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Case Report

Alazami syndrome in an Afghani girl: A case report and review of literature

Abstract

Purpose: Alazami syndrome is a rare autosomal recessive disorder with core phenotypic manifestations of short stature, mild facial dysmorphism, and global developmental delay evolving to severe intellectual disability. Homozygous loss-of-function mutations in *LARP7* gene, which encodes a chaperone protein of the noncoding RNA 7SK, have been detected in patients with Alazami syndrome. Since its first description in 2012, only six families with Alazami syndrome have been reported to date. This case is reported to expand the phenotypic description to include small kidneys.

Methods: The patient was referred for Clinical Genetics evaluation at Rady Children's Hospital San Diego due to intellectual disability and growth delay. Whole exome sequencing was performed (GeneDx) after informed consent.

Result: Whole exome sequencing identified a homozygous pathogenic variant in exon 12 of *LARP 7*(c.1620_1623delACAG; p.Ala542Aspfs*15), conferring a diagnosis of Alazami syndrome. The clinical features of a 16-year-old Afghani girl with Alazami syndrome are reported and compared to features of previously reported Alazami syndrome cases. In addition to sharing many features of previously reported cases, the subject of this report also had small kidneys and pre-hypertension.

Conclusion: This case report broadens the phenotype of Alazami syndrome to include small kidneys and behavioral problems related to anxiety.

Introduction

Alazami syndrome (OMIM: 615071) is a genetic disorder caused by homozygous or compound heterozygous mutations in *LARP7*, which encodes a chaperone of the 7SK noncoding (nc) RNA [1]. Alazami et al., [2], first described this syndrome in a large consanguineous Saudi Arabian family, where ten affected children showed primordial dwarfism (PD) having growth parameters at least 3.5 SD below the mean, severe intellectual disability, and facial dysmorphism consisting of malar hypoplasia, short philtrum, triangular face, deep-seated eyes, broad nose, narrow palpebral fissures, and microstomia [1-3]. Additionally, some nonspecific skeletal abnormalities such as scoliosis and mild epiphyseal changes in proximal phalanges without clear dysplasia were observed [2]. Genome-wide linkage analysis of affected individuals, their parents, and some of the unaffected siblings detected an extended 26.5- Mb homozygous region between SNPs surrounding chromosome 4q24-4q28.2 among all patients but not in unaffected relatives. Molecular functional studies and sequencing of a list of candidate genes in this region showeda homozygous 7 bp duplication in exon 8 of *LARP 7* gene (c.1024_1030dupAAGGATA, p.T344K*fs**9), causing a frameshift mutation that resulted in premature truncation of the peptide [2]. A complete absence of LARP7 protein was also observed in the patients suggesting that mutation produced a null phenotype [2].

Najmabadi et al., [4], conducted a large study including 136 consanguineousIranianfamilies with autosomal-recessive intellectual disability and microcephaly and determined the etiology to be a frameshift mutation (Lys276fs) in *LARP 7*. Furthermore, Ling et al., [3], detected compound heterozygous frameshift variants in *LARP7*: c.213_214dup (p.Ser72fs) and c.651_655del (p.Lys219fs) in a 2-year old Caucasian girl with Alazami syndrome. Hollink et al., [1], reported two unrelated Alazami syndrome patients with homozygous loss-of-function variants in *LARP7*. Dateki et al., [5], reported another patient with Alazami syndrome having unique compound heterozygous mutations in *LARP7* [5]. Recently Imbert-Bouteille M et al., [6], reported two sisters with Alazami syndrome with homozygous frameshift variant in exon7 of *LARP7*:c.524_525ins (p.Ala176Leufs).

Herein we report a new case of Alazami syndrome with a homozygous 4-bp deletion in exon 12 of *LARP7*. The clinical features of the patient in the present case report are compared

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with other previously reported Alazami syndrome patients to portray further phenotypic manifestations related to this syndrome.

Case Presentation

The patient wasa 16-year-old girl of Afghan origin with primary complaints of intellectual disability, growth and motor development delay, and dysmorphic facial features, who was referred for outpatient clinical genetics consultation. She was the product of a consanguineous union, and there was a family history of intellectual disability in a paternal aunt and paternal grandmother. Mother reported poor fetal movement, a 7 kg weight loss and depression during the pregnancy. She was delivered at term by cesarean section weighing1.8 kg. Although her growth in the neonatal period was normal, her psychomotor development was delayed and she was able to talk and walk at 3 years age. She is unable to speak full sentences and usually gives one-word answers, fails to follow commands, requires assistance to get dressed, and shows situational anxiety. Physical examination revealed a height of 144.5 cm (z=-2.82) and head circumference of 51.8 (z=-2.5) with narrow, prominent forehead and low posterior hairline. Her nose was broad with a bulbous tip. She had a short philtrum, widely spaced teeth, deeply set eyes, malar flattening and mildly short palpebral fissures (2.5cm) (Figure1). Finger pads were prominent, and the great toes were shorter than the second toes. Streaky hyperpigmentation was observed on her right lateral chest and back of the legs. There was a grey macule on the dorsum of her left hand. She could walk steadily with a wide-based gait but was unable to run. She has hyperopia and strabismus, but is noncompliant with wearing spectacles.

Renal ultrasound with Doppler detected a small left kidney (4^{th}centile); DMSA scan showed equal flow of blood in both the kidneys and normal renal function. Due to strong family history of hypertension, amlodipine was started for prehypertension. Echocardiogram was normal. Audiological evaluation revealed mild conductive hearing loss in both ears. An oligonucleotide SNP microarray showed regions of homozygosity totaling at least 103 Mb, consistent with parental first-cousin relationship, and a 109 kb microdeletion of chromosome 16q21, interpreted as a variant of uncertain significance.

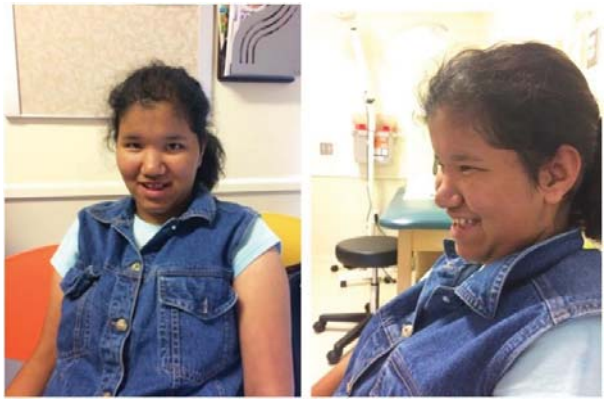

Figure 1: Narrow, prominent forehead, low posterior hair line, broad nose with a bulbous tip, a short philtrum, widely spaced teeth, deeply set eyes, malar flattening and mildly short palpebral fissures.

Whole exome sequencing analysis revealed a homozygous 4 bp deletion in exon 12 of *LARP7*, resulting in a frameshift and creating a premature stop codon (c.1620_1623delACAG; p.A542Nfs*15). Her parents were heterozygous for the c.1620_1623delACAG variant in the *LARP7* (Table 1).

Discussion

We presentan additional case of Alazami syndrome characterized by severe intellectual disability, mild facial dysmorphism, mild short stature, and microcephaly due to a novel homozygous frameshift loss-of-function variant in *LARP7*. LARP7 belongs to the La Autoantigen related protein family and is responsible for regulation of 7SK-mediated transcription by binding to the 3'-terminal domain of 7SK RNA and becoming an intrinsic part of it [7]. LARP7inhibits RNA Polymerase II-transcribed genes by means of the 7SK small ribonucleoprotein (snRNP) system [8]. 7SK snRNP controls the function of the positive transcription elongation factor P-TEFb that facilitates transcription elongation mediated by RNA Polymerase-II. 7SK snRNP sequesters with P-TEFb and inactivates it by inhibiting its kinase activity [9]. Inactive P-TEFb prevents RNA Polymerase-II phosphorylation and elongation of transcripts [2,7,8]. Thus, depletion of 7SK RNA might be expected to result in growth delay. In fact, loss of LARP7 protein expression due to mutation of *LARP7* gene and consequent reduction in the level of 7SK RNA [8], was detected in the affected individuals of the Saudi family [1,2]. Okamura et al., [9], identified gene-specific as well as celltype-specific transcription activation in mouse embryos due to 7SK snRNP mediated regulation of P-TEFb activity, thus proposing *LARP-7* mediated transcription regulation incites cell cycle progression in actively proliferating primordial germ cells (PGCs), which proliferate excessively in early mammalian embryos. In addition, Dai et al., [10], determined that knockdown of *LARP 7* downregulates*Lin28*, a positive regulator of organismal growth, causing premature differentiation of embryonic stem cells, resulting in growth deficiency.

All cases of Alazami syndrome have been due to homozygous or compound heterozygous frameshift variants in *LARP7* [1-6]. The mutational mechanism is loss-of-function presumably due tononsense-mediated mRNA decay [1,5]. Consistent features among nearly all cases include global developmental delay evolving to severe intellectual disability, growth retardation, and dysmorphic facial features [1-3,5,6]. The patient presented herein has distinct facial features, highly impaired motor skills and language skills. Recently Dateki et al., [5], reported a Japanese patient with Alazami syndrome having compound heterozygous mutation in *LARP7*and showing facial features as well as intellectual and motor developmental delayquite similar to our patient, suggesting these manifestations are the most consistentfeatures of Alazami syndrome.

Some cases have had normal prenatal growth but considerable postnatal growth restriction [3,5]. Our patient's final adult height is not as significantly impaired as the initial case descriptions [2,3,6] and not in the range typical for primordial dwarfism, and more in accordance with the growth reported byHollink et al., [1] and Dateki et al. [5].

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Table 1: Clinical and genetic features of Alazami syndrome patients.

	Alazami et al., [2]	Ling et al., [3]	Holink et al., [1]		Holohan et al., [11]	Dateki S et al., [5]	Imbert-BouteilleM et al., [6]		Present case	Total
Case #	1-9	10	11	12	13	14	15	16	17	17
Age at last examination (years)	5 - 22	2.5	6	2.5	8	2	26 and 22		17	
Gender	5 Male, 4 Female	Female	Male	Male	Male	Male	Female		Female	Male-56% Female-44%
LARP7 mutations	c.1024_1030dup p.Thr344Lysfs* (homozygous)	c.213_214dup p.Ser72fs c.651_655delp. Lys219fs	c.1091_1094del p.Arg364fs (homozygous)	c.1045_1051dup p.Thr351fs* (homozygous)	c.756_757del p.Arg253fs* (homozygous)	c.370delG p.Glu124fs c.641_667+25 delp.Phe192fs	c.524_525insTT p.Ala176Leufs* (homozygous)		c.1620_1623del ACAGp. A542NfsX15 (homozygous)	
Gestational age	NR	40	40.4	NR	NR	38	NR		unknown	
Birth parameters: weight (SD), height (SD), FOC (SD)	NR	2608 g (−1.35), 47.6 cm (−0.91), 32.4 cm (−1.35)	2980 g, 45 cm, 34 cm	2000 g, NR, NR	NR	2444 g (−1.1), 46.3 cm (−1.3), 33 cm (−0.1)	NR		1800 g, unknown, unknown	
Growth parameters at last evaluation: weight (SD), height (SD), FOC (SD)	Weight (-4.5to -2.0) Height (-10.5 to -3.6) FOC(-7.0 to -1.5)	7.6 kg (−5.5), 72.7 cm (−4.0), 46 cm (−1.0)	16.5 kg (−1.0), 107.4 cm (−2.5), 48.4 cm (−2.0)	9.1 kg (−3.0), 81 cm (−3.0), 44.5 cm (−4.0)	NR, (<−3.5), NR	9.75 kg (−1.1), 82 cm (−1.4), 45 cm (−1.5)	Weight (-2.8 to -3.5) Height (-6.5 to -6.8) FOC (-3.5 to -3.5)		47.5 kg (-1.14), 145.3 cm (-2.73), 51.8 cm (-2.5)	
Motor delay	9 out of 9	+	+	+	+	+	NR		+	88%
Intellectual disability	9 out of 9	+	+	+	+	+	+		+	100%
Triangular face	9 out of 9	+	–	+	NR	–	–		–	65%
Prominent forehead	9 out of 9	+	+	+	+	+	–		+	88%
Deeply-set eyes	9 out of 9	+	+	+	NR	+	1/2		+	82%
Short palpebral fissures	7 out of 9	–	–	+	NR	+	1/2		+	65%
Sparse eyebrows	9 out of 9	NR	–	+	NR	–	1/2		+	70%
Broad nose	9 out of 9	+	+	+	+	+	+		+	100%
Low-set ears	6 out of 9	+	–	–	NR	–	–		–	40%
Wide mouth	9 out of 9	+	–	+	NR	–	+		–	76%
Full lips	5 out of 9	+	+	+	NR	+	+		–	65%
Widely spaced teeth	7 out of 9	+	+	+	NR	–	+		+	76%
Malar hypoplasia	8 out of 9	+	–	+	NR	+	1/2		+	76%
Strabismus	4 out of 9	NR	–	–	NR	–	–		+	29%
Thickened skin over hands	3 out of 9	NR	+	–	NR	–	+		–	35%
Scoliosis	2 out of 9	NR	+	–	NR	–	1/2		–	24%
Other findings	Short Achilles' tendon, Blue/ grey sclera, easily anxious and agitated.	Clinodactyly of the big toes	Cleft palate, torticollis	Hypertelorism, hypotonia, small hands	Hypospadias, inguinal hernia, small kidneys, hypertelorism, hypotonia		Seizures (1/2) Keratoconus (1/2) Atrial septal defect (1/2) Disturbed sleep/sleep apnea Episodes (2/2)		Small kidneys, Prehypertension	

NR=Not reported

Behavioral abnormalities have been reported in Alazami syndrome.Hyperactive behavior was reported by Hollink et al., [1], in one patient and in both patients reported by Imbert-Bouteille M et al., [6]. Furthermore, anxiety, frequent tantrums, and hypersensitivity to stimuli were observed in the patient reported by Ling et al., [3]. Our patient exhibits situational anxiety. These findings suggest that behavioral abnormalitiesare an important feature ofAlazami syndrome.

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Our patient has pre-hypertension with a family history of early-onset of hypertension.Additionally, our patient possesses small-sized kidneys (between 4-14% tile). To date, only one other patient has exhibited this feature: Holahan et al., [11], reported small sized kidneys (between 5-10%). Whether the small kidney size is a congenital defect or acquiredand whether this phenotype belongs to the spectrum of billaelic*LARP7* mutations remain to be determined.

With more widespread use of WES, we anticipate that the diagnosis of Alazami syndrome will be made in additional patients of all racial/ethnic backgrounds, and we expect the clinical spectrum to continue to broaden.

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