd (left ventricular systolic diameter); 4.81cm. b,c,d. T1-weighted MRI scans illustrating qualitative neuroradiological abnormalities detected in the ALMS patient. (1.5 Tesla MR system (Gyrosan Intera Release Philips, Netherlands). Section thickness=5mm, intersection gap=1mm, Field of View (FOV)=205×260). MR T1-weighted sagittal image show b) thin corpus callosum infundibulum (arrow). MR T2- weighted flair axial images showing c) prominent peripheral and central cerebrospinal fluid distance secondary to cortical atrophy d) prominent cerebellar hemisphere folium because of atrophy (arrows). e) Pedigree of family. Circles: females; squares: males; blackened square (arrow) indicates affected proband; half filled circles and squares are carriers of the affected haplotype. Parents were healthy first degree cousins who had three other unaffected male children, ages 39, 24, and 19 y. Slashed symbols indicate five additional children with uncertain diagnosis who had previously died: 2 males and 1 female at 5 months, 1 female at 6 months, and one male at 40 days. The parents described nystagmus in one of the deceased female children, suggesting that the child may have had ALMS. The haplotypes segregating with the *ALMS1* locus are boxed. The affected individual is homozygous for a common haplotype defined by markers D2S16770GT, D2S2110, D2S1394, D2S2111, D2S109 (MWG-Biotech Inc., High Point, NC, USA). f) Chromatograph depicting the novel c.9749C>A (p.Ser3250X) mutation in exon 11 of *ALMS1* (indicated by the arrow) The position of the predicted premature termination codon (X) at the protein sequence level is indicated (p). Sequences were

compared to *ALMS1* (GenBank NM_015120.4) using MacVector™ 7.2.3. Nucleotide and amino acid numbering of mutation sites began at the start codon, ATG (Met) of the open reading frame, originally described by Collin et al. (3). The nomenclature was established according to the Mutalyzer sequence variant nomenclature check v. 1.0.1 (<http://www.LOVD.nl/mutalyzer>).

Fig. 2.

Fig. 3.