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A New Novel Mutation of AMER1 Gene with Osteopathia Striata with Cranial Sclerosis: Case and Review

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Abstract: To highlight the phenotype and genotype of osteopathia striata with cranial sclerosis (OSCS), and report a novel mutation in the *AMER1* gene. We describe an 11-month-old girl diagnosed with OSCS caused by a novel c.705del mutation in the *AMER1* gene, confirmed as a de novo mutation through whole-exome sequencing. The patient exhibited characteristic obvious longitudinal striations, facial feature, and developmental delays, and other clinical features, broadening the phenotypic spectrum of OSCS. Whole-exome sequencing identified a novel de novo pathogenic mutation, c.705del (p. Pro237Glnfs*45). The identification of a novel mutation expands the mutational spectrum of the *AMER1* gene and contributes to the understanding of the genetic heterogeneity of OSCS. Genetic testing remains critical for accurate diagnosis, particularly in cases with complex phenotypes.

1. Introduction

Osteopathia striata with cranial sclerosis (OSCS, OMIM 300373) is a rare X-linked dominant inheritance disease caused by mutations in the APC Membrane Recruitment 1(*AMER1)* gene (OMIM 300647, previously known as Wilms Tumor on X Chromosome (WTX) and FAM123B. It is characterized by distinct radiographic features, including cranial sclerosis and longitudinal striations on the skeleton. Despite advancements in genetic testing, OSCS remains diagnosis difficultly due to its broad phenotypic spectrum and overlapping clinical features with other skeletal dysplasia. Given the low incidence of OSCS, we reviewed the existing literature to emphasize the genetic diversity, clinical variability, and potential complications. However, the scarcity of reported cases and the variability in associated phenotypes make it difficult to establish clear genotype-phenotype correlations, posing significant challenges for accurate diagnosis. Expanding the genetic profile and understanding the clinical manifestations of OSCS is crucial for unraveling the underlying mechanisms of the disease.

Herein, we reported an 11-month-old girl with OSCS induced by a novel mutation of *AMER1* gene, emphasizing the phenotype and genotype of the disorder to contribute to the growing understanding of OSCS.

2. Case Presentation

An 11-month-old girl was admitted to our unit due to her developmental delay. She was the third pregnancy and second live (G3P2) of healthy and non-consanguineous parents. She was born at term (38 weeks) via eutocia with a birth weight of 3.6 kg. She presented with a congenital laryngeal web, laryngeal stridor, and ankyloglossia. Feeding difficulties and hypotonia were observed within the first two months. A patent ductus arteriosus and a 7mm pericardial effusion were detected at birth but resolved by four months of age. At 10 months, she was hospitalized for afebrile convulsions. A magnetic resonance imaging (MRI) of brain showed a slightly widened bilateral frontotemporal extra-axial space, and mild left ventricular dilation, with regular follow-up. An electroencephalogram (EEG) indicated paroxysmal δ activity with partial sharp waveform during sleep. She has since been managed with long-term oral sodium valproate without further seizure recurrence.

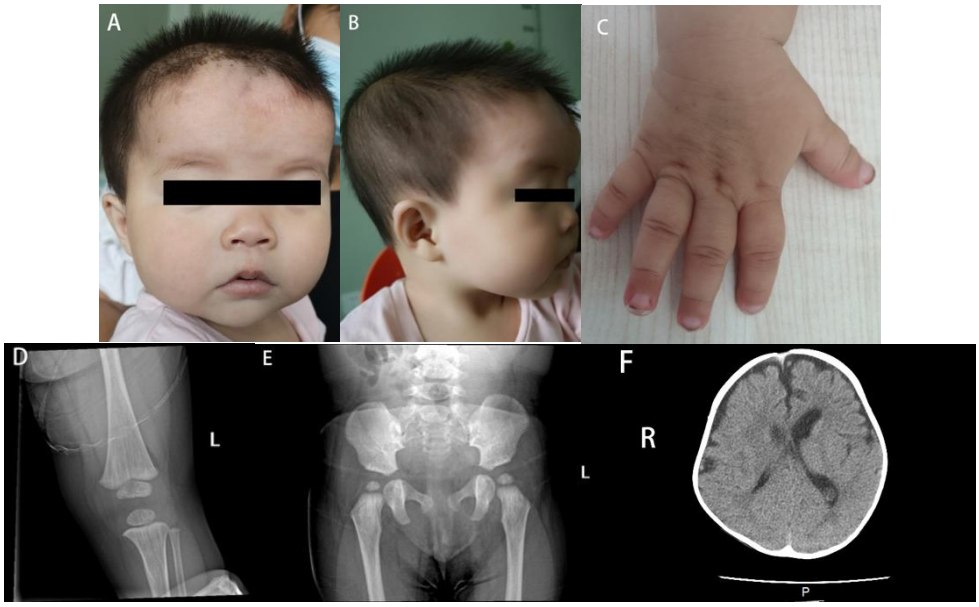

Figure 1. Clinical Presentation and Radiological Images (X-ray and Head CT) of the Patient

Physical examination revealed a height of 67 cm (<3rd percentile), weight of 9.5 kg, head circumference of 47.5 cm (approximately 97th percentile), and a 5 cm anterior fontanelle. She exhibited macrocephaly with a squared skull, characteristic facial features, including frontal bossing, widely spaced eyes, a flat nose, low-set and small ears, and micrognathia (Figure 1A-1B). Additional findings include a cleft palate, high-arched palate, widely spaced nipples, fifth finger clinodactyly, and slight finger contractures were noted (Figure 1C). She had relatively thinning hair and a short neck. No other abnormalities were noted in the skin, chest, or abdomen. Her motor development was delayed, as she could only sit but not stand or walk independently. She has not yet been able to say “mama” or “baba”. The patient’s 3-year-old sister is healthy.

Laboratory evaluations revealed approximately normal liver function tests, except for hyperammonemia. Blood cell counts, kidney function, blood phosphorus and calcium, parathyroid hormone, vitamin D, and thyroid hormone were all within normal ranges. Ultrasound examination of the genitourinary system revealed no abnormalities. X-ray showed obvious longitudinal striations the knee and pelvic bone (Figure 1D-1E). A computed tomography (CT) of the brain revealed widened bilateral frontoparietal-temporal extra-axial spaces, deeper and wider sulci, slightly enlarged bilateral lateral ventricles, and thickened vascular shadows on the brain surface, with no intracranial space-occupying lesions observed (Figure 1F).

Trio-whole exome sequencing (Illumina, PE150) analysis in our unit identified a c.705del heterozygous variation in exon 2 of the *AMER1* gene, confirmed by Sanger sequencing. Bioanalysis indicated that this variation results in the early termination of peptide chain synthesis (p. Pro237Glnfs*45). This variation was not found in ExAC, GnomAD, and 1000 Genomes databases, suggesting that c.705del is a novel mutation. Furthermore, this variation and clinical phenotype was absent in her parents, indicating a de novo mutation in this girl. According to ACMG criteria, it is classified as a pathogenetic mutation. Based on clinical feathers and genetic analysis, the patient was diagnosed with OSCS.

Our case adds to the existing body of knowledge by identifying a novel heterozygous c.705del mutation in the *AMER1* gene, thereby expanding the mutational spectrum associated with OSCS. According to our literature review, more than 110 cases have been diagnosed with OSCS through comprehensive genetic testing with additional cases diagnosed based on clinical presentations. Our findings contribute valuable data to this limited pool of reported cases, expanding genetic landscape of OSCS and emphasizing the genetic heterogeneity of the disease, and providing a reference point for future genetic screenings and researches.

The identified c.705del mutation of the *AMER1* gene results in a frameshift, leading to premature termination of the protein (p. Pro237Glnfs*45). This mutation is predicted to produce a truncated protein, likely resulting in loss of function. The de novo nature of the mutation, as evidenced by its absence in the parents, highlights the importance of considering de novo mutations in sporadic OSCS cases. Approximately 21 cases involved deletions of the *AMER1* gene [1-12], within 13 of these cases also showing mutations in adjacent genes[3, 4, 6-10]. Among point mutations, substitutions and deletions are most common types. According to the reviews of published loci and phenotypes, no clear genotype-phenotype correlations have been found among reported *AMER1* mutations and their clinical manifestations. While *AMER1* mutations have historically been regarded as causative for OSCS, challenge to this notion have emerged. Of the OSCS cases reported, 2 involved mutations in non-coding regions [7, 13] and 1 case involved a mutation in *CTNNB1* gene[14]. These findings suggest that phenotypic variability may be influenced by other genetic, epigenetic, or environmental factors, not only gene mutations.

Our patient exhibits a phenotype consistent with previously reported cases, including macrocephaly, characteristic facial features, skeletal striations, and developmental delays. Although the specific c.705del mutation does not appear to confer a distinct phenotypic profile compared to other mutations in *AMER1* gene. The presence of congenital laryngeal web not universally reported, adds to the spectrum of possible anomalies associated with OSCS. Early symptoms such as hypotonia and feeding difficulties, though nonspecific, are common in pediatric conditions and complicate early diagnosis, which emphasizes the necessity of considering genetic testing, particularly whole-exome sequencing, in patients with complex, multisystemic presentations.

Management of OSCS is primarily symptomatic and requires a multidisciplinary approach with ongoing developmental support. In our patient, epilepsy was effectively controlled with sodium valproate, and developmental delays are being addressed with supportive therapies. Previous studies have reported varying degrees of developmental delays in patients, affecting language, motor, or multiple aspects of development, with some individuals showing improvement in adulthood [13, 15].This observation does not support the hypothesis of certain intracranial metabolites accumulating over time. Holman et al.[4] suggested that neurodevelopmental capability may relate to the number of mutated copies. The delayed neurological development may originate during the embryonic stage, as suggested by prenatal findings of polyhydramnios in some case[2, 8, 12, 16-20]. Regular monitoring for associated complications is crucial, given the risk profile associated with *AMER1* mutations. In addition to cranial sclerosis and hearing loss, vigilance is needed for tumor, particularly Wilms tumors [5, 10, 21-23] and hepatoblastomas [19]. Cerebrovascular accidents have

also been reported in patients with OSCS [12, 24], emphasizing the broad spectrum of potential complications.

Further research is needed to elucidate the mechanisms contributing to the phenotypic variability in OSCS. Accumulating data from more cases is essential to identify potential genotype-phenotype correlations and understand the complete clinical spectrum of OSCS. Establishing an international registry for rare genetic diseases, such as OSCS, could facilitate data sharing and collaborative research efforts, ultimately enhancing our understanding and management of these diseases.

3. Conclusion

This case of an 11-month-old girl with OSCS, harboring a novel *AMER1* c.705del mutation, underscores the genetic diversity of the disorder and highlights the critical role of genetic testing in its diagnosis. The identification of a new mutation enriches the current genetic knowledge base and supports the continued exploration of *AMER1*-related pathophysiology. Enhanced awareness and early genetic intervention are essential for improving diagnostic accuracy and patient outcomes in OSCS.

Abbreviations

AMER1: APC Membrane Recruitment 1
CT: Computed Tomography
CTNNB1: catenin-β 1
EEG: electroencephalogram
MRI: magnetic resonance imaging
OSCS: osteopathia striata with cranial sclerosis
WTX: Wilms Tumor on X Chromosome

Ethical approval

Written informed consent for participation and publication of images was obtained from the patient's parents. The study was approved by the Ethics Committee of Children's Hospital of Zhejiang University School of Medicine. Our study does not involve human or animal test subjects, this statement is not applicable.

Consent for Publication

Written informed consent for the patient's participation and the publication of their images was obtained from the patient's parents. Additionally, all individuals depicted in the images, videos, and recordings included in this manuscript have provided written informed consent for their publication.

Data availability

All data are included within the manuscript and its supplementary materials, with no additional materials provided. All images are original and were created by the authors.

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Competing interest

The authors declare that they have no competing interests.

Author Contributions

HUANG Yu, QIN Lu, CHEN Yi, and YANG Tong-yu designing the work, collecting data, reviewing the literature, and interpreting the results. HUANG Yu drafted the manuscript. TANG Lan-Fang reviewed and approved the final version of the manuscript and agreed to take full responsibility for all aspects of the work, ensuring that any concerns regarding the accuracy or integrity of any part of the work are appropriately addressed. All authors have reviewed and approved the final manuscript and consented to its publication.

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Authors declarations

The authors declare that the submitted manuscript is original, has not been published elsewhere or is under consideration by another journal.

Figure declaration

Written informed consent for the publication of patient images was obtained from the patient's parents. All photographs were processed using Adobe Photoshop version 2023 to resize images, crop backgrounds, remove privacy information, and obscure the patients' eyes to protect their privacy. These modifications are minor and do not alter the scientific interpretation of the images. The authors affirm that all images are original and were created by them.

References

[1] Savarirayan R, Nance J, Morris L, Haan E, Couper R. Osteopathia striata with cranial sclerosis: highly variable phenotypic expression within a family. Clinical genetics. Oct 1997;52(4):199-205. doi:10.1111/j.1399-0004.1997.tb02547.x

[2] Perdu B, de Freitas F, Frints SG, et al. Osteopathia striata with cranial sclerosis owing to WTX gene defect. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. Jan 2010;25(1):82-90. doi:10.1359/jbmr.090707

[3] Jenkins ZA, van Kogelenberg M, Morgan T, et al. Germline mutations in WTX cause a sclerosing skeletal dysplasia but do not predispose to tumorigenesis. Nature genetics. Jan 2009;41(1):95-100. doi:10.1038/ng.270

[4] Holman SK, Morgan T, Baujat G, et al. Osteopathia striata congenita with cranial sclerosis and intellectual disability due to contiguous gene deletions involving the WTX locus. Clinical genetics. Mar 2013;83(3):251-256. doi:10.1111/j.1399-0004.2012.01905.x

[5] Holman SK, Daniel P, Jenkins ZA, et al. The male phenotype in osteopathia striata congenita with cranial sclerosis. American journal of medical genetics Part A. Oct 2011;155a(10):397-408. doi:10.1002/ajmg.a.34178

[6] Chénier S, Noor A, Dupuis L, Stavropoulos DJ, Mendoza-Londono R. Osteopathia striata with cranial sclerosis and developmental delay in a male with a mosaic deletion in chromosome region Xq11.2. American journal of medical genetics Part A. Nov 2012;158a(11):46-52. doi:10.1002/ajmg.a.35619

[7] Heikoop D, Brick L, Chitayat D, et al. The phenotypic spectrum of AMER1-related osteopathia striata with cranial sclerosis: The first Canadian cohort. American journal of medical genetics Part A. Dec 2021;185(12):3793-3803. doi:10.1002/ajmg.a.62452

[8] Herman SB, Holman SK, Robertson SP, Davidson L, Taragin B, Samanich J. Severe osteopathia striata with cranial sclerosis in a female case with whole WTX gene deletion. American journal of medical genetics Part A. Mar

2013;161a(3):94-95. doi:10.1002/ajmg.a.35716
[9] Vuillaume ML, Valard AG, Houcinat N, et al. First female prenatal case of osteopathia striata with cranial sclerosis in a fetus carrying a de-novo 1.9 Mbp interstitial deletion at Xq11.1q11.2. Clinical dysmorphology. Oct 2017;26(4):231-234. doi:10.1097/mcd.0000000000000192
[10] Bach A, Mi J, Hunter M, et al. Wilms tumor in patients with osteopathia striata with cranial sclerosis. European journal of human genetics : EJHG. Mar 2021;29(3):396-401. doi:10.1038/s41431-020-00718-4
[11] Yamagishi H, Monden Y, Michigami T, et al. A case of osteopathia striata with cranial sclerosis with facial nerve palsies. Pediatrics international : official journal of the Japan Pediatric Society. Jan-Dec 2023;65(1):e15648. doi:10.1111/ped.15648
[12] Scrimshaw L, Gorman K, Mansour S, Ganesan V, Sabir A. Moyamoya disease/cerebral vasculopathy in osteopathia striata with cranial sclerosis: a rare but important complication. Clinical dysmorphology. 2024;33(1):31-37. doi:10.1097/MCD.0000000000000479
[13] Mi J, Parthasarathy P, Halliday BJ, et al. Deletion of Exon 1 in AMER1 in Osteopathia Striata with Cranial Sclerosis. Genes. Nov 30 2020;11(12)doi:10.3390/genes11121439
[14] Huybrechts Y, Appelman-Dijkstra NM, Steenackers E, et al. A mosaic variant in CTNNB1/β-catenin as a novel cause for osteopathia striata with cranial sclerosis. The Journal of clinical endocrinology and metabolism. Jan 4 2024;doi:10.1210/clinem/dgad757
[15] Katsevman GA, Turner RC, Lucke-Wold BP, Sedney CL, Bhatia S. Osteopathia striata with cranial sclerosis (OSCS): review of the literature and case report demonstrating challenges of spinal fusion after trauma. Acta neurochirurgica. Jun 2016;158(6):15-20. doi:10.1007/s00701-016-2794-4
[16] Barbosa M, Perdu B, Senra V, et al. [Osteopathia striata with cranial sclerosis]. Acta medica portuguesa. Nov-Dec 2010;23(6):1147-50. Osteopatia estriada com esclerose craniana.
[17] Perdu B, Lakeman P, Mortier G, Koenig R, Lachmeijer AM, Van Hul W. Two novel WTX mutations underscore the unpredictability of male survival in osteopathia striata with cranial sclerosis. Clinical genetics. Oct 2011;80(4):83-88. doi:10.1111/j.1399-0004.2010.01553.x
[18] Ciceri S, Cattaneo E, Fossati C, Radice P, Selicorni A, Perotti D. First evidence of vertical paternal transmission of osteopatia striata with cranial sclerosis. American journal of medical genetics Part A. May 2013;161a(5):73-76. doi:10.1002/ajmg.a.35813
[19] Fujita A, Ochi N, Fujimaki H, et al. A novel WTX mutation in a female patient with osteopathia striata with cranial sclerosis and hepatoblastoma. American journal of medical genetics Part A. Apr 2014;164a(4):998-1002. doi:10.1002/ajmg.a.36369
[20] Quélin C, Loget P, D'Hervé D, et al. Osteopathia striata with cranial sclerosis: when a fetal malformation syndrome reveals maternal pathology. Prenatal diagnosis. Feb 2015;35(2):200-210. doi:10.1002/pd.4502
[21] Sperotto F, Bisogno G, Opocher E, et al. Osteopathia striata with cranial sclerosis and Wilms tumor: Coincidence or consequence? Clinical genetics. Dec 2017;92(6):674-675. doi:10.1111/cge.13082
[22] Quarello P, Perotti D, Carli D, et al. Wilms tumour occurring in a patient with osteopathia striata with cranial sclerosis: A still unsolved biological question. Pediatric blood & cancer. Sep 2021;68(9):e29132. doi:10.1002/pbc.29132
[23] Sinibaldi L, Micalizzi A, Serra A, et al. Osteopathia striata with cranial sclerosis: a new case supporting the link with bilateral Wilms tumor. European journal of human genetics : EJHG. Mar 2022;30(3):262-264. doi:10.1038/s41431-021-01035-0
[24] Ndoro S, Ndoro S, F S, Murray D, J C. Osteopathia Striata with Cranial Sclerosis Associated with Moyamoya Disease in a 3-Year-Old Girl. Surgical Case Reports. 2020:1-3. doi:10.31487/j.SCR.2020.07.06