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Case Report

A Rare Consanguineous Case of Alazami Syndrome in a Jordanian Family: Clinical Presentation, Genetic Analysis, and Therapeutic Approaches - A Case Report

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Abstract

Objective: Alazami syndrome (AS) is an infrequent genetic disorder inherited in an autosomal recessive pattern, characterized by the presence of multiple congenital abnormalities. This study explores a case of a 4-year-old girl with AS, examining symptoms, genetic factors, and treatment efficacy.

Case report: A 4-year-old girl, born to consanguineous Jordanian parents, displayed dysmorphic features including low birth weight, microcephaly, hyperthyroidism, short stature, blue sclera, triangular-shaped face, deep-set eyes, narrow palpebral fissures, and a prominent forehead. Examination revealed height (92 cm) and weight (7.7 kg) below the 5th and 3rd percentiles respectively. Blood tests and renal ultrasound were normal. Whole exome sequencing (WES) identified a homozygous eight-base pair deletion within exon 5 of the LARP7 gene on chromosome 4q25, confirming the diagnosis of AS, an autosomal recessive disorder. This variant induces frameshift mutations leading to premature stop codons, suggesting a probable mechanism of illness via loss of function. Treatment involving growth monitoring and therapy led to significant improvements in height, weight, and communication skills within three months.

Conclusion: We describe a rare autosomal recessive AS case due to consanguinity, with a frameshift mutation in the LARP7 gene found via WES. Our AS treatment program effectively alleviates symptoms and enhances developmental progress.

More Information

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Introduction

In 2012, Dr. Anas Alazami identified a rare genetic disorder within a consanguineous Saudi Arabian family, which he subsequently named Alazami Syndrome (AS) [1]. According to previous investigations, AS is often diagnosed between the ages of 2 and 26, with a higher frequency in consanguineous families. Although this condition was first connected with consanguineous marriages, AS is now increasingly being detected in non-consanguineous relationships. This investigation also revealed that this syndrome is characterized as a congenital abnormality, with primordial dwarfism and a variety of clinical symptoms that include both physical and developmental components. The clinical manifestations and signs of this syndrome vary greatly, demonstrating remarkable variety not just within the subtype but also across affected siblings [2-6]. It is worth noting that the AS may be subject to underdiagnosis in the studied region, with cases potentially surpassing the current diagnostic frequency. Therefore, the rarity and clinical heterogeneity of the syndrome pose considerable challenges in the realms of diagnosis and management.

Genetic studies on AS patients have revealed that the disease is genetic, with mutations in the LARP7 gene on chromosome 4q25, also known as PIP7s or ALAZS [1-4]. This rare condition appears as homozygous or compound heterozygous, implying that certain genetic variants or mutations are the underlying cause. These mutations disrupt normal cellular processes, resulting in developmental and physiological abnormalities. Furthermore, detailed molecular analysis revealed that the LARP7 gene encodes a chaperone protein, crucial for RNA 75K's function, influencing its folding and stability through its encoded chaperone protein.

An in-depth investigation into mutations reported in the LARP7 gene has elucidated that this syndrome is primarily distinguished by pathogenic protein-truncating mutations in the La-related protein 7 (LARP7). These analyses established that LARP7 functions as a transcriptional regulator situated within the 7SK small nuclear ribonucleoprotein complex [4-10]. Despite growing research, much remains unknown about the precise genetic underpinnings and mechanisms leading to clinical outcomes in AS.

In reality, diagnosing rare genetic diseases requires a profound understanding of their molecular underpinnings, which can be challenging due to their infrequency and complexity. However, advancements in genetic sequencing technology, coupled with multinational collaborations, hold promise for enhancing diagnostic precision, genetic testing efficacy, and counseling practices. Whole-exome sequencing (WES) is one such genomic sequencing technology that has lately acquired popularity and is becoming more widely used. Further, the WES has emerged as a valuable tool, effectively screening protein-coding regions of the genome and facilitating rapid and accurate diagnosis of rare diseases. Through its comprehensive analysis, the WES facilitates the identification of new disease-associated genes. This insight allows for early intervention and treatment strategies, ultimately leading to enhanced quality of life for both patients and their families [6-9].

Here, we present a case study of AS in a consanguineous Jordanian family, emphasizing a four-year-old female. The study examines AS symptoms, investigates related genetic factors via WES, and assesses the efficacy of therapeutic interventions.

Case presentation

The case involves a female born on 19/01/2019 with consanguineous parents. Physical examination revealed that the patient exhibited signs of low birth weight, microcephaly, hyperthyroidism, short stature, and blue sclera. Additionally, dysmorphic facial features were observed, including a triangular-shaped face, deep-set eyes, narrow palpebral fissures, a tilted nose, a prominent forehead, a long philtrum, and a narrow upper lip. As a result, the patient was referred to Royal Medical Services for additional assessment, diagnosis, and treatment. During the physical assessment, the patient exhibited a stature of 92 centimeters, falling below the 5th percentile concerning her age, indicating a condition of short stature. Additionally, her weight was measured at 7.7 kilograms, positioning her below the 3rd percentile for her age, indicative of suboptimal weight gain. Further diagnostic evaluations encompassed hematological examinations, including a complete blood count and a metabolic panel, all of which yielded results within the expected normal range. A heart and renal ultrasound, skeletal survey, brain MRI, hearing examination, and ophthalmologic examination were all performed, with no evident abnormalities found (Table 1). These diagnostic findings, coupled with clinical manifestations, indicate the existence of autosomal recessive AS. Besides, previous investigations have shown that AS is an autosomal recessive condition characterized by congenital growth limitation, significant intellectual disability, and specific facial traits, supporting the aforementioned conclusion [1-10].

Given the variety of clinical symptoms observed in our case study, investigating potential multiple gene variations is critical to understanding our patient's presentation. This underscores the need for a comprehensive genetic analysis to pinpoint predisposing genetic factors. To address this, WES was employed to investigate genetic predispositions in our female patient diagnosed primarily with AS. Indeed, WES generates sequence data, allowing for in-depth genomic examination of our patient's genomes. The data also helps us precisely identify disease-related genetic variants in our patient, offering light on the genetic foundations of her disease. In our case, a mutation was discovered in the LARP7 gene on chromosome 4, emphasizing its importance in AS pathophysiology. Subsequently, a genetic variant analysis was conducted utilizing data from the Online Mendelian Inheritance in Man (OMIM) database [11]. Additionally, we followed the revised standardized guidelines for interpreting sequence variations issued by the Association for Clinical Genomic Science (ACGS) and the American College of Medical Genetics and Genomics (ACMG) [12]. These guidelines outline a systematic approach for identifying, classifying, and interpreting clinically significant genetic variants. These variant classification guidelines apply universally to variants within all Mendelian genes and have been adopted on a global scale. More significantly, following these guidelines increases consistency and precision in patient treatment and genetic counseling, especially in complicated instances.

The results of this molecular genetic testing and analysis revealed that this patient is homozygous for a likely pathogenic variant [NM_016648.4: c.422_429delTTGAAAGA; p.(Ile141SerfsTer17)] in the LARP7 gene on chromosome 4 (Table 2). This variant is an eight-base pair deletion in exon 5 of the LARP7 gene. The findings indicate that the deletion

Table 1: The phenotypic characteristics of the 4-year-old female patient diagnosed with Alazami Syndrome.

Parameter	Description of phenotypic features
Weight (Kg)	7.7
Height (cm)	92
Face	Triangular-shaped face
Eyes	Deep-set eyes, narrow palpebral fissures, and blue sclera
Hear	Appear normal
Head	A prominent forehead and microcephaly
Thyroid gland	Thyroid gland-Hyperthyroidism
Heart	No abnormality
Hematological	In the expected normal range
Renal ultrasound	Common renal morphology and function

Table 2: The following relevant variant related to the clinical indication has been identified in a 4-year-old female patient diagnosed with Alazami Syndrome

Gene (OMIM)	Genomic Position (GRCh37)	Nucleotide Change (TRANSCRIPT)	Protein Change (EFFECT)	Zygosity	Inheritance	*Variant Classification	Disease (OMIM)**
LARP7, PIP7S, ALAZS (*612026)	Chr4: 113567979_113567986del	NM_016648.4: c.422_429del TTGAAAGA	p.Ile141SerfsTer17 Frameshift	Homozygous	Autosomal Recessive	Likely Pathogenic	Alazami syndrome (#615071)

*Variant classification based on ACMG Guidelines and ACGS Guidelines. **OMIM: Online Mendelian Inheritance in Man [11,12].

induces a frameshift mutation, resulting in premature termination of the protein synthesis, specifically occurring 17 amino acids after codon 141 in the altered coding frame. This frameshift mutation or variant in the LARP7 gene is associated with AS with an autosomal recessive mode of inheritance. Besides, these clinical signs and manifestations align with those documented in AS cases and are very closely linked with loss-of-function mutations in the LARP7 gene, as observed in previous reports [1-10]. Based on these findings, the patient was definitively identified as having AS.

The combination of clinical symptoms and genetic data generated from WES supports robust clinical decision-making procedures, making it simpler to develop appropriate treatment plans. As a result, it is evident that AS therapy requires a multidisciplinary approach that includes clinical geneticists, pediatricians, neurologists, physical therapists, occupational therapists, speech therapists, and genetic counselors. This comprehensive approach aims to address both the genetic basis and clinical symptoms of AS. Treatment consists of frequent growth and development monitoring, physical, occupational, and speech therapies, genetic counseling, and targeted mutation testing for at-risk family members. The purpose of these treatments is to enhance growth, development, and symptom reduction. After three months of treatment, positive outcomes are observed, including increased height and weight percentiles, improved dysmorphic features, communication abilities, and daily functioning. To track her ongoing growth and development, the patient will continue with regular follow-up visits.

Discussion

In this case study, we look at a four-year-old child who has AS and was born to couples who are blood-related. AS has been investigated in consanguineous families, with a substantially higher prevalence among such offspring. AS, once considered to be exceptional, is becoming more frequent among the offspring of non-consanguineous couples. This trend is noteworthy since AS has long been associated with cultures where consanguinity was common [1-5]. More importantly, our patients had low birth weight, microcephaly, dysmorphic characteristics such as hyperthyroidism, small height, and blue sclera. Indeed, our patient's clinical symptoms are consistent with the diagnostic criteria set by Alazami et al. in 2012 [1]. It is also very clear that the symptoms and signs observed in our patients align closely with the clinical presentation of AS, as outlined in current medical literature [1-10]. The occurrence of these particular symptoms in our patient leads to the suspicion of AS. Moreover, this patient demonstrates unique phenotypic traits not previously documented, thereby expanding the spectrum of clinical manifestations associated with AS.

Previous and recent research indicates that diseases sharing similarities often stem from common molecular causes. Symptoms and signs are intrinsic features of a disease, yet alone they do not confirm the syndrome due to overlaps between different disorders or syndromes. These genetic similarities can result in similar roles and interactions amongst gene products, confounding the identification of disease-causing genes [13,14]. As a result, more effective sequencing technology of WES was utilized in our case to tackle this challenge. Through this analysis, we successfully identified the disease-causing gene, elucidating probable genetic determinants of AS. In our case, the WES method found a homozygous eight-base pair deletion in exon 5 of the LARP7 gene on chromosome 4 [NM_016648.4:c.422_429delTTGAAAGA; p.(Ile141SerfsTer17)] as potentially pathogenic. Upon thorough analysis of sequencing data following ACGS and ACMG guidelines, it was found that the mutation identified in the LARP7 gene aligns with an autosomal recessive mode of inheritance. It could be concluded that the successful use of WES enabled the accurate identification of pathogenic genetic variation that was connected with the clinical symptoms described in our patient. Similarly, previous investigations have shown that WES analysis is effective at confirming AS by identifying related molecular markers and genetic variants among patients. Additionally, these investigations have identified harmful homozygous mutations in the LARP7 gene in AS, aligning with our findings and reinforcing the significant role of the LARP7 protein in AS pathogenesis [1-10]. According to these findings, the LARP7 gene was discovered to encode a nuclear protein that is essential for ribosomal RNA processing and controls mRNA translation. Taken together, mutations in LARP7 affect this process, leading to reduced protein synthesis and, finally, AS.

In reality, it is well documented that efficient therapy of uncommon disorders necessitates close collaboration among practitioners from diverse medical specialties within a genuinely multidisciplinary framework [15,16]. Utilizing the provided recommendations, we developed a comprehensive treatment plan suited to our four-year-old patient diagnosed with AS. This plan aims to improve her general well-being and satisfaction during the treatment process. This strategy combines many disciplines, such as growth monitoring, physical and speech therapy, genetic counseling, and mutation testing, to improve therapeutic outcomes and

address the complex elements of AS care. After three months of intense therapy, our four-year-old AS patients experienced significant improvements in growth, speech development, overall developmental progress, and symptom reduction. These promising findings demonstrate the effectiveness of a scientific, multidisciplinary approach in addressing several aspects of the patient's health. We believe that continued therapy, genetic counseling, lifelong surveillance, and early proactive diagnosis are essential for at-risk family members.

Conclusion

This report documents a unique case involving a 4-year-old girl born to consanguineous Jordanian parents, detailing symptoms, genetic factors, and successful multidisciplinary treatment. The patient's presentation includes hyperthyroidism, dysmorphic facial features, and other indicative signs, consistent with the diagnosis of AS. Molecular diagnosis confirmed by WES identifying a homozygous deletion in exon 5 of the LARP7 gene, considered potentially pathogenic. Treatment integrates growth monitoring, and physical, and speech therapy, leading to notable improvements. Implementing familial segregation study, genetic counseling, and targeted mutation testing critical for at-risk family members. Besides, this case study expands our comprehension of AS treatment management, facilitating the development of personalized intervention strategies.

Declaration of patient consent: The patient gave informed consent for the publication of this study on July 10, 2022.

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References

1. Alazami AM, Al-Owain M, Alzahrani F, Shuaib T, Al-Shamrani H, Al-Falki YH, Al-Qahtani SM, Alsheddi T, Colak D, Alkuraya FS. Loss of function mutation in LARP7, chaperone of 7SK ncRNA, causes a syndrome of facial dysmorphism, intellectual disability, and primordial dwarfism. Hum Mutat. 2012 Oct;33(10):1429-34. doi: 10.1002/humu.22175. Epub 2012 Aug 30. PMID: 22865833.

2. Bajafar A, Rifai F, Al-Said Y, Cupler E. Alazami syndrome due to LARP7 gene mutation: Expanding the phenotype. Journal of the Neurological Sciences. 2019; 405: 272-273.

3. Al-Hinai A, Al-Hashmi S, Ganesh A, Al-Hashmi N, Al-Saegh A, Al-Mamari W, Al-Murshedi F, Al-Thihli K, Al-Kindi A, Al-Maawali A. Further phenotypic delineation of Alazami syndrome. Am J Med Genet A. 2022 Aug;188(8):2485-2490. doi: 10.1002/ajmg.a.62778. Epub 2022 May 14. PMID: 35567578.

4. 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 Neurol Open. 2023 Jul 27;10:2329048X231190784.doi:10.1177/2329048X231190784.PMID: 7529055; PMCID: PMC10388622.

5. Soengas-Gonda E, Pérez de la Fuente R, Arteche-López A, Gómez-Cano MLÁ, Quesada-Espinosa JF, Palma Milla C, Lezana Rosales JM, Mayo de Andrés S, Sánchez-Calvín MT, Gómez-Rodríguez MJ, Sierra Tomillo O, Juarez Rufian A, Ramos Gomez P, Herrero-Forte C, Fenollar-Cortés M, Cotarelo-Pérez C, García Ron A, Pérez Rodríguez O, Oancea-Ionescu R, Moreno-García M. Expanding the Phenotypic Spectrum of Alazami Syndrome: Two Unrelated Spanish Families. Neuropediatrics. 2023 Feb;54(1):31-36. doi: 10.1055/a-1947-8411. Epub 2022 Sep 20. PMID: 36126956.

6. 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. Am J Med Genet A. 2016 Jan;170A(1):217-9. doi: 10.1002/ajmg.a.37396. Epub 2015 Sep 16. PMID: 26374271.

7. Dateki S, Kitajima T, Kihara T, Watanabe S, Yoshiura KI, Moriuchi H. Novel compound heterozygous variants in the *LARP7* gene in a patient with Alazami syndrome. Hum Genome Var. 2018 Mar 29;5:18014. doi: 10.1038/hgv.2018.14. PMID: 29619239; PMCID: PMC5874394.

8. Hasler D, Meduri R, Bąk M, Lehmann G, Heizinger L, Wang X, Li ZT, Sement FM, Bruckmann A, Dock-Bregeon AC, Merkl R, Kalb R, Grauer E, Kunstmann E, Zavolan M, Liu MF, Fischer U, Meister G. The Alazami Syndrome-Associated Protein LARP7 Guides U6 Small Nuclear RNA Modification and Contributes to Splicing Robustness. Mol Cell. 2020 Mar 5;77(5):1014-1031.e13. doi: 10.1016/j.molcel.2020.01.001. Epub 2020 Feb 3. PMID: 32017898.

9. Imbert-Bouteille M, Mau Them FT, Thevenon J, Guignard T, Gatinois V, Riviere JB, Boland A, Meyer V, Deleuze JF, Sanchez E, Apparailly F, Geneviève D, Willems M. LARP7 variants and further delineation of the Alazami syndrome phenotypic spectrum among primordial dwarfisms: 2 sisters. Eur J Med Genet. 2019 Mar;62(3):161-166. doi: 10.1016/j.ejmg.2018.07.003. Epub 2018 Jul 10. PMID: 30006060.

10. 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. Am J Med Genet A. 2019 Aug;179(8):1565-1569. doi: 10.1002/ajmg.a.61189. Epub 2019 May 10. PMID: 31074943; PMCID: PMC6663627.

11. Amberger J, Bocchini C, Hamosh A. A new face and new challenges for Online Mendelian Inheritance in Man (OMIM®). Hum Mutat. 2011 May;32(5):564-7. doi: 10.1002/humu.21466. Epub 2011 Apr 5. PMID: 21472891.

12. Durkie M, Cassidy E-J, Ian Berry I, Owens M, Turnbull C, Scott RH, Taylor RW, Deans ZC, Ellard S, Baple EL, Dominic J McMullan DJ. ACGS Best Practice Guidelines for Variant Classification in Rare Disease 2024. Recommendations ratified by The Association for Clinical Genomic Science (ACGS) Quality Subcommittee on 20th February 2024. https://www.acgs.uk.com/media/12533/uk-practice-guidelines-for-variant-classification-v12-2 024. pdf.

13. Cheng L, Zhao H, Wang P, Zhou W, Luo M, Li T, Han J, Liu S, Jiang Q. Computational Methods for Identifying Similar Diseases. Mol Ther Nucleic Acids. 2019 Dec 6;18:590-604. doi: 10.1016/j.omtn.2019.09.019. Epub 2019 Sep 28. PMID: 31678735; PMCID: PMC6838934.

14. Woodward AA, Urbanowicz RJ, Naj AC, Moore JH. Genetic heterogeneity: Challenges, impacts, and methods through an associative lens. Genet Epidemiol. 2022 Dec;46(8):555-571. doi: 10.1002/gepi.22497. Epub 2022 Aug 4. PMID: 35924480; PMCID: PMC9669229.

15. 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. Am J Med Genet A. 2019 Aug;179(8):1565-1569. doi: 10.1002/ajmg.a.61189. Epub 2019 May 10. PMID: 31074943; PMCID: PMC6663627.

16. Meyer S, Yeh EA, Brunner J, Semler O, Gropman A. Editorial: New Therapeutic Options for Rare Diseases. Front Pediatr. 2022 Jan 24;9:832395. doi: 10.3389/fped.2021.832395. PMID: 35141184; PMCID: PMC8820370.