Balkan Med J 2026;43:163-5



# Novel SHOX Variant in Léri-Weill Dyschondrosteosis with Madelung Deformity

Jing Luo[1], Xiaoli Wang[2]

[1]Clinic of Endocrinology and Metabolism, Tieling Central Hospital, Tieling, China

[2]Department of Endocrinology and Metabolism, Institute of Endocrinology, NHC Key Laboratory of Diagnosis and Treatment of Thyroid Diseases, The First Hospital of China Medical University, Shenyang, China

A 38-year-old woman with a short stature presented with bilateral wrist pain that she had been suffering from since childhood. She reported that her height had been consistently below the third percentile for age since primary school. Moreover, her wrist pain exacerbates with activities such as lifting heavy objects or prolonged wrist flexion, which had gradually affected her daily housework over the past 5 years. She denied a history of trauma, endocrine disorders, or chronic illnesses. Her physical examination results revealed the following: a height of 150 cm (sitting height/height ratio: 0.567), an arm span/height ratio of 0.9, a weight of 51 kg, and a body mass index of 22.67 kg/m$^2$. The bilateral forearms showed obvious radial deviation with a limited wrist extension (active extension range: 0°–30°, normal range: 0°–70°). The palpation of the distal ulna revealed mild tenderness without abnormal masses.

The forearm morphology and radiographs demonstrated a typical Madelung deformity characterized by bilateral shortened and curved radii, distal radial epiphyseal dysplasia with a triangular appearance, distal ulnar dislocation, compact carpal bones with reduced interosseous space, and decreased carpal angle (Figure 1a). The patient's parents had normal heights (father: 175 cm; mother: 162 cm) without similar forearm manifestations or wrist pain. No other family members reported a short stature or any sort of skeletal deformities.

The characteristic triad of mesomelia (i.e., shortened forearms and lower legs relative to the trunk), short stature, and Madelung deformity strongly suggested a Léri-Weill dyschondrosteosis (LWD, OMIM #127300) diagnosis.[1,2] To confirm this diagnosis, genetic testing was performed on the patient and her parents. Prior to the procedure, a written informed consent was obtained from all participants according to the Declaration of Helsinki. Subsequently, 5 mL each of peripheral venous blood samples was collected. Genomic DNA was extracted using a blood DNA purification kit (Tianjing Biochemical Technology Co., Ltd., Beijing, China) following the manufacturer's standard protocol. Whole-exome sequencing was conducted on the Illumina NovaSeq 6000 platform. The variants were annotated and interpreted using the VeritaTrekker® Variant Site Detection System and the Enliven® Variant Site Annotation & Interpretation System (Berry Genetics) with reference to the latest versions of public databases, such as dbSNP, 1000 Genomes Project, gnomAD, CADD, ClinVar, and HGMD.

This analysis identified a heterozygous frameshift variant in the *SHOX* gene (NM_000451.4): c.237_243del (p.Lys79Asnfs*2). The patient's parents do not carry this variant, suggesting that this mutation is a *de novo* variant, as depicted in Figure 1b. Notably, this variant has not been previously reported in any public genetic databases, including ClinVar, HGMD, and gnomAD, or peer-reviewed literature, thereby confirming it as a novel variant. The 2015 ACMG/AMP Standards and Guidelines for Variant Interpretation[3] classifies this variant as pathogenic (PVS1 + PS2 + PP3). It involves a seven-base pair deletion that induces a frameshift starting at codon 79 and results in a premature termination of the protein translation at codon 80 (Figure 1c). The truncated SHOX protein lacks a functionally critical homeodomain and a C-terminal transcription activation region, leading to a SHOX haploinsufficiency. Compared with the previously reported *SHOX* gene variants associated with LWD, the patient's phenotype is consistent with the typical manifestations of the heterozygous SHOX variants.[4]

**Corresponding author:** Xiaoli Wang, Department of Endocrinology and Metabolism, Institute of Endocrinology, NHC Key Laboratory of Diagnosis and Treatment of Thyroid Diseases, The First Hospital of China Medical University, Shenyang, China

**e-mail:** wlittlepear@163.com

**Received:** September 25, 2025 **Accepted:** November 06, 2025 **Available Online Date:** March 02, 2026 • **DOI:** 10.4274/balkanmedj.galenos.2025.2025-9-241

Available at www.balkanmedicaljournal.org

**ORCID iDs of the authors:** X.W. 0000-0002-9388-0734; J.L. 0009-0005-5443-5696.

**Cite this article as:** Wang X, Luo J. Novel SHOX Variant in Léri-Weill Dyschondrosteosis with Madelung Deformity. Balkan Med J.; 2026; 43(3): 163-5

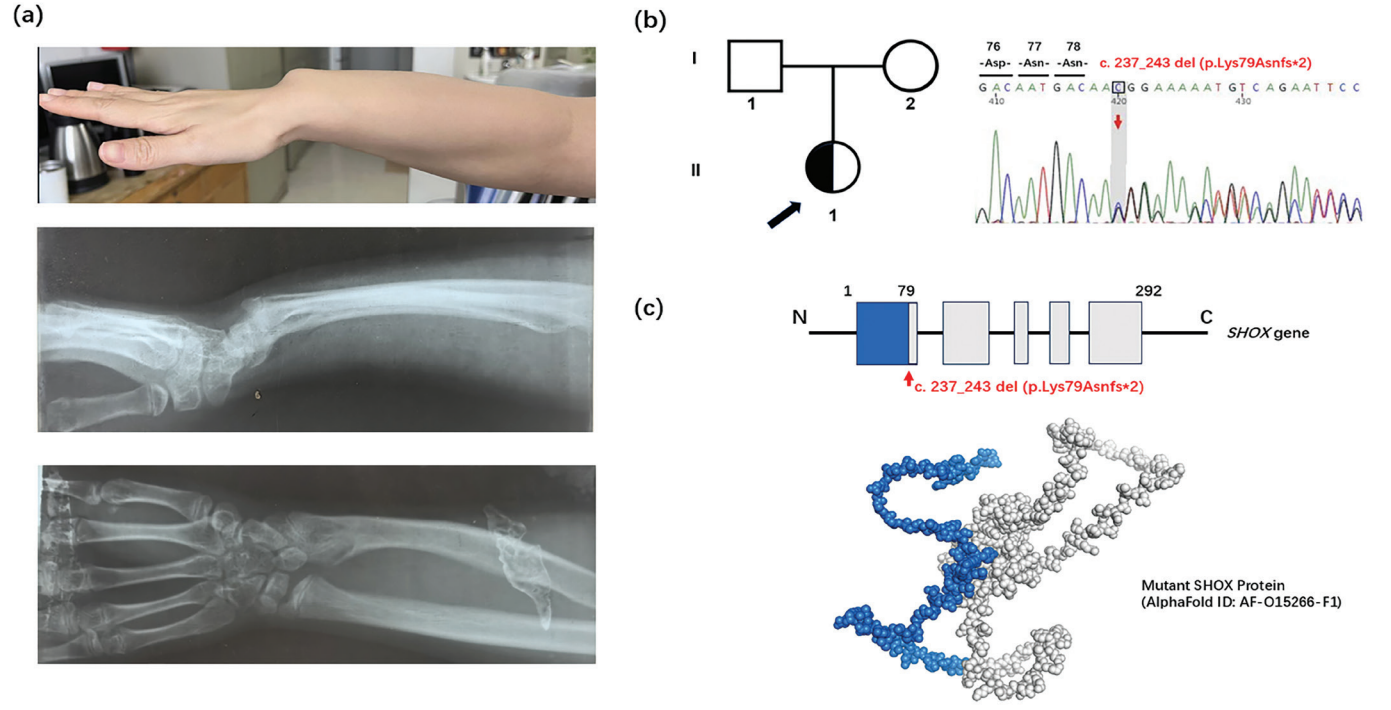


**FIG. 1.** Clinical, radiological and genetic findings. (a) Right forearm with "fork-like" radial deviation; wrist direct radiography showing Madelung deformity (shortened, curved radius, ulnar dislocation). (b) Pedigree chart of the patient and Sanger sequencing electropherogram of the c.237_243del variant. (c) Upper panel: Schematic of the *SHOX* gene structure highlighting the c.237_243del variant location; lower panel: AlphaFold3-predicted 3D structure of the mutant SHOX protein (AlphaFold ID: AF-O15266-F1), with blue indicating the retained N-terminal segment (residues 1-78) and gray denoting the truncated C-terminal region (residues 79-292) resulting from the frameshift variant.

The *SHOX* gene encodes a homeodomain-containing transcription factor playing a critical role in regulating chondrocyte proliferation and differentiation in the growth plate and the development of the forearms, lower legs, and axial skeleton.[2] Its haploinsufficiency is associated with a spectrum of height-related disorders that range from idiopathic short stature (i.e., mild phenotype, no skeletal deformities) to LWD (i.e., moderate phenotype with mesomelia and Madelung deformity) and a more severe Langer mesomelic dysplasia (i.e., homozygous or compound heterozygous variants, severe mesomelia, and short stature).[4,5] The latest HGMD Professional Database shows that 406 variants related to SHOX-related disorders have been reported to date. Among these, 25 are frameshift variants; 237 are gross fragment deletion variants; six are inframe variants; 15 are splice-site variants; 92 are missense variants; eight are non-coding region variants; and 23 are non-sense variants. Among the abovementioned variants, 183 are associated with LWD. Clinically, a Rappold score > 5 strongly predicts SHOX-related disorders.[5] For pediatric patients with LWD, an early diagnosis (prepubertal period) combined with recombinant human growth hormone therapy (0.3–0.45 mg/kg/week, administered subcutaneously) can significantly improve the final adult height by 5–10 cm, while the regular monitoring of the thyroid function and the glucose metabolism is required during treatment.[4] For adult patients with severe wrist deformities and persistent pain affecting function, surgical interventions such as distal radial osteotomy, ulnar shortening osteotomy, and wrist arthrodesis may be considered to correct the alignment and relieve the symptoms.[4] In the present case, the patient declined surgical treatment considering her mild symptoms and was advised to avoid heavy manual labor. She was also advised to use wrist braces during activities and undergo a regular radiological follow-up every 2 years.

**Acknowledgements:** The authors extend their sincere gratitude to the patient and her family members for their participation in this study.

**Informed Consent:** Prior to the procedure, written informed consent was obtained from all participants in accordance with the Declaration of Helsinki

**Authorship Contributions:** Concept- J.L.; Design- X.W.; Supervision- J.L.; Data Collection or Processing- X.W.; Analysis and/or Interpretation- X.W., J.L.; Literature Review- X.W.; Writing- X.W.; Critical Review- X.W., J.L.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Funding:** The authors declared that no funding was received for this study.

## REFERENCES

1. Marchini A, Ogata T, Rappold GA. A track record on SHOX: from basic research to complex models and therapy. *Endocr Rev.* 2016;37:417-448. [CrossRef]
2. Binder G, Rappold GA. SHOX Deficiency Disorders. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 2005 Dec 12 [updated 2024 May 23]. [CrossRef]

3. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405-424. [CrossRef]
4. Binder G. Short stature due to SHOX deficiency: genotype, phenotype, and therapy. *Horm Res Paediatr.* 2011;75:81-89. [CrossRef]
5. Rappold G, Blum WF, Shavrikova EP, et al. Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. *J Med Genet.* 2007;44:306-313. [CrossRef]