Radiology Case Reports 20 (2025) 2619–2623

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Alazami syndrome with a single LARP7 variant and concurrent osteo-oto-hepato-enteric syndrome: A case of complex genetic interplay ☆

Ayman Thouqan, MD[a,b,†], *Aya Janem, RN*[c], *Rawan Ghanayem, MD*[b], *Abdullah Janem, MD*[a,b,†,*]

[a] *Department of Internships, Ministry of Health, Nablus, Palestine*
[b] *Department of Medicine, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, 4439, Palestine*
[c] *Department of Nursing, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, 4439, Palestine*

ARTICLE INFO

Article history:
Received 27 December 2024
Revised 18 January 2025
Accepted 25 January 2025

Keywords:
Alazami syndrome
LARP7 mutation
Osteo-Oto-Hepato-Enteric syndrome (O2HE)
UNC45A mutation

ABSTRACT

Alazami syndrome is a rare autosomal recessive disorder characterized by primordial dwarfism, intellectual disability, and distinct facial features, primarily caused by biallelic mutations in the LARP7 gene. Osteo-oto-hepato-enteric (O2HE) syndrome is another rare autosomal recessive disorder resulting from mutations in the UNC45A gene, presenting with congenital diarrhea, neonatal cholestasis, deafness, and bone fragility.

We report a unique case of an 11-month-old male patient exhibiting clinical features consistent with Alazami syndrome, including developmental delay, intellectual disability, and characteristic facial dysmorphisms (triangular face, deep-set eyes, and prominent forehead). Genetic analysis revealed a single pathogenic variant in the LARP7 gene inherited from the father, which is atypical for an autosomal recessive condition. Additionally, the patient presented with features of O2HE syndrome and was found to carry compound heterozygous mutations in the UNC45A gene. The presence of only one LARP7 variant suggests an alternative genetic mechanism, such as uniparental disomy (UPD) or a second undetected variant.

This case challenges the conventional autosomal recessive inheritance model of Alazami syndrome by presenting with a single detectable LARP7 variant. It underscores the necessity for comprehensive genetic evaluations, including investigations for UPD or structural variants, in patients with suspected Alazami syndrome but only one identified pathogenic

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

* Corresponding author.
E-mail address: drajanem@gmail.com (A. Janem).

† Abdullah Janem and Ayman Thouqan contributed equally to the work and should be considered co-first authors.

https://doi.org/10.1016/j.radcr.2025.01.082

allele. Furthermore, the co-occurrence of O2HE syndrome highlights the complexity of diagnosing patients with multiple overlapping genetic disorders. This report contributes to expanding the genetic and phenotypic spectrum of Alazami syndrome and emphasizes the importance of considering multifactorial genetic mechanisms in rare congenital disorders.

Introduction

Alazami syndrome, a rare autosomal recessive disorder first described in 2012, is characterized by primordial dwarfism or short stature, intellectual disability, and distinct facial features [1,2]. The syndrome results from biallelic mutations in the LARP7 gene, which encodes a chaperone protein crucial for the stability and function of 7SK, a noncoding RNA. Specifically, LARP7 protects 7SK from degradation, and the 7SK snRNA complex, along with associated cellular proteins, regulates the activity of the positive transcription elongation factor P-TEFb, which is involved in transcription by RNA polymerase II [1,3,4]. Consequently, the depletion of 7SK RNA due to LARP7 mutations disrupts normal cellular processes, leading to the complex phenotype observed in affected individuals [1].

Since its initial description, fewer than 53 cases of Alazami syndrome have been reported in the literature. Most reported cases involve homozygous mutations in the LARP7 gene, though compound heterozygous mutations have also been documented [3,5]. The phenotypic spectrum of Alazami syndrome is broad, with patients exhibiting varying degrees of severity. Most patients present with short stature or primordial dwarfism. Additionally, patients display developmental delay and intellectual disability, with speech development being particularly affected [6], distinctive craniofacial features are also common in Alazami syndrome, including a triangular face, prominent forehead, deep-set eyes with narrow palpebral fissures, broad nose, malar hypoplasia, short philtrum, and full lips [2,7]. Other clinical features that may be present include skeletal anomalies such as scoliosis and mild epiphyseal changes, behavioral issues like hyperactivity, anxiety, and self-mutilation [7], and ocular anomalies, including strabismus. Some individuals with Alazami syndrome may also have congenital heart defects like an atrial septal defect, and small kidneys, sometimes with prehypertension [8]. Less common findings include cleft palate, hand wringing, and periventricular nodular heterotopia [2,8]. These additional features tend to be more severe in homozygous individuals, with consanguinity likely playing a significant role.

Recently, osteo-oto-hepato-enteric (O2HE) syndrome has been described as an autosomal recessive pleiotropic disorder characterized by congenital diarrhea, neonatal cholestasis, deafness, and bone fragility [9]. This condition stems from loss-of-function mutations in the UNC45 myosin chaperone A (UNC45A) gene, which encodes a protein involved in regulating cytoskeletal processes by assisting in the proper folding and function of myosin motors [10]. When UNC45A is deficient, the clinical spectrum can range from congenital diarrhea and cholestasis to bone fragility and deafness.

In this report, we present a unique case of Alazami syndrome in a patient who carries only a single pathogenic allele of the LARP7 gene. Despite this atypical genetic finding, the patient exhibits a range of features consistent with Alazami syndrome, including developmental delay, intellectual disability, and facial dysmorphisms (triangular face, deep-set eyes, and prominent forehead) [2,7]. In addition, the patient also carries compound heterozygous mutations in the Unc-45 Myosin Chaperone A (UNC45A) gene; known to be associated with O2HE syndrome.

This case challenges the existing understanding of the genetic basis of Alazami syndrome and raises the possibility of alternative mechanisms contributing to its phenotypic expression. Furthermore, the occurrence of 2 distinct gene mutations in the same patient emphasizes the complexity of this case and the challenges in diagnosis and management. We aim to review the documented cases in the literature and explore this unusual presentation, with a particular focus on expanding the recognized genetic and phenotypic spectrum of the disease.

Case presentation

The patient is the product of conception by healthy parents. He was delivered by cesarean section at 36+2 weeks of gestation due to intrauterine growth restriction (IUGR) and oligohydramnios, with Apgar scores of 8 and 9 at 1 and 5 min, respectively. His birth weight was 1,460 g (−2.89 SD, <1st percentile), length was 42 cm (−2.94 SD, <1st percentile), and head circumference was 28 cm (−2.87 SD, <1st percentile). Nonspecific discrete dysmorphic features were observed in the boy after delivery. However, the patient was admitted to the neonatal intensive care unit (NICU) for 3 months due to symmetrical IUGR. Additionally, the patient experienced transient tachypnea of the newborn and failure to thrive.

The patient had normal body imaging except for a transfontanelle brain ultrasound, which revealed grade 2 intraventricular hemorrhage (IVH) with no ventricular dilation or midline shifting. Subsequent imaging, however, showed no abnormalities. Furthermore, since the age of one month, the patient has exhibited involuntary right-hand movements in the form of dyskinesia, up-rolling of the eyes, and mouth deviation.

Several episodes of diarrhea occurred after each feed, in addition to episodes of cholestasis represented by jaundice and conjugated hyperbilirubinemia. The patient also had a decrease in galactose-1-phosphate uridyltransferase; therefore, galactosemia was suspected. However, later urine tests were negative for reducing substances.

At 7 months of age, the patient underwent extensive imaging and clinical evaluations. Auditory brainstem response testing demonstrated bilateral profound sensorineural hear-

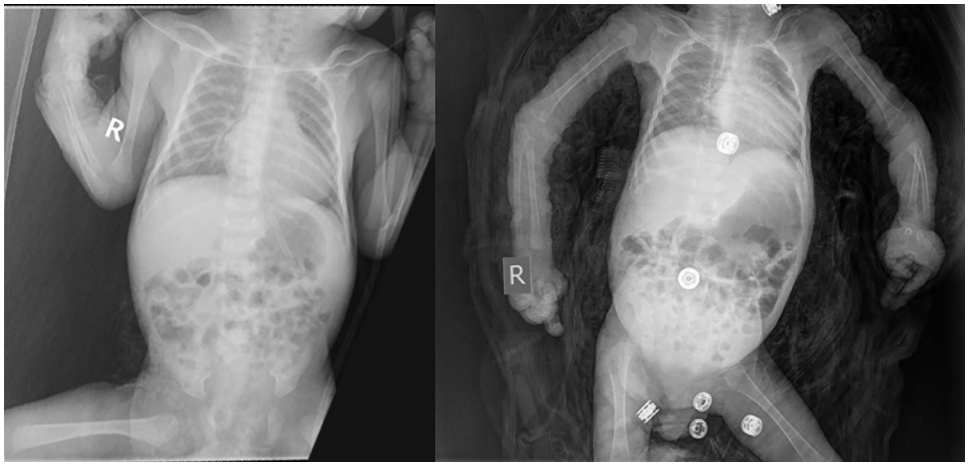

Fig. 1 – Chest radiograph demonstrating an abnormal cardiac silhouette, a narrow, bell-shaped thorax, and thin, under-mineralized bones in a 7-month-old patient with significant growth restriction.

ing loss. A brain MRI revealed hyperintensity within the internal capsule and a thin corpus callosum, but otherwise normal findings. Abdominal ultrasound showed minimal dilation of the left renal pelvis (2 mm in the anterior–posterior diameter). Echocardiography confirmed a patent ductus arteriosus (PDA) with a left-to-right shunt and left atrial enlargement. Notably, chest X-rays displayed an abnormal cardiac silhouette with a disproportionately small, bell-shaped thorax. The bones appeared markedly thin and under-mineralized, reflecting the patient's significant growth restriction. These radiographic features, particularly the narrow rib cage and low bone density, are consistent with a syndromic presentation of skeletal and systemic involvement (Fig. 1).

A single exome analysis was performed at the age of 8 months. Genomic amplification and direct sequencing detected the following variants: c.604_605delAA, p.Lys202fs*5 on exon 6 of the LARP7 gene; c.323T>C, p.Leu108Pro and c.1409G>A, p.Arg470Gln on exons 7 and 13 of the UNC45A gene, respectively; and c.490C>T, p.Arg164Trp on exon 4 of the TRAPPC3 gene. Furthermore, the father and mother each carried the aforementioned variants in the UNC45A gene, and his 3-year-old sister has both variants of the same gene despite being healthy. For the LARP7 gene, only the father had the same variant as his son.

At the last visit, the patient was an 11-month-old boy with delayed growth parameters (weight: 4.4 kg (–7.96 SD, <1st percentile), length: 59 cm (–6.70 SD, <1st percentile), head circumference: 35.5 cm (–9.03 SD, <1st percentile)) and several dysmorphic features, including a triangular face, broad forehead, deep-set eyes, low-set ears, large ears, full lower lip, micrognathia, malar hypoplasia, high-arched palate, torticollis, overlapping toes, joint hypermobility, widely spaced nipples, undescended testes, and behavior of self-mutilation. Developmentally, despite being 11 months of age, he presented with the skills of a typical 6-month-old. He was unable to roll over from a supine to a prone position, sit unsupported, or produce meaningful vocalizations, indicating a significant global delay across multiple developmental domains.

Discussion

Alazami et al. first described a distinct form of primordial dwarfism, commonly referred to as Alazami syndrome, which is characterized by severe intellectual disability and various facial dysmorphisms. To date, only around 53 cases of Alazami syndrome have been reported worldwide. Table 1 summarizes the most commonly reported features across at least ten cases from the literature, alongside the current case [1–3,5,7,8,11–19].

Clinically, notable dysmorphic features may raise suspicion for Alazami syndrome; however, confirmatory genetic testing is necessary for diagnosis. Pathogenic variants in LARP7 have been identified as the primary driver of Alazami syndrome, which follows an autosomal recessive inheritance, in which, 2 pathogenic variants ("2 hits") in LARP7 must be present for the disease phenotype to manifest [1]. According to Table 1, the majority (84.90%) of previously reported patients are homozygous for the LARP7 variant, while the remainder are compound heterozygotes (2 different mutated alleles at the same gene locus).

Parental consanguinity has been documented in 47% of reported cases, which helps explain homozygous variants. Even so, there can be complexities in detecting both pathogenic variants in some individuals. In our case, only the father was found to carry the known pathogenic variant in LARP7, resulting in the child apparently carrying just one pathogenic allele. This observation questions the documented inheritance model of Alazami syndrome. Nonetheless, there are potential theories that can hold an explanation including the presence of an undetected second variant missed by exome sequencing (e.g., large deletions, deep intronic changes, or low-level mosaicism), or the possibility of uniparental disomy (UDP). A recent case report described Alazami syndrome arising from UPD on chromosome 4, in which a 45 Mb region of loss of heterozygosity revealed a single frameshift variant in LARP7, effectively rendering it homozygous and clinically manifesting as Alazami syndrome [19]. This underscores how UPD can give

Table 1 – Commonly reported features in previous Alazami syndrome cases.

Feature	Previous reported cases n (%)	Current case
Consanguinity	25/53 (47%)	Yes
Gender	28/53 Male (53%)	Male
Zygosity	Homozygous 45/53 (85%), Compound heterozygous 8/53 (15%)	Heterozygous
Motor developmental delay	49/51 (96%)	Yes
Intellectual disability	50/50 (100%)	Yes
Face		
Triangular face	24/39 (62%)	Yes
Prominent forehead	16/19 (84%)	No
Sparse eyebrows	18/36 (50%)	Yes
Malar hypoplasia	21/35 (60%)	Yes
Eyes		
Narrow and short palpebral fissure	18/36 (49%)	No
Deep-seated eyes	25/36 (69%)	Yes
Strabismus	13/33 (39%)	No
Hypertelorism	9/13 (69%)	No
Nose		
Prominent nose	9/10 (90%)	No
Broad nose	32/40 (80%)	Yes
Ears		
Low set ears	18/39 (46%)	Yes
Philtrum		
Short philtrum	26/36 (72%)	No
Mouth and oral region		
Wide mouth	21/38 (55%)	No
Full lips	17/37 (46%)	Yes
Widely spaced teeth	20/26 (77%)	-

rise to a recessive phenotype despite the absence of a second familial variant. Thus, further genetic investigations (e.g., SNP microarray or multiplex ligation-dependent probe amplification [MLPA]) might reveal a second "hidden" variant or confirm a UPD event.

Beyond the LARP7 finding, this patient's exome sequencing also revealed 3 additional variants in 2 different genes. Two of these variants were in UNC45A, which is implicated in Osteo-Oto-Hepato-Enteric syndrome (O2HE), an autosomal recessive pleiotropic syndrome characterized by variable presentations, including congenital diarrhea, cholestasis, bone fragility, and deafness [9]. To our knowledge, this syndrome is extremely rare, as less than 20 cases have been reported to date. Consequently, further studies are needed to explain the relationship between the disease genotype and phenotype.

Additionally, a substitution in TRAPPC3 was detected, predicted to result in abnormal protein translation. While TRAPPC3 has been implicated in neurodevelopmental disorders, its role is not as well-established as UNC45A. Other genes in the TRAPP complex, including TRAPPC6B, which interacts with TRAPPC3, are associated with various neurodevelopmental phenotypes. Further research is necessary to assess the clinical relevance of this specific TRAPPC3 variant in our patient [20].

Conclusion

In this report, we present a rare and complex case of Alazami syndrome in an 11-month-old patient who carries only a single pathogenic variant of the LARP7 gene, alongside compound heterozygous mutations in the UNC45A gene associated with O2HE syndrome. This atypical genetic presentation challenges the established autosomal recessive inheritance model of Alazami syndrome and suggests the involvement of alternative genetic mechanisms such as uniparental disomy or undetected second variants. The co-occurrence of 2 distinct genetic disorders in the same patient underscores the necessity for thorough and comprehensive genetic testing in individuals presenting with multiple syndromic features.

Our findings highlight the importance of considering broader genetic analyses, including SNP microarrays and MLPA, to uncover hidden genetic abnormalities that may not

be detected through standard exome sequencing. Additionally, this case emphasizes the need for heightened clinical awareness and multidisciplinary approaches in diagnosing and managing patients with overlapping phenotypes of rare genetic disorders. By documenting and analyzing such unique cases, we aim to enhance the understanding of the genetic architecture and phenotypic variability of Alazami syndrome, ultimately improving diagnostic accuracy and genetic counseling for affected families.

Patient consent

Written informed consent was obtained from the patient's legal guardians for the publication of this case report, including all accompanying images and relevant clinical information. The guardians have reviewed the final manuscript and agreed to its publication. All personal identifiers have been removed or disguised to protect the patient's privacy.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2025.01.082.

REFERENCES

[1] Alazami AM, Al-Owain M, Alzahrani F, Shuaib T, Al-Shamrani H, Al-Falki YH, et al. Loss of function mutation in LARP7, chaperone of 7SK ncRNA, causes a syndrome of facial dysmorphism, intellectual disability, and primordial dwarfism. Hum Mutat 2012;33:1429–34. doi:10.1002/humu.22175.

[2] Imbert-Bouteille M, Mau Them FT, Thevenon J, Guignard T, Gatinois V, Riviere J-B, et al. LARP7 variants and further delineation of the Alazami syndrome phenotypic spectrum among primordial dwarfisms: 2 sisters. Eur J Med Genet 2019;62:161–6. doi:10.1016/j.ejmg.2018.07.003.

[3] Ivanovski I, Caraffi SG, Magnani E, Rosato S, Pollazzon M, Matalonga L, et al. Alazami syndrome: the first case of papillary thyroid carcinoma. J Hum Genet 2020;65:133–41. doi:10.1038/s10038-019-0682-5.

[4] Peterlin BM, Brogie JE, Price DH. 7SK snRNA: a noncoding RNA that plays a major role in regulating eukaryotic transcription. Wiley Interdiscip Rev RNA 2012;3:92–103. doi:10.1002/wrna.106.

[5] Ling TT, Sorrentino S. Compound heterozygous variants in the *LARP7* gene as a cause of Alazami syndrome in a Caucasian female with significant failure to thrive, short stature, and developmental disability. American J of Med Genetics Pt A 2016;170:217–19. doi:10.1002/ajmg.a.37396.

[6] Elmas M, Yıldız H, Erdoğan M, Gogus B, Avcı K, Solak M. Comparison of clinical parameters with whole exome sequencing analysis results of autosomal recessive patients; a center experience. Mol Biol Rep 2019;46:287–99. doi:10.1007/s11033-018-4470-7.

[7] Hollink IH, Alfadhel M, AS Al-Wakeel, Ababneh F, Pfundt R, De Man SA, et al. Broadening the phenotypic spectrum of pathogenic LARP7 variants: two cases with intellectual disability, variable growth retardation and distinct facial features. J Hum Genet 2016;61:229–33. doi:10.1038/jhg.2015.134.

[8] Fauntleroy-Love KD, Wilson TE, Padem N, Golomb MR. A 2-year-old child with Alazami syndrome with newly reported findings of immune deficiency, periventricular nodular heterotopia, and stroke; broadening the phenotype of Alazami. Child Neurology Open 2023;10:2329048X231190784. doi:10.1177/2329048X231190784.

[9] Esteve C, Francescatto L, Tan PL, Bourchany A, De Leusse C, Marinier E, et al. Loss-of-function mutations in UNC45A cause a syndrome associating cholestasis, diarrhea, impaired hearing, and bone fragility. Am J Hum Genet 2018;102:364–74. doi:10.1016/j.ajhg.2018.01.009.

[10] Duclaux-Loras R, Lebreton C, Berthelet J, Charbit-Henrion F, Nicolle O, Revenu des Courtils C, et al. UNC45A deficiency causes microvillus inclusion disease–like phenotype by impairing myosin VB–dependent apical trafficking. J Clin Invest;132:e154997. https://doi.org/10.1172/JCI154997.

[11] Wojcik MH, Linnea K, Stoler JM, Rappaport L. Updating the neurodevelopmental profile of Alazami syndrome: illustrating the role of developmental assessment in rare genetic disorders. American J of Med Genetics Pt A 2019;179:1565–9. doi:10.1002/ajmg.a.61189.

[12] Gana S, Plumari M, Rossi E, Saracino A, Iorio M, Zanaboni MP, et al. Alazami syndrome: phenotypic expansion and clinical resemblance to Smith–Lemli–Opitz syndrome. American J of Med Genetics Pt A 2020;182:2722–6. doi:10.1002/ajmg.a.61832.

[13] Das S, Godbole K, Abraham SSC, Ganesan P, Kamdar P, Danda S. Alazami syndrome: report of three Indian patients with phenotypic spectrum from adolescence to adulthood. American J of Med Genetics Pt A 2021;185:1606–9. doi:10.1002/ajmg.a.62118.

[14] Mazen SA, Lynne MB. Alazami syndrome in an Afghani girl: a case report and review of literature. Glob J Rare Dis 2019;4:003–6. doi:10.17352/2640-7876.000012.

[15] Dateki S, Kitajima T, Kihara T, Watanabe S, Yoshiura K, Moriuchi H. Novel compound heterozygous variants in the LARP7 gene in a patient with Alazami syndrome. Hum Genome Var 2018;5:18014. doi:10.1038/hgv.2018.14.

[16] Patalan M, Leśniak A, Bernatowicz K, Romanowska H, Krzywińska-Zdeb E, Walczak M, et al. Patient with phenylketonuria and intellectual disability—Problem not always caused exclusively by insufficient metabolic control (Coexistence of PKU and Alazami Syndrome). IJERPH 2022;19:2574. doi:10.3390/ijerph19052574.

[17] Bajafar A, Rifai F, Al-Said Y, Cupler E. Alazami syndrome due to LARP7 gene mutation: expanding the phenotype. J Neurolog Sci 2019;405:272–3. doi:10.1016/j.jns.2019.10.1326.

[18] Holohan B, Kim W, Lai T-P, Hoshiyama H, Zhang N, Alazami AM, et al. Impaired telomere maintenance in Alazami syndrome patients with LARP7 deficiency. BMC Genomics 2016;17:749. doi:10.1186/s12864-016-3093-4.

[19] Amélie B-S, Julien T, Kevin Y, Marie-Emmanuelle N, Jean-Marc C, Fanny D-T, et al. Exome sequencing detects uniparental disomy of chromosome 4 revealing a pathogenic variant responsible for Alazami Syndrome: a case report. Am J Med Genet Part A: e63891. https://doi.org/10.1002/ajmg.a.63891.

[20] Almousa H, Lewis SA, Bakhtiari S, Nordlie SH, Pagnozzi A, Magee H, et al. TRAPPC6B biallelic variants cause a neurodevelopmental disorder with TRAPP II and trafficking disruptions. Brain 2024;147:311–24. doi:10.1093/brain/awad301.