A rare variant of osteopoikilosis: a case report

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ABSTRACT

Background: Osteopoikilosis (OPK) is a rare, benign bone disorder, inherited in an autosomal dominant pattern. Also referred to as disseminated condensing osteopathy, spotted bone disease, or osteopecilia, consists of hyperostotic areas in periarticular osseous regions. Clinically, OPK is often asymptomatic or associated with mild, nonspecific symptoms, such as diffuse bone pain. Diagnosis is usually incidental and readily made through plain radiography, which reveals characteristic multiple small, round or ovoid sclerotic lesions. The condition has been linked to heterogeneous mutations in the *LEMD3* gene.

Case presentation: A 17-year-old male patient presented with an index finger fracture following a motor vehicle collision. He reported no history of bone pain, polyarthralgia, or involvement of either large or small joints. There were no complaints of prior skin lesions, nor were any observed upon hospital admission. Radiologic examination of the wrist revealed numerous well-defined, symmetric sclerotic lesions, localized in the area of the fracture. To further characterize these findings, a whole-body computed tomography scan was performed, confirming the presence of similar lesions in multiple skeletal sites. Genetic analysis subsequently identified a novel mutation in the LEMD3 gene. Based on these clinical, radiologic, and genetic findings, a diagnosis of OPK was established.

Conclusion: A previously unreported splicing mutation in the *LEMD3* gene was identified in a young, asymptomatic male patient with OPK. The diagnosis was made incidentally during routine imaging following a car accident, highlighting the typically silent clinical course of OPK and the importance of imaging in uncovering such skeletal disorders. This novel mutation expands the known mutational spectrum of *LEMD3*-related bone disorders.

Keywords: Osteopoikilosis, osteopathy, osteopecilia, *LEMD3* variant, diagnosis.

Type of Article: CASE REPORT **Specialty:** Traumatology

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Background

First described in 1915 by Albers-Schonberg, *Osteopoikilosis* (OPK) is a rare autosomal dominant osteosclerotic dysplasia marked by distinct radiological features [1]. It manifests in speckled, striped, or mixed patterns [2] and is caused by heterozygous loss-of-function variants in the LEMD3 (MAN1) gene, which regulates bone morphogenesis via TGF-β and BMP signaling pathways [3]. Disrupted LEMD3 function leads to abnormal bone remodeling and characteristic sclerotic lesions [3–6], often due to excessive bone matrix deposition [3–6], and may cause bone dysplasia [4]. Though usually asymptomatic, OPK has been occasionally linked to spinal stenosis, dacryocystitis, and rare malignant transformation [5].

When associated with skin lesions, OPK is termed *Buschke-Ollendorff* syndrome [6], which may also present with *dermatofibrosis lenticularis disseminata* and *palmar-plantar keratoderma* due to fibroblast proliferation [2,6]. The disease affects men and women equally [1–6].

Here, we report the association of a previously undescribed LEMD3 variant with OPK. Our findings highlight the significance of genetic alterations in OPK pathogenesis and emphasize the value of molecular profiling for accurate diagnosis, differential diagnosis, and personalized follow-up strategies.

Case Report

A 17-year-old male patient was involved in a motor vehicle accident, resulting in a proximal phalanx fracture and degloving injury of the index finger. He was admitted to the emergency department and promptly referred for diagnostic imaging. Plain radiographs (Rx) of the injured hand and wrist were promptly obtained, revealing an unusual

spotted appearance of the bone in the wrist images (Figure 1).

Surgical repair of the fractured finger was performed. Once the fracture had been reduced and stabilized, a detailed medical history was obtained. The proband was 189 cm tall, weighed 57 kg, and exhibited no facial dysmorphisms. Prenatal, gestational, and family histories were unremarkable. The patient reported no symptoms at the time of evaluation. Dermatological examination revealed no skin lesions. No physical disabilities or suggestive findings in musculoskeletal disorders were identified. The patient denied any history of back pain, limb pain, joint stiffness, or paresthesia.

Based on the spotted appearance of the bone observed on wrist Rx, a whole-body computed tomography (CT) scan was performed, revealing a characteristic diffuse spotted bone pattern, with prominent hyperostotic areas particularly evident in the pelvis (Figure 2).

These findings raised clinical suspicion for OPK. Given the radiological resemblance to other pathologies, differential diagnosis is crucial and should include bone metastases, primary bone tumors, mastocytosis, tuberous sclerosis, synovial chondromatosis, melorheostosis, and osteopathia striata [1]. Because of this broad differential and the potential overlap with malignant or systemic conditions, genetic testing was deemed necessary to support a definitive diagnosis and avoid unnecessary invasive procedures. In particular, molecular analysis was pursued to confirm the suspected diagnosis of OPK and to exclude other skeletal displasia or neoplastic processes with similar radiological features.

Consequently, genetic testing was performed to confirm the diagnosis, specifically targeting heterozygous mutations in the *LEMD3* gene located on chromosome 12q14 [7]. As the patient was a minor, written informed consent for genetic analysis was obtained from his mother.

Exome panel (ClinEx Pro Kit-4Bases) was performed on genomic DNA patient extracted from circulating leukocytes [8]. Surprisingly, a novel heterozygous splice-site variant, c.2493+1G>A, was identified in exon 11 of the *LEMD3* gene (NM_014319.5). This variant affects the canonical donor splice site, a region essential for proper mRNA processing [6,9]. The splicing alteration was confirmed by Sanger sequencing and has not been previously reported in the literature or in major population databases, including dbSNP, the 1000 Genomes Project, Geno2MP, and gnomAD. Based on the *American College of Medical Genetics and Genomics* (ACMG) criteria and a high *Combined Annotation Dependent Depletion* score (CADD 34.00), the variant was classified as likely pathogenic (Class 4) (Figure 3).

Diagnosis of OPK was finally established. A clinical and imaging follow up was set at 1 and 4 months from the car accident, confirming the resolution of the wrist and the diffuse spotted bone pattern and hyperostotic areas, particularly in the pelvis (data not shown).

Discussion

Sclerotic foci in the humeral and femoral heads, as well as in the hands and wrists, are common radiological findings

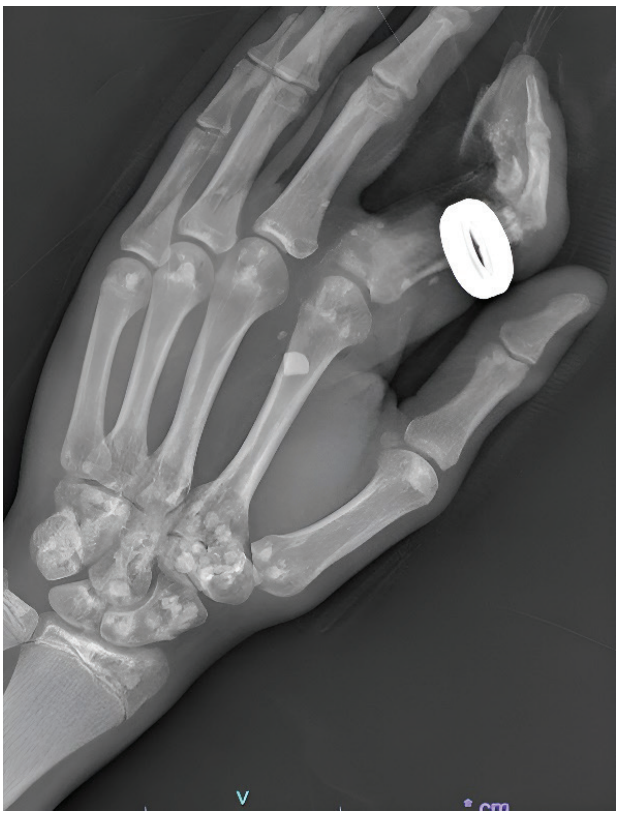

Figure 1. *Rx of the patient wrist, showing hyperostotic areas in different parts of the skeleton.*

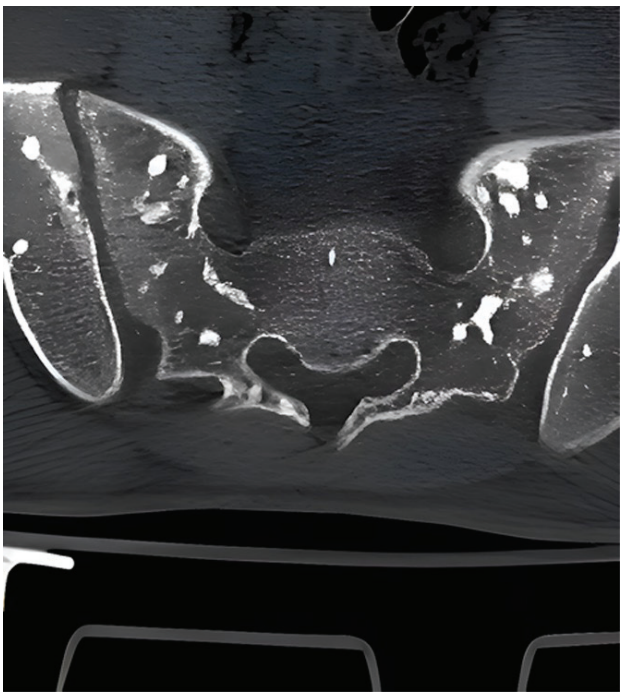

Figure 2. *The CT of the pelvis showing hyperostotic areas.*

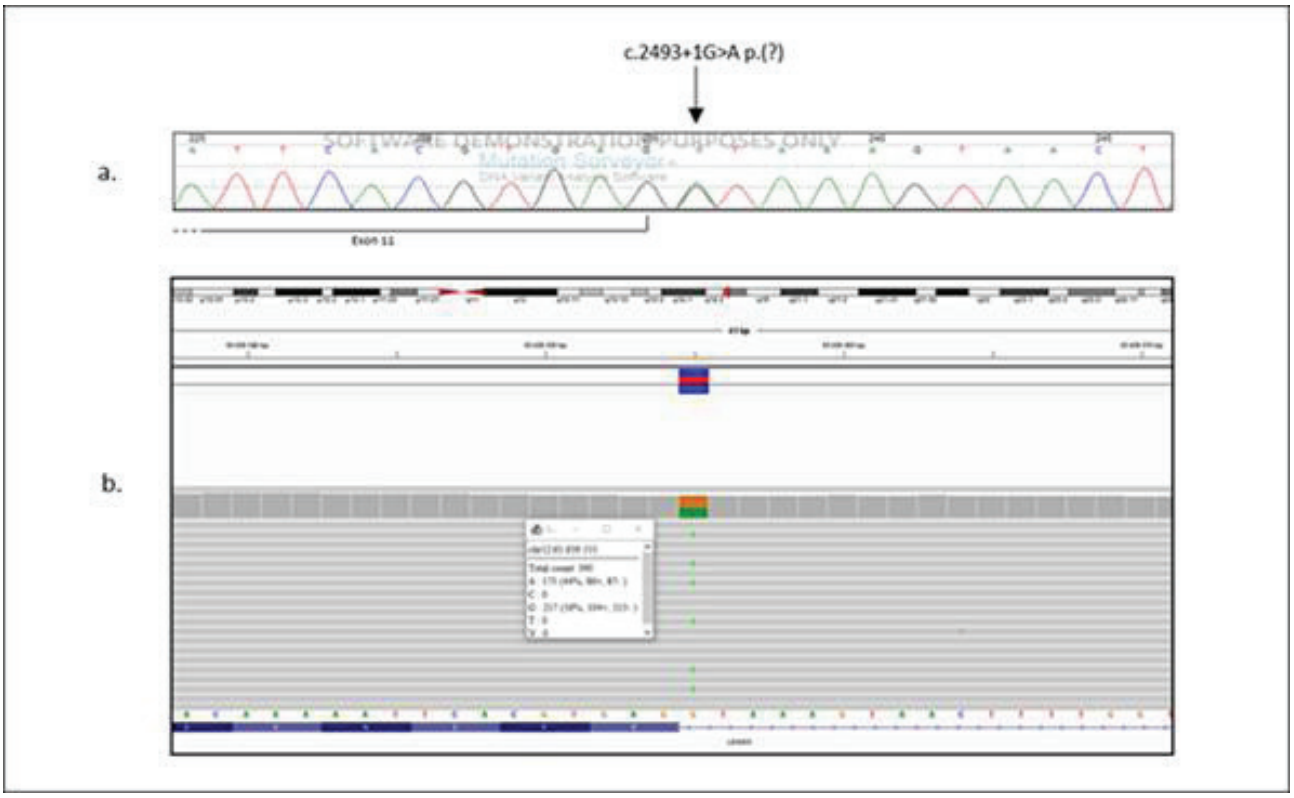

Figure 3. *Direct sequencing identified the novel LEMD3 c.2493+1G>A variant. (a) Sanger sequencing electropherogram, highlighting the novel c.2493+1G>A p.(?) mutation. (b) Splice donor mutation displayed in the genome browser Integrative Genomics Viewer (IGV).*

suggestive of OPK. This condition is considered a benign sclerosing bone dysplasia, typically characterized by symmetrical radio-dense lesions predominantly located in the epiphyses and metaphysis of long bones [1–6]. Despite its benign nature, OPK presents with highly variable clinical scenarios, ranging from completely asymptomatic individuals to patients with systemic manifestations or associated syndromic features [9].

In fact, OPK has been reported in association with a wide array of clinical conditions, including skeletal abnormalities (e.g., dwarfism), cardiovascular malformations (e.g., coarctation of the aorta), urogenital anomalies (e.g., double urethra), neurological involvement (e.g., spinal canal stenosis), and cutaneous or autoimmune disorders, such as tuberous sclerosis, scleroderma, discoid lupus erythematosus, and psoriatic arthritis. It has also been linked to endocrine and metabolic disorders (e.g., precocious puberty and diabetes mellitus), as well as musculoskeletal conditions like fibromyalgia, and even rare associations such as familial Mediterranean fever and reactive arthritis [9].

Histopathological examination of OPK lesions typically reveals focal condensation of compact lamellar bone within the spongiosa, particularly in the epiphyseal or metaphyseal regions of long bones [1–6]. Given the radiological resemblance to other pathologies, differential diagnosis is crucial and should include bone metastases, primary bone tumors, mastocytosis, tuberous sclerosis, synovial chondromatosis, melorheostosis, and osteopathia striata [1].

OPK is associated with germline mutations in LEMD3, which encodes the inner nuclear membrane protein MAN1, a modulator of TGF-β/BMP signaling [3–6,10]. Somatic mutations in *MAP2K1* and other related genes, such as *K-RAS*, have been identified in melorheostosis lesions [11]. Germline *LEMD3* mutations are rare in sporadic cases of isolated melorheostosis [12]. These mutations typically result in loss-of-function of MAN1, contributing to the OPK phenotype [12]. A specific C>T substitution at position 2032 (cDNA) in exon 8 of LEMD3 introduces a premature stop codon at amino acid 678, and co-segregates with OPK [13]. An Italian case series recently reported five additional OPK cases linked to LEMD3 germline mutations, supporting existing literature [14]. Moreover, a splice site mutation (IVS12 + 1delG) was identified in a 13-year-old boy with Buschke-Ollendorff syndrome, severe skeletal deformities, polyostotic melorheostosis, and OPK [15].

This report describes a young asymptomatic male who came to clinical attention following a car accident. Radiological evaluation revealed numerous, symmetrical, well-defined sclerotic lesions in the wrist, coinciding with a proximal phalanx fracture. To further characterize these bone abnormalities, a whole-body CT scan was performed, confirming lesions consistent with OPK. Subsequent high-throughput sequencing detected the novel LEMD3

splicing mutation. A novel heterozygous splicing mutation (c.2493+1G>A) in the LEMD3 gene was identified, thereby providing molecular confirmation of the OPK diagnosis. This previously unreported variant expands the mutational spectrum of *LEMD3* and reinforces the clinical utility of genetic testing in differentiating OPK from other sclerotic bone disorders. The identification of this mutation not only supports a benign diagnosis, sparing the patient from unnecessary investigations or interventions, but also contributes to the broader understanding of the genetic basis of OPK.

Conclusion

OPK is a rare, benign, and typically asymptomatic bone dysplasia that is most often diagnosed incidentally during radiological examinations performed for unrelated reasons. Despite its benign nature, the radiographic appearance of OPK can mimic that of more serious conditions, such as osteoblastic metastases, which may lead to diagnostic uncertainty and unnecessary clinical investigations.

In the present case, molecular analysis revealed a novel splice-site mutation in the LEMD3 gene, suggesting a potential role in the pathogenesis of OPK. This finding underscores the importance of integrating genetic and molecular profiling into the diagnostic workup, particularly in cases with atypical or ambiguous clinical presentations.

Such an approach not only facilitates a more accurate diagnosis but also aids in differentiating OPK from malignant or systemic bone disorders, which may present with similar radiologic features. It further supports the development of personalized follow-up strategies based on the underlying genetic alterations.

In this case, the diagnosis of OPK was made incidentally during routine imaging following a car accident, reflecting the typically asymptomatic and indolent nature of the disease. The identification of this previously unreported mutation expands the mutational spectrum of LEMD3-associated skeletal dysplasia, contributing valuable insights to the understanding of its genetic basis.

Early and precise diagnosis not only reassures patients but also helps avoid unnecessary diagnostic procedures, reduce healthcare costs, and improve overall clinical management.

The main limitation of the current study is that it reports on a single case. Therefore, further research involving larger cohorts is warranted to better explore the genetic landscape of OPK and to validate the pathogenic role of the novel splice variant we have described in its etiology.

What is new?

OPK is a rare and benign bone condition, often found incidentally. Its similarity to malignant lesions can cause diagnostic confusion. A possible link to splice variants suggests that genetic and molecular analyses may aid diagnosis, especially in atypical cases. Accurate identification helps avoid unnecessary tests and improves patient care. In the present case, molecular analysis revealed the involvement of splice variants, suggesting a possible role in the pathogenesis of OPK.

Conflict of interests

The authors declare that they have no conflict of interest regarding the publication of this case report.

Funding

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Consent for publication

Written consent was obtained from the patient.

Ethical approval

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

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References

1. Di Primio G. Benign spotted bones: a diagnostic dilemma. CMAJ. 2011;183(4):456–9. https://doi.org/10.1503/cmaj.091740
2. Ruaro B, Sulli A, Alessandri E, Ravera F, Cutolo M. Coexistence of osteopoikilosis with seronegative spondyloarthritis and Raynaud's phenomenon: first case report with evaluation of the nailfold capillary bed and literature review. Reumatismo. 2012;64(5):335–9. https://doi.org/10.4081/reumatismo.2012.335
3. Baasanjav S, Jamsheer A, Kolanczyk M, Horn D, Latos T, Hoffmann K, et al. Osteopoikilosis and multiple exostoses caused by novel mutations in LEMD3 and EXT1 genes respectively-coincidence within one family. BMC Med Genet. 2010;11(1):110. https://doi.org/10.1186/1471-2350-11-110
4. Ellanti P, Clarke B, Gray J. Osteopoikilosis. Ir J Med Sci. 2010;179(4):615–6. https://doi.org/10.1007/s11845-010-0595-y
5. Demir SE, Özaras N, Poyraz E, Toprak H, Güler M. Coexistence of osteopoikilosis with seronegative spondyloarthritis and spinal stenosis. J Phys Ther Sci. 2015;27(5):1625–7. https://doi.org/10.1589/jpts.27.1625
6. Hellemans J, Preobrazhenska O, Willaert A, Debeer P, Verdonk PC, Costa T, et al. Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff

syndrome and melorheostosis. Nat Genet. 2004;36(11):1213–8. https://doi.org/10.1038/ng1453
7. Buysse K, Reardon W, Mehta L, Costa T, Fagerstrom C, Kingsbury DJ, et al. The 12q14 microdeletion syndrome: additional patients and further evidence that HMGA2 is an important genetic determinant for human height. Eur J Med Genet. 2009;52(2–3):101–7. https://doi.org/10.1016/j.ejmg.2009.03.001
8. Crossley BM, Bai J, Glaser A, Maes R, Porter E, Killian ML, et al. Guidelines for Sanger sequencing and molecular assay monitoring. J Vet Diagn Invest. 2020;32(6):767–75. https://doi.org/10.1177/1040638720905833
9. Woyciechowsky TG, Monticielo MR, Keiserman B, Monticielo OA. Osteopoikilosis: what does the rheumatologist must know about it? Clin Rheumatol. 2012;31(4):745–8. https://doi.org/10.1007/s10067-011-1916-x
10. Borman P, Ozoran K, Aydog S, Coskun S. Osteopoikilosis: report of a clinical case and review of the literature. Joint Bone Spine. 2002;69(2):230–3. https://doi.org/10.1016/S1297-319X(02)00375-5
11. Kang H, Jha S, Deng Z, Fratzl-Zelman N, Cabral WA, Ivovic A, et al. Somatic activating mutations in MAP2K1 cause melorheostosis. Nat Commun. 2018;9(1):1390. https://doi.org/10.1038/s41467-018-03720-z
12. Hellemans J, Debeer P, Wright M, Janecke A, Kjaer KW, Verdonk PC, et al. Germline LEMD3 mutations are rare in sporadic patients with isolated melorheostosis. Hum Mutat. 2006;27(3):290. https://doi.org/10.1002/humu.9403
13. Couto AR, Bruges-Armas J, Peach CA, Chapman K, Brown MA, Wordsworth BP, et al. A novel LEMD3 mutation common to patients with osteopoikilosis with and without melorheostosis. Calcif Tissue Int. 2007;81(2):81–4. https://doi.org/10.1007/s00223-007-9043-z
14. Gnoli M, Staals EL, Campanacci L, Bedeschi MF, Faletra F, Gallone S, et al. Melorheostosis and osteopoikilosis clinical and molecular description of an Italian case series. Calcif Tissue Int. 2019;105(2):215–21. https://doi.org/10.1007/s00223-019-00565-6
15. Gutierrez D, Cooper KD, Mitchell AL, Cohn HI. Novel somatic mutation in LEMD3 splice site results in Buschke-Ollendorff syndrome with polyostotic melorheostosis and osteopoikilosis. Pediatr Dermatol. 2015;32(5):e219–20. https://doi.org/10.1111/pde.12634

Summary of the case

1	Patient (gender, age)	17, male
2	Final diagnosis	Osteopoikilosis in a patient with orthopedic trauma.
3	Symptoms	Proximal phalanx fracture with degloving of the index finger
4	Medications	Surgery
5	Clinical procedure	Surgery
6	Specialty	Traumatology and orthopedics