Spectrum of *LRP5*-Related Bone Disease Within a Single Family: Osteoporosis-Pseudoglioma Syndrome in Two Siblings and Adult-Onset Osteoporosis in their Mother

Espectro da Doença Óssea Relacionada com *LRP5* numa Família: Síndrome Osteoporose-Pseudoglioma em Dois Irmãos e Osteoporose de Início Adulto na Mãe

Christine Canizes Paiva*[1], Tiago Jorge Costa*[1], Odete Duarte[1], Joana Cascais Costa[1], Hélder Esperto[1,2]

Abstract:

Mutations in the low-density lipoprotein receptor-related protein 5 (*LRP5*) gene are associated with a wide spectrum of bone phenotypes, ranging from severe osteoporosis-pseudoglioma syndrome (OPPG) to isolated early-onset osteoporosis. We describe a family with compound heterozygous *LRP5* mutations causing OPPG in two siblings, characterized by congenital or progressive blindness, severe osteoporosis and recurrent fractures, and a heterozygous *LRP5* mutation in their mother, presenting as adult-onset primary osteoporosis without ocular involvement. Bone mineral density was markedly reduced in all cases. Bisphosphonate therapy and calcium-vitamin D supplementation were initiated, with stabilization or modest improvement in bone density. This family illustrates the broad phenotypic variability of *LRP5*-related bone disease and highlights the importance of genetic evaluation in familial or unexplained osteoporosis. Recognition of *LRP5* mutations enables accurate diagnosis, appropriate treatment and targeted family screening.

Keywords: Low Density Lipoprotein Receptor-Related Protein-5; Osteoporosis

Resumo:

As mutações no gene da proteína 5 relacionada ao recetor de lipoproteína de baixa densidade (*LRP5*) estão associadas a um amplo espectro de fenótipos ósseos, desde a síndrome osteoporose-pseudoglioma (OPPG) grave até à osteoporose isolada de início precoce. Descreve-se uma família com mutações heterozigóticas compostas no gene *LRP5* responsáveis por OPPG em dois irmãos, caracterizada por cegueira congénita ou progressiva, osteoporose grave e fraturas recorrentes, e uma mutação heterozigótica no gene *LRP5* na mãe, manifestando-se como osteoporose primária de início adulto sem envolvimento ocular. A densidade mineral óssea encontrava-se significativamente reduzida em todos os casos. Iniciou-se terapêutica com bifosfonatos e suplementação de cálcio e vitamina D, com estabilização ou melhoria modesta da densidade óssea. Este caso familiar ilustra a variabilidade fenotípica das doenças ósseas relacionadas com o gene *LRP5* e reforça a importância da avaliação genética na osteoporose familiar.

Palavras-chave: Osteoporose; Proteína-5 Relacionada a Receptor de Lipoproteína de Baixa Densidade.

Learning Points

1. *LRP5* mutations are associated with a wide spectrum of bone phenotypes, from severe OPPG to isolated adult-onset osteoporosis.
2. Genetic evaluation should be considered in patients with familial, early-onset or unexplained osteoporosis, as identifying pathogenic variants may guide management and prompt screening of at-risk relatives.
3. Bisphosphonate therapy remains the cornerstone of treatment in *LRP5*-related osteoporosis, improving bone mineral density and reducing fracture risk, even in genetically determined bone disease.

Introduction

Osteoporosis is defined by a reduction in bone mass accompanied by disruption of bone microarchitecture, resulting in increased susceptibility to fractures.[1,2] While most cases are related to ageing or the postmenopausal period, monogenic forms of primary osteoporosis are being recognised with increasing frequency, particularly among individuals with early disease onset or a marked familial aggregation.[2]

The *LRP5* gene encodes the low-density lipoprotein receptor-related protein 5, which functions as a co-receptor in the canonical Wnt/β-catenin signalling pathway, a key regulator of osteoblast differentiation and bone formation.[2,3]

*Joint first authors
[1] Internal Medicine Service, Unidade Local de Saúde de Coimbra, Coimbra, Portugal
[2]Faculty of Medicine, Universidade de Coimbra, Coimbra, Portugal

https://doi.org/10.60591/crspmi.536

Variants that lead to loss of *LRP5* function attenuate Wnt signalling, compromising bone accrual and ultimately resulting in reduced bone mineral density.[2,3]

The most severe clinical presentation linked to loss-of-function *LRP5* mutations is osteoporosis-pseudoglioma syndrome (OPPG), a rare autosomal recessive condition characterised by congenital or early-onset visual impairment and severe juvenile osteoporosis, often complicated by recurrent low-impact fractures.[4,5] By contrast, heterozygous *LRP5* variants are typically associated with milder phenotypes, including isolated early-onset or adult-onset osteoporosis without ocular involvement.[4,5]

Descriptions of families exhibiting both recessive and heterozygous *LRP5*-related phenotypes are uncommon.[5] Here, we describe a family that exemplifies the broad clinical spectrum of *LRP5*-associated bone disease, including two siblings with OPPG and their mother, who presents with heterozygous *LRP5*-related adult-onset osteoporosis.

Case Report

Cases 1 and 2: Two siblings with osteoporosis-pseudoglioma syndrome

Two male siblings, both in their early twenties, were evaluated for a constellation of findings compatible with OPPG. They were born in Brazil and later relocated to Portugal. Before their diagnosis, there was no known family history of skeletal fragility or ocular disease.

The younger sibling presented at birth with congenital amaurosis, accompanied by hypotonia and marked psychomotor developmental delay. From the age of three years, he experienced recurrent fractures, including bilateral foot fractures, a T12 vertebral fracture, and fractures of the clavicle and femur, the latter requiring surgical management. Skeletal complications progressed to include spinal deformity, namely scoliosis.

The older brother developed visual impairment early in life, with congenital amaurosis affecting one eye and a progressive decline in vision in the contralateral eye during childhood. Between one and three years of age, he sustained multiple fractures involving both feet.

Dual-energy X-ray absorptiometry demonstrated severe osteoporosis in both patients, with lumbar spine T-scores of –3.9 and –5.7, respectively. Plain radiographs revealed generalized osteopenia, thinning of diaphyseal cortices and bowing of the long bones (Figs. 1 and 2).

Ophthalmological assessment identified microphthalmia, corneal opacities and posterior synechiae in both siblings, findings that were corroborated by brain magnetic resonance imaging, which confirmed structural ocular abnormalities (Fig. 3).

Molecular analysis revealed compound heterozygosity for two LRP5 variants: a likely pathogenic frameshift variant, c.346dup p.(Asp116Glyfs*36), and a missense variant, c.1385G>A p.(Arg462Gln). These results established the diagnosis of OPPG.

Treatment with bisphosphonates was initiated in both patients. The younger sibling received intravenous pamidronate initially, followed by oral alendronate, while the older

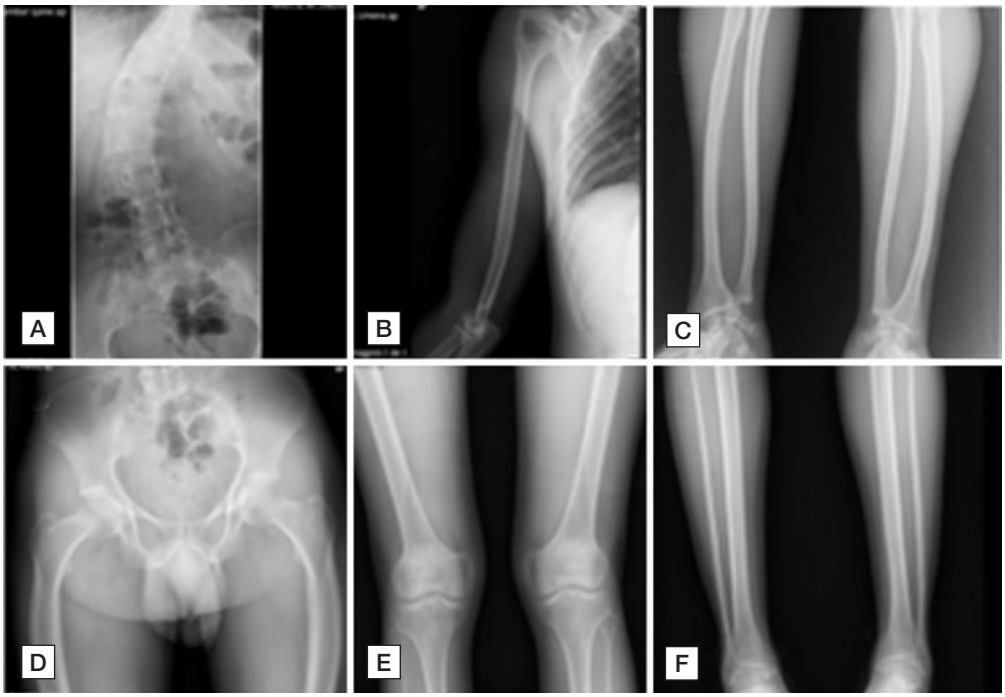

Figure 1: Skeletal radiograph of the older brother. Marked scoliosis **[A]**. Long bones appear radio-lucent with thin cortices. Severely thinned diaphyseal cortices ("pencil-thin") can easily be seen in umerus **[B]**, radius and ulna **[C]**, femur **[D,E]** and tibia and fibula **[F]**. Femur lateral bowing **[D]**.

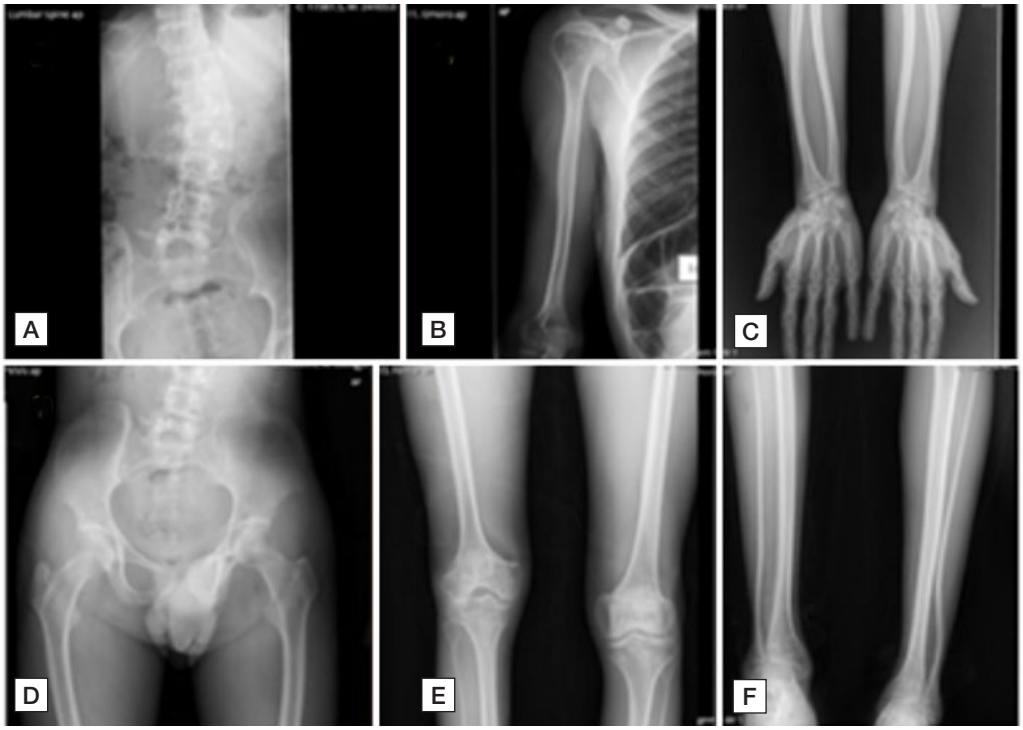

Figure 2: Skeletal radiograph of the younger brother. Similar features can be seen. There is a greater thinning of the femur **[E]** and fibula **[F]**. Chilaiditi's sign was identified as a probable incidental finding **[B]**.

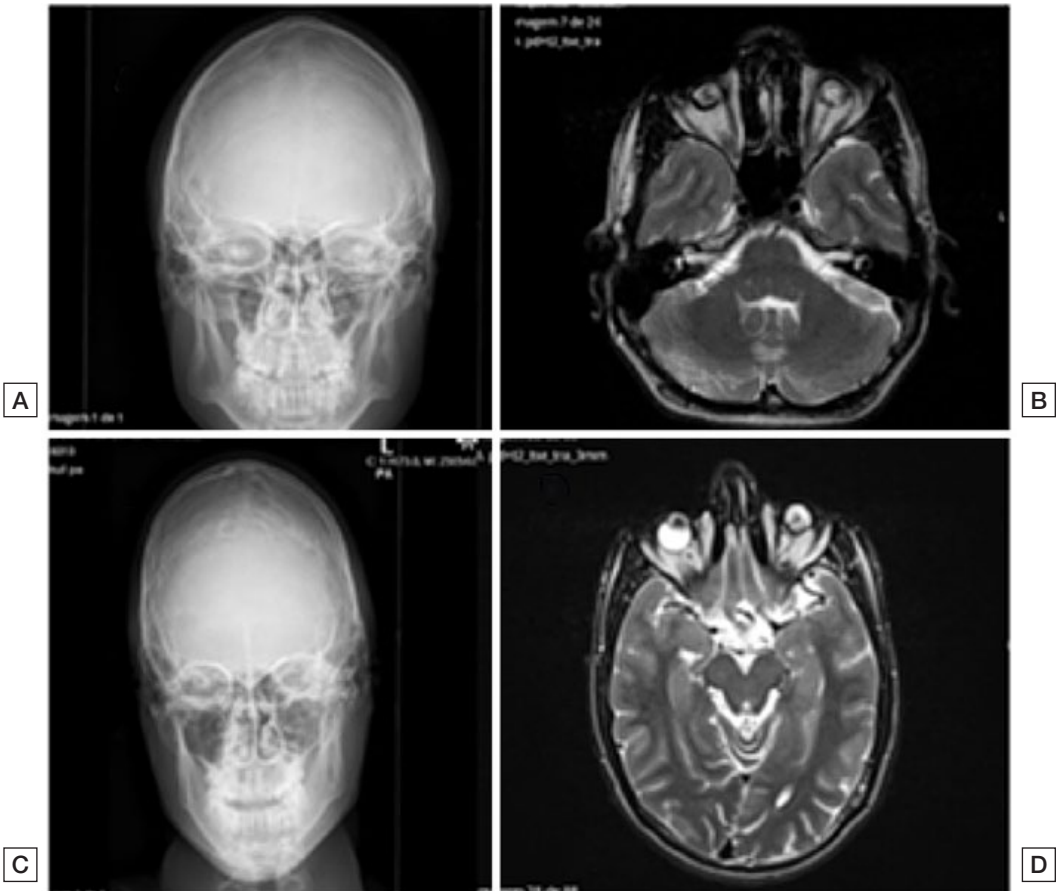

Figure 3: Skull radiograph and head MRI of the older **[A** and **B]** and younger **[C** and **D]** brothers. Dolichocephaly is more pronounced in the younger sibling **[C]**. Microphthalmia **[B** and **C]**.

sibling was treated with oral alendronate from the onset. Both also received calcium and vitamin D supplementation. Follow-up showed stabilisation and modest improvement in bone mineral density; however, both individuals continue to be at high risk for fractures. Visual impairment remained unchanged despite ongoing ophthalmological follow-up.

Case 3: Mother with heterozygous *LRP5* variant and adult-onset osteoporosis

The siblings' mother, a 50-year-old woman, was referred for evaluation following her sons' diagnosis. Her medical history included glaucoma and migraine, with no prior history of fragility fractures. She reported intermittent pain in the lower limbs, lasting less than 24 hours and occurring approximately once a month for over two decades.

Dual-energy X-ray absorptiometry revealed osteoporosis at several skeletal sites, with T-scores of –2.6 at the lumbar spine, –2.9 at the total left femur and –3.3 at the femoral neck (Figs. 4 A and B). Laboratory investigations were unremarkable, apart from marked vitamin D deficiency (5.3 ng/mL; deficiency level < 10 ng/mL), with normal serum calcium of 9.1 mg/dL (reference range: 8.8–10.6 mg/dL).

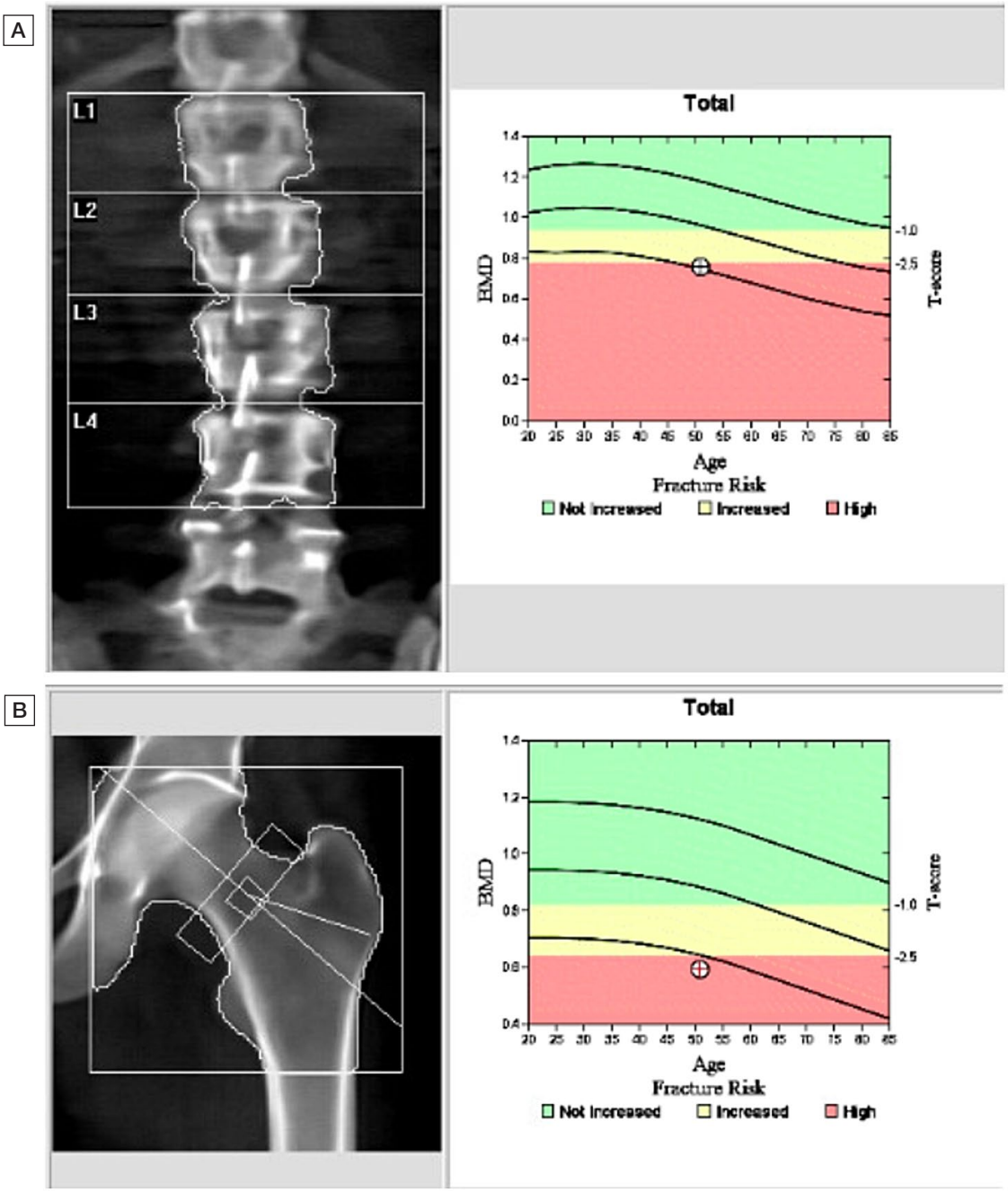

Figure 4: Dual-energy X-ray absorptiometry of the lumbar spine, L1-L4 **[A]** and left femoral neck **[B]** showing a T-score of ≤ –2.5, compatible with osteoporosis, with increased fracture risk.

Given her strong family history, she was referred to genetic testing, which identified a heterozygous frameshift variant in *LRP5*, c.356dup p.(Asp11Glyfs*36), a variant previously associated with an increased risk of primary osteoporosis. Ophthalmological evaluation showed no evidence of ocular involvement, consistent with the fact that this variant is not typically linked to visual impairment.

She initiated calcium and vitamin D supplementation together with weekly oral alendronate. At one-year follow-up, she remained clinically well, had sustained no fractures and continued antiresorptive therapy.

Discussion

This family exemplifies the wide phenotypic variability of bone disease associated with *LRP5*, ranging from severe autosomal recessive OPPG to milder, heterozygous adult-onset osteoporosis. The coexistence of both phenotypes within the same family lineage highlights the dose-dependent effect of *LRP5* dysfunction on skeletal integrity and ocular development.[4,6]

In OPPG, biallelic loss-of-function variants in *LRP5* result in marked disruption of canonical Wnt/β-catenin signalling, leading to profoundly impaired osteoblast activity and abnormal eye development.[4,7] By contrast, heterozygous variants typically cause a partial reduction in Wnt signalling, which is sufficient to compromise bone mass acquisition while usually sparing ocular structures.[2,6]

The diagnosis of *LRP5*-related osteoporosis may be particularly challenging in adults, especially in the absence of fragility fractures or visual abnormalities. Nevertheless, the identification of pathogenic *LRP5* variants carries important clinical implications, including optimisation of therapeutic strategies and the opportunity for targeted genetic counselling and family screening.[7,8]

Bisphosphonates currently represent the basis of treatment for *LRP5*-related osteoporosis and have been shown to increase bone mineral density and reduce fracture risk in both paediatric and adult patients, including those with OPPG.[1,8-10] Denosumab has also been used in selected cases, but longterm data are limited.[11] There is ongoing research into therapies targeting Wnt signalling, but these are not yet standard of care.[9] Therefore, data on longterm outcomes, fracture prevention and optimal treatment duration remain limited.

This case series highlights the importance of considering monogenic causes in patients with familial or otherwise unexplained osteoporosis and illustrates the value of a multidisciplinary approach involving internal medicine, medical genetics and ophthalmology. ■

Awards and Previous Presentations

This case was presented in the 30th edition of the European Congress of Internal Medicine.

Contributorship Statement

CCP and TJG – Preparation, conceptualization, literature review, and manuscript revision.

OD and JCC – Literature review and manuscript revision.

HE – Conceptualization and manuscript revision.

All authors approved the final version to be published.

Declaração de Contribuição

CCP e TJG – Elaboração, concepção, revisão da literatura e do manuscrito.

OD e JCC – Revisão da literatura e do manuscrito.

HE – Concepção e revisão do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Corresponding Author / Autor Correspondente

Christine Joannie Canizes Paiva – joanniecp@gmail.com

Serviço de Medicina Interna, Unidade Local de Saúde de Coimbra, Coimbra, Portugal

Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal

Received / Recebido: 23/12/2025

Accepted / Aceite: 23/02/2026

Published online / Publicado online: 31/07/2026

Published / Publicado: 31/07/2026

REFERENCES

1. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagno-sis and management of osteoporosis in postmenopausal wom--en. Osteoporos Int. 2019;30:3–44. doi: 10.1007/s00198-018-4704-5

2. Mäkitie RE, Costantini A, Kämpe A, Alm JJ, Mäkitie O. New In-sights Into Monogenic Causes of Osteoporosis. Front. Endocrinol. 10:70. doi: 10.3389/fendo.2019.00070
3. Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nat Med.2013;19:179–92. DOI: 10.1038/nm.3074
4. Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, Reginato AM, et al. LDL receptor–related protein 5 (LRP5) affects bone accrual and eye develop-ment. Cell. 2001;107:513–23. doi: 10.1016/s0092-8674(01)00571-2
5. Littman J, Yang W, Olansen J, Phornphutkul C, Aaron RK. LRP5, Bone Mass Polymorphisms and Skeletal Disorders. Genes. 2023;14:1846. doi: 10.3390/genes14101846
6. Korvala J, Jüppner H, Mäkitie O, Sochett E, Schnabel D, Mora S, et al. Mutations in LRP5 Cause Primary Osteoporosis Without Features of OI by Reducing WNT Signaling Activity. BMC Med Genet. 2012;13:26. doi: 10.1186/1471-2350-13-26
7. Stürznickel J, Rolvien T, Delsmann A, Butscheidt S, Barvencik F, Mundlos S, et al. Clinical Phenotype and Relevance of LRP5 and LRP6 Variants in Pa-tients With Early-Onset Osteoporosis (EOOP). J Bone Mineral Res. 2021;36:271-82. doi: 10.1002/jbmr.4197
8. Streeten EA, McBride D, Puffenberger E, Hoffman ME, Pollin TI, Donnelly P et al. Osteoporosis-pseudoglioma syndrome: description of 9 new cases and bene-ficial response to bisphosphonates. Bone. 2008;43:584-90. doi: 10.1016/j.bone.2008.04.020
9. Ren N, Lv S, Li X, Shao C, Wang Z, Mei Y, et al. Clinical Features, Treatment, and Follow-Up of OPPG and High-Bone-Mass Disorders: LRP5 Is a Key Regula-tor of Bone Mass. Osteoporos Int. 2024;35:1395-406. doi: 10.1007/s00198-024-07080-x.
10. Stringer F, Sims NA, Sachithanandan N, Aleksova J. Severe Osteoporo--sis with Pathogenic LRP5 Variant. JCEM Case Rep. 2024;2:luae021. doi: 10.1210/jcemcr/luae021
11. Miyazawa S, Nakamura Y, Kosho T, Kawame H, Narumi S, Hasegawa T, et al. Efficacy of denosumab therapy for osteoporosis-pseudoglioma syndrome with osteoporosis: a case report. Modern Rheumatol Case Rep. 2019; 3:45–8. doi:10.1080/24725625.2018.1454573