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Phenotypic heterogeneity in two siblings with pathogenic PLOD3 variants

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Abstract
Background
Pathogenic variants in the PLOD3 gene cause a rare autosomal recessive inherited connective tissue disorder, clinically evident due to a deficiency in the enzyme lysyl hydroxylase 3. This study aims to describe the clinical features of two siblings with homozygous pathogenic variants in the PLOD3 gene and demonstrate their phenotypic heterogeneity.
Case Presentation
The first case, a 16-year-old boy, exhibited symptoms such as unilateral eyelid ptosis, flat face profile, long philtrum, low set ears, and short nose with anteverted nares at birth. He also displayed developmental delay and impaired hand function. The second case, a 6-year-old girl, showed intrauterine growth retardation and had complications like frequent skin blistering, cognitive impairment, sensorineural hearing loss, and developmental dysplasia of the hip. Both siblings had homozygous pathogenic nonsense variant PLOD3 NM_001084 (PLOD3): c.1354C>T; p.(R452X), previously reported to cause pathogenic disease.
Conclusion
This study highlights the consequences of a homozygous PLOD3 mutation in two patients with extensive connective tissue abnormalities. The phenotypic heterogeneity between the siblings suggests the possible influence of other gene interactions. Early diagnosis is crucial due to potential severe vascular and ocular complications.

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I. Introduction

Pathogenic variants of the PLOD3 gene lead to a rare autosomal recessive inherited connective tissue disorder (1,2). These clinical features result from a deficiency of the lysyl hydroxylase 3 (LH3) enzyme, which plays a crucial role in the hydroxylation of lysine residues and their subsequent glycosylation preceding chain association and the formation of a triple-helical structure, a significant posttranslational modification of collagen (5).

Cases involving pathogenic variants in the PLOD3 gene have presented with joint contractures, scoliosis, low bone mineral density, fractures, sensorineural deafness, myopia, ocular abnormalities, vascular aneurysm ruptures, skin and nail abnormalities, and dysmorphic features (1). This study explores the clinical features of two siblings with homozygous pathogenic variants in the PLOD3 gene, highlighting phenotypic heterogeneity between them.

Case Presentation

We encountered two affected siblings of Saudi descent, born to first-cousin parents, with three unaffected siblings. Table 1 presents a summary of phenotypic features for each sibling.

First sibling:

A 16-year-old boy presented with birth-related unilateral eyelid ptosis, a flat facial profile, a long philtrum, low-set ears, and a short nose with anteverted nares. Ophthalmologic surgery corrected his unilateral ptosis at nine months. He exhibited bilateral hand and foot camptodactyly, long and ulnar swept fingers, bilateral middle finger fixed flexion contractures, and reduced palmar creases. These physical features led to significant hand function impairment, managed with physical and occupational therapy and surgical finger-straightening procedures. His developmental delay was evident, with no head control at six months, inability to sit at 10 months, and delayed walking until two years. However, by 16 years, his cognitive development was normal, and he was performing well in school.

His weight and height measurements were below the fifth percentile, with head circumference HC at the 50th percentile. His craniofacial features included a triangular-shaped face, shallow orbits, down slanting

palpebral fissures, malar or midface hypoplasia, a flat facial profile, a short, upturned nose, low-set ears, and downturned corners of the mouth. His hands had bilateral camptodactyly, fixed flexion of multiple joints, distal tapering, and reduced palmar creases. Despite his soft skin, no blistering or bruising was present. Hearing and ophthalmology assessment results were within reference ranges.

Second sibling:

A 6-year-old girl was born at 39 weeks via cesarean section due to breech presentation after a pregnancy complicated by intrauterine growth retardation. Her birth weight was 1.5 kg (below the 5th percentile), length was 48 cm (25th percentile), and HC was 35 cm (50th percentile). Like her brother, she presented with bilateral hand and foot camptodactyly and impaired hand function managed with physical and occupational therapy. She experienced frequent skin blistering on her fingers and toes, healing without scarring, and easy bruising with mild trauma. Despite these symptoms, her prothrombin and partial thromboplastin times and platelet counts were within reference ranges. At six years, she exhibited cognitive impairment and immobility due to unrepaired developmental dysplasia of the hip and had not yet enrolled in school. Her hearing assessment revealed bilateral moderate to severe sensorineural hearing loss requiring hearing aids, but the ophthalmology assessment results were within reference ranges.

Her weight and height measurements were below the fifth percentile, with HC at the 50th percentile. Dysmorphic craniofacial features included a triangular-shaped face, bilateral ptosis, shallow orbits, down slanting palpebral fissures, malar or midface hypoplasia, a flat facial profile, a short, upturned nose, low-set ears, and downturned corners of the mouth with a long philtrum (Figure 1). Like her brother, she had bilateral camptodactyly, fixed flexion of multiple joints of the hands, distal tapering, and reduced palmar creases (Figure 2, Figure 3). Additional physical features included elbow contracture and mild thoracic scoliosis. Her skin was soft without any presence of blistering or bruising.

A typical female pattern was observed in her chromosomes (46, XX). Brain magnetic resonance imaging and abdominal ultrasound results were unremarkable. However, a skeletal survey revealed scoliosis in the dorsolumbar spine, dislocation of the left hip joint with dysplasia of the left acetabulum, and mild subluxation of the right hip joint with dysplasia of the right acetabulum. Bilateral coxa valga and flexion deformities in the proximal interphalangeal joints of both hands' second to fifth fingers and mild flexion in both elbow joints were also present.

Whole-exome sequencing identified a homozygous pathogenic (2) nonsense variant PLOD3 NM_001084 (PLOD3): c.1354C>T; p.(R452X) in both siblings, with no other variants in genes related to connective tissue disorders identified. This variant was previously reported to be pathogenic.

Table 1. Phenotypic features

Clinical features	Case 1	Case 2
Age	16	6
Sex	Male	Female
Weight at birth	2 kg	1.5 kg
Development delay	Yes	Yes
Cognitive impairment	No	Yes
Clinical dysmorphism (eyelid ptosis; downslanting palpebral fissure; depressed nasal bridge; midfacial hypoplasia; short, upturned nose)	Yes	Yes
Short stature	Yes	Yes
Skeletal findings	Yes	Yes
Finger contracture	Yes	Yes
Scoliosis	No	Yes
Hip dislocation	No	Yes
Visual Myopia, early cataract, lens dislocation	No	No
Sensorineural Hearing loss	No	Yes
Ectodermal	No	Skin blistering
Vascular	No	Easy bruising
Aneurism or arterial dissection	N/A	N/A

Abbreviation: N/A, not applicable.

II. Discussion

Pathogenic variants in the PLOD3 gene cause a rare autosomal recessive connective tissue disorder that primarily affects the eyes, ears, skin, and skeletal and vascular systems and creates distinctive craniofacial dysmorphology. Ocular features include early cataract formation, myopia, and flat retinae (1-4).

The first reported case of a family with PLOD3 mutations involved a proband compound heterozygous for c.668A>G, p. Asn223Ser; c.2071delT, p. Cys691AlafsX9. These mutations, located in different parts of LH3, are responsible for lysyl hydroxylation and hydroxylysine glycosylation activities. The patients in this case report exhibited an extremely complex phenotype, including deafness, myopia, arterial ruptures, osteopenia, joint

contractures, bone fractures, and cataracts, along with clinically observed skin blistering, indicating a deficiency in both lysyl hydroxylation and glycosylation of hydroxylysyl residues (1).

This case report discusses family members exhibiting the same clinical features previously described but without ocular or retinal involvement. The affected sister displayed a more severe clinical phenotype than her brother, with a left hip dislocation affecting her mobility and marked speech impairment due to hearing loss alongside evidence of cognitive impairment. This phenotypic heterogeneity might be related to other sex-related genes, an observation that warrants further research.

III. Conclusion

In summary, our study elucidates the impacts of a homozygous PLOD3 mutation in patients with extensive connective tissue abnormalities. Early diagnosis is vital in affected individuals to mitigate potential severe vascular and ocular complications. Clinician and patient awareness and appropriate surveillance can help manage these potential complications.

References

[1]. Salo AM, Cox H, Farndon P, Moss C, Grindulis H, Risteli M, et al. A connective tissue disorder caused by mutations of the lysyl hydroxylase 3 gene. Am J Hum Genet. 2008;83:495-503. doi:10.1016/j.ajhg.2008.09.004

[2]. Maddirevula S, Alzahrani F, Al-Owain M, Al Muhaizea MA, Kayyali HR, Al Hashem A, et al. Autozygome and high throughput confirmation of disease genes candidacy. Genet Med. 2019;21:736-742. doi:10.1038/s41436-018-0138-x

[3]. Ewans LJ, Colley A, Gaston-Massuet C, Gualtieri A, Cowley MJ, McCabe MJ, et al. Pathogenic variants in PLOD3 result in a Stickler syndrome-like connective tissue disorder with vascular complications. J Med Genet. 2019;56:629-638. doi:10.1136/jmedgenet-2019-106019

[4]. Vahidnezhad H, Youssefian L, Saeidian AH, Touati A, Pajouhanfar S, Baghdadi T, et al. Mutations in PLOD3, encoding lysyl hydroxylase 3, cause a complex connective tissue disorder including recessive dystrophic epidermolysis bullosa-like blistering phenotype with abnormal anchoring fibrils and type VII collagen deficiency. Matrix Biol. 2019;81:91-106. doi:10.1016/j.matbio.2018.11.006

[5]. Salo AM, Sipila L, Sormunen R, Ruotsalainen H, Vainio S, Myllyla R. The lysyl hydroxylase isoforms are widely expressed during mouse embryogenesis, but obtain tissue- and cell-specific patterns in the adult. Matrix Biol. 2006;25:475-483. doi:10.1016/j.matbio.2006.08.260

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Figure 1. *[*second sibling facial features, triangular-shaped face, bilateral ptosis, shallow orbits, down slanting palpebral fissures, malar or midface hypoplasia, flat facial profile, a short, upturned nose, low-set ears and downturned corners of the mouth with a long philtrum*]*

Figure 2. [second sibling hands showing bilateral fingers contracture.]

Figure 3. [second sibling, hands showing bilateral second to fifth fingers fixed flexion contractures and reduced palmar creases.]

Acknowledgements: none.

List of Abbreviations

Abbreviation	Definition
HC	Head Circumference
LH3	Lysyl Hydroxylase 3
PLOD3	Procollagen-Lysine,2-Oxoglutarate 5-Dioxygenase 3
XX	Female Chromosome Pattern

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Ethical Approval: Ethical approval is not required at our institution to publish an anonymous case report.

Figure 1. *[*second sibling facial features, triangular-shaped face, bilateral ptosis, shallow orbits, down slanting palpebral fissures, malar or midface hypoplasia, flat facial profile, a short, upturned nose, low-set ears and downturned corners of the mouth with a long philtrum*]*

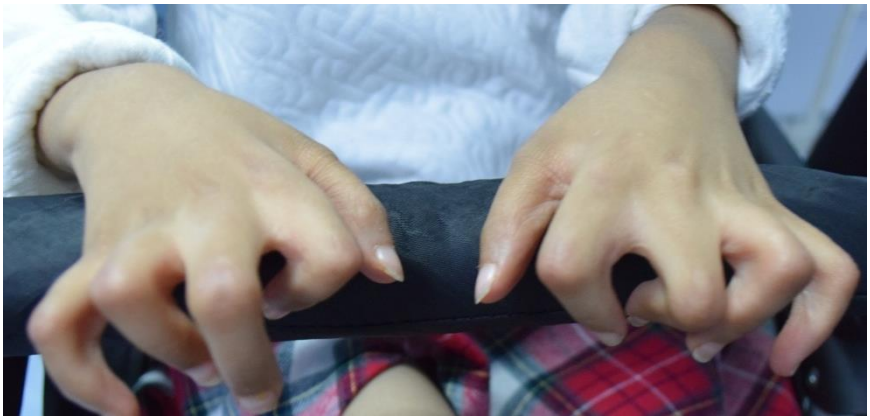

Figure 2. [second sibling hands showing bilateral fingers contracture.]

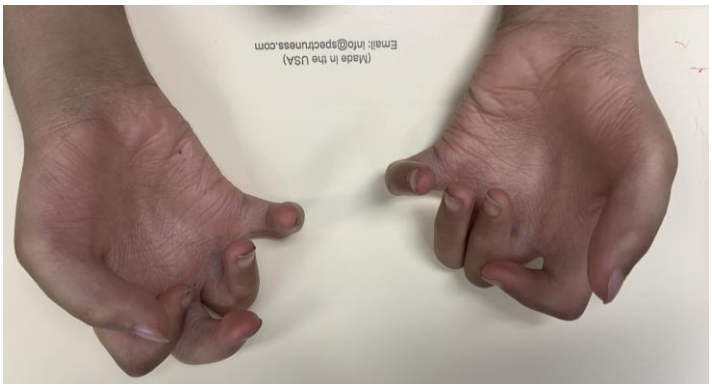

Figure 3. [second sibling, hands showing bilateral second to fifth fingers fixed flexion contractures and reduced palmar creases.]