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Case Report

LRP5 Variant Without Pseudoglioma in a Young Man With Fragility Fractures

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Abstract

Osteoporosis in children and young adults is relatively rare. Hereditary causes are often overlooked in the absence of a positive family history. We report a 29-year-old male presenting with recurrent fragility fractures since 6 years of age. Secondary causes, such as celiac disease, inflammatory disorders, and hypogonadism, were ruled out. Family history was negative for any bone disease. Exome sequencing revealed 2 variants of *LRP5* gene—intron 5 c.1015 + 1G > A and exon 5 c.892C > T. Although the former variant has been described in literature as a cause of osteoporosis in homozygous state only, it manifested as osteoporosis in our patient, in the heterozygous state, in presence of a second variant of uncertain significance. However, eye involvement, which is classically seen in "osteoporosis-pseudoglioma syndrome" homozygote, was absent in our patient. Genetic analysis of the parents revealed father to be a carrier of intron 5 c.1015 + 1G > A and mother exon 5 c.892C > T variants of the *LRP5* gene. However, none of them had osteoporosis on bone densitometry. The patient was subsequently treated with IV zoledronic acid (planned to be administered annually) and showed improvement in bone density by 11% at the spine and 9.5% at the left femur; there were no further fractures over 1 year of follow-up.

Key Words: young osteoporosis, osteoporosis-pseudoglioma, *LRP5* variant

Abbreviations: aBMD, areal bone mineral density; DXA, dual-energy X-ray absorptiometry; LRP5, lipoprotein receptor-related protein-5; OPPG, osteoporosis-pseudoglioma syndrome.

Introduction

Osteoporosis in younger adults poses a challenge because of the absence of a clear definition and well-established management guidelines. Peak bone mass is determined by environmental and genetic factors (1). Once secondary causes of low bone mass have been ruled out, genetic testing is warranted to determine the cause of young-onset osteoporosis. We report a young adult with childhood-onset recurrent fractures resulting from 2 heterozygous variants in the *LRP5* gene—intron 5 c.1015 + 1G > A and exon 5 c.892C > T. The *LRP5* gene has been well described in the context of osteoporosis-pseudoglioma syndrome (OPPG). However, the aforementioned variants have not previously been described to cause osteoporosis in the heterozygous state (2). OPPG has classical eye involvement ranging from mild vitreoretinal changes to complete blindness (3), which was absent in our case. The existence of these variants may imply lifelong surveillance for other clinical associations of OPPG and vigilance in future family planning for the index patient.

Case Presentation

A 29-year-old male was referred to our endocrine clinic in view of young-onset osteoporosis. He had complaint of mild (diffuse) backache for 1 year. There was a history of multiple fractures during childhood: right humerus (at age 6 years), right fibula (at age 10 years), and the 12th thoracic vertebra (T12, compression fracture) (at age 16 years). Slip-and-fall events (low trauma) resulted in the former 2 fractures, whereas the latter was spontaneous. There was no skeletal deformity, ligament laxity, or blue sclera. There was no history of visual abnormalities.

The patient was the first and single-born child of a nonconsanguineous marriage, preterm (32-week) vaginal delivery, with catch-up growth after birth. Major milestones and teeth eruption were achieved on time. Scholastic performance was above average. There was no history of any bone disease/fractures in the family. The patient denied any addictions. There was no history of chronic use of any medications known to cause metabolic bone disease, such as antiepileptics, steroids, antidepressants, or proton pump inhibitors. There were no signs or symptoms of other endocrinopathies such as hypogonadism, diabetes, Cushing syndrome, thyroid disorder, or hyperparathyroidism. There were no features suggestive of malabsorption or renal tubular acidosis. There was no history of any autoimmune or inflammatory illnesses. At presentation, his height was 165 cm and his weight was 68 kg (body mass index, 25 kg/m^2). The general physical examination revealed normal findings.

Diagnostic Assessment

Laboratory investigations showed serum total calcium 9.9 mg/dL (2.47 mmol/L) (normal reference range: 8.7-10.4 mg/dL;

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2.17-2.60 mmol/L), phosphorus 4.6 mg/dL (1.49 mmol/L) (normal reference range: 2.4-5.1 mg/dL; 0.77-1.65 mmol/L), 25-hydroxyvitamin D 33 ng/mL (82.3 nmol/L) (normal reference range: 30-100 ng/mL; 75-250 nmol/L), alkaline phosphatase 55 IU/mL (normal reference range: 38-126 IU/mL), intact PTH 38 pg/mL (4.03 pmol/L) (normal reference range: 18.5-88 pg/mL; 1.96-9.33 pmol/L), TSH 4.9 µIU/mL (normal reference range: 0.55-4.78 µIU/mL), and total testosterone 411 ng/dL (14.25 nmol/L) (normal reference range: 197-669 ng/dL). He was normoglycemic, and renal and liver function tests and blood-gas analysis were normal. Magnetic resonance imaging of the spine (Fig. 1) and a bone scan (Fig. 2) showed anterior wedge collapse of the eighth thoracic vertebra (T8) with a moderate decrease in anterior vertebral body height (50%-60%). Dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy advance DXA system) showed a reduced areal bone mineral density (aBMD): spine 0.772 (*Z*-score: −3.3), left femur 0.694 (*Z*-score: −2.5), and neck of left femur 0.872 (*Z*-score: −1.2). He was further evaluated for causes of secondary osteoporosis. Inflammatory markers and serum tryptase levels were within normal ranges. Celiac screen and antinuclear antibodies were negative. The 24-hour urinary calcium was 203 mg/day (normal reference range: 100-300 mg/day). Bone turnover markers serum β C-terminal crosslinked telopeptide of type I collagen was 474 pg/mL (normal reference range: <584 pg/mL), and amino-terminal propeptide of type 1 collagen was 66.4 ng/mL (normal reference range: <36.4 ng/mL).

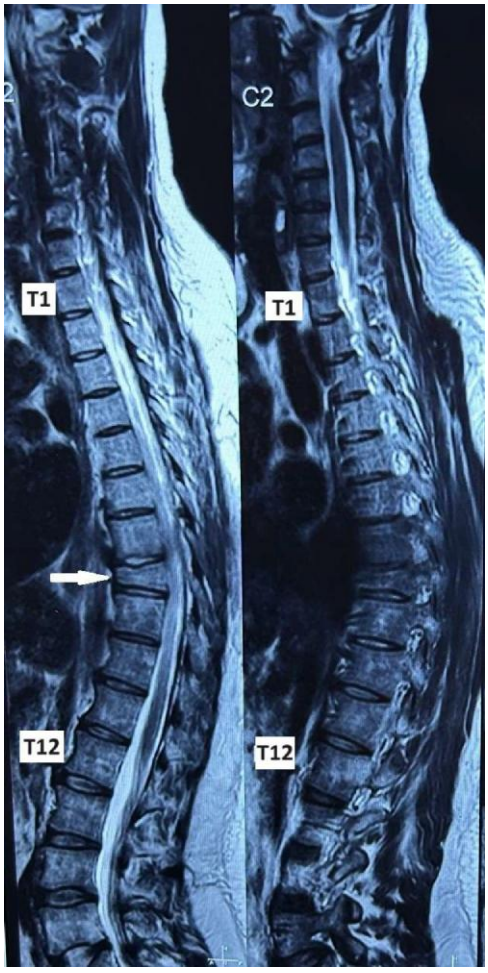

Figure 1. MRI of the spine showing anterior wedge fracture (white arrow) of the eighth thoracic vertebra (T8).

Because of the lack of any obvious secondary cause for low aBMD, we performed genetic testing with exome sequencing. The latter was done using massively parallel sequencing (next-generation sequencing), which showed 2 variants in the *LRP5* gene intron 5 c.1015 + 1G > A (heterozygous) and exon 5 c.892C > T (heterozygous). Subsequent genetic analysis of the parents revealed the father (unaffected) to be a carrier of intron 5 c.1015 + 1G > A and the mother (unaffected) exon 5 c.892C > T in the *LRP5* gene. The mother, a 57-year-old postmenopausal woman, had T-scores of −2.1 at the spine and −2.1 at the left neck of the femur. DXA scan of the father was normal, with T-scores of 1.1 and 0.6 in the spine and left neck of the femur, respectively. Fundus examinations of both parents were normal.

Detailed ophthalmological evaluation showed no abnormality. The final diagnosis in our patient was OPPG.

Treatment

The patient was administered the first dose of IV zoledronic acid (5 mg) infusion and planned for further annual doses.

Outcome and Follow-up

At follow-up, β C-terminal crosslinked telopeptide of type I collagen reduced to 101 pg/mL at 6 months, followed by a marginal rise to 115 pg/mL at 9 months and 158 pg/mL at 12 months. Bone densitometry was repeated at 1 year, which showed striking improvement with aBMD in the spine of 0.854 (*Z*-score: −2.8), left femur 0.758 (*Z*-score: −2.1), and the neck of the left femur 0.972 (*Z*-score: −0.6). There was a change of +11% at the spine, +9.5% at the left femur, and +11.5% at the neck of the left femur. The patient remained fracture-free (spine and elsewhere) after 1 year of zoledronic acid. Subsequently, a second dose of IV zoledronic acid (5 mg) was administered.

Discussion

Osteoporosis in children and young adults should be evaluated extensively for secondary causes for timely diagnosis and management. Peak bone mass is affected by multiple factors, such as genetics, environment, and hormones, among others (1). Thus, once secondary causes are ruled out, genetic testing is warranted.

Collet et al performed next-generation sequencing to look for genetic causes in young adults with primary osteoporosis (2). Sixteen novel variants of the *LRP5* gene were described. However, the variants detected in our patient, intron 5 c.1015 + 1G > A and exon 5 c.892C > T, were not listed.

OPPG is an autosomal recessive disorder caused by homozygous or compound heterozygous mutation in a gene encoding low-density lipoprotein receptor-related protein-5 (LRP5) on chromosome 11q13. There are 23 coding exons of the *LRP5 gene*. LRP5 protein is a transmembrane Wingless (Wnt) co-receptor for members of the Frizzled receptor family, responsible for regulating the growth and differentiation of osteoblasts (3). In addition to the mentioned direct effect, it may also act indirectly through inhibition of tryptophan hydroxylase 1, further leading to inhibition of osteoblast

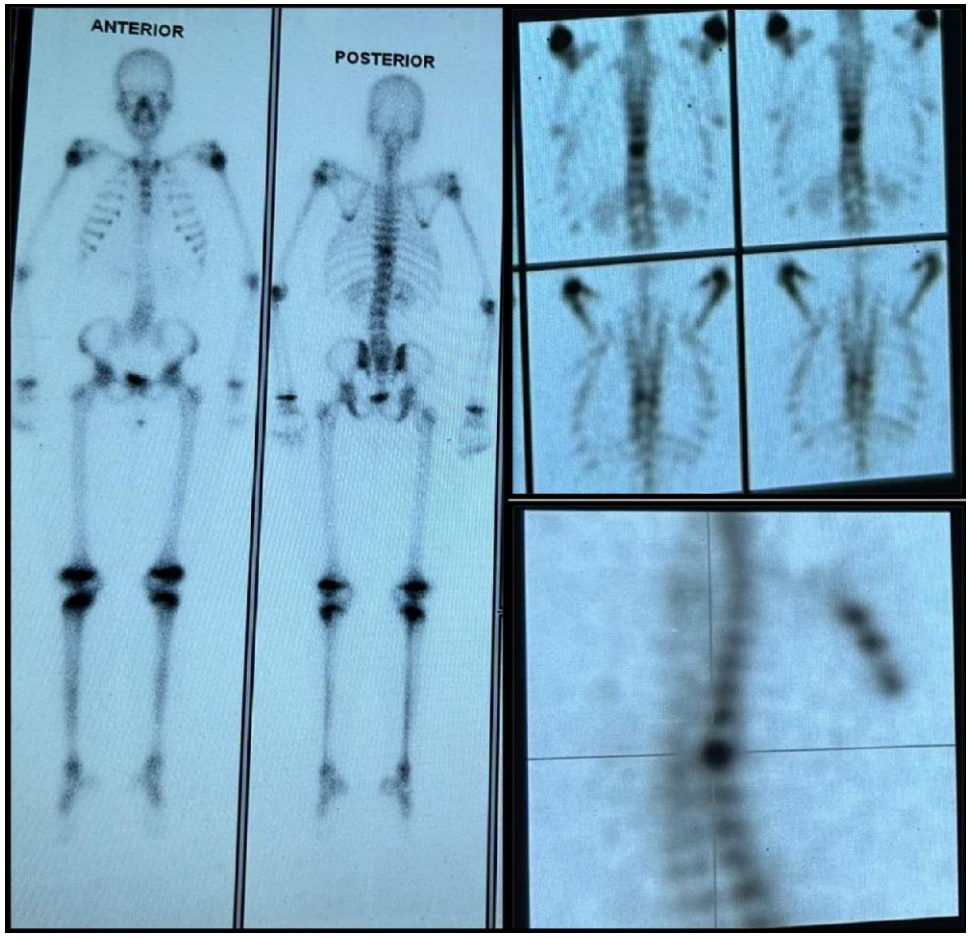

Figure 2. Bone scan showing fracture of the eighth thoracic vertebra (T8).

proliferation (4). Patients usually present in early childhood with recurrent fractures. Defective vascularization leads to eye involvement, which may range from mild vitreoretinal changes to complete blindness. Most patients are blind by the age of 25 years (5). Some degree of intellectual disability is another common association.

Laine et al (6) reported 1 case with splice-site mutation c.1015 + 1G > T (intron 5) in the *LRP5* gene in an 11-year-old boy from Iran. He was congenitally blind and had a history of multiple fractures in childhood, along with intellectual disability. Both parents had osteopenia with no visual problems.

Cheung et al (7) reported 2 novel mutations involving exon 7 of the *LRP5* gene in a family of 4 children. Three children had blindness and multiple childhood fractures. The fourth unaffected child had an *LRP5* gene variant similar to his father—c.1432T > A (p.W478R)—in a heterozygous state, resulting in a low bone mineral density without any visual complaints. The 3 affected children had *LRP5* gene variants in compound heterozygous state—c.1432T > A (p.W478R)—inherited from the father and c.1515G > T (p.W504C) inherited from the mother.

Stürznickel et al (8) genotyped 372 individuals with young-onset osteoporosis, of which 50 were found to harbor variants affecting *LRP5* or *LRP6* genes. No association was found between classes of genetic variants and disease severity. Although the ophthalmological involvement was not studied, the single individual with compound heterozygous mutation (as opposed to homozygous mutation in others) manifested with congenital retinoschisis and intellectual disability along with early onset osteoporosis.

Our patient had heterozygous variants of the *LRP5* gene—intron 5 c.1015 + 1G > A and exon 5 c.892C > T. He had no visual or intellectual abnormalities. Neither side of the family had any history of recurrent bone fractures or vision abnormalities. Laine et al (6) performed a heterologous splicing assay to study the effect of the variant intron 5 c.1015 + 1G > T in a homozygous state, which showed that exon 5 and its adjoining introns were incorrectly spliced out because of the mutation, resulting in a shorter vector product with 263-bp instead of 395-bp product with wild-type exon 5 fragment. Despite having the variant intron 5 c.1015 + 1G > A in a heterozygous state, our patient manifested in the form of osteoporosis in the presence of another coexisting variant of the *LRP5* gene at exon 5 c.892C > T. This variant is nonsynonymous, leading to amino acid change at position 298 from arginine to cysteine (p.Arg298Cys). Per the structural domains of LRP5 protein described by Ren et al (9), this amino acid position is located in the first of the 4 β-propeller domains of LRP5 protein, which lies extracellularly and is responsible for binding Wnt ligands and their inhibitors, such as Dickkopf-related protein 1 and sclerostin.

The overall heritability of low BMD is 60% to 80% in twin studies, and that of osteoporotic fractures is 50% to 70% (10). We thus highlight the importance of genetic testing in

young-onset osteoporosis, even without any family history, if the secondary causes have been excluded. This may clinch the diagnosis, offer timely treatment, and help in family planning in a given patient. Also, the coexisting common clinical associations can be monitored. Although our patient had a normal ophthalmological evaluation, the existing gene variants keep him at risk, necessitating a close follow-up in future.

Learning Points

- Genetic analysis is important in young osteoporosis when secondary causes have been ruled out.
- Two novel variants in the *LRP* gene (intron 5 c.1015 + 1G > A and exon 5 c.892C > T) add to the pathogenic genetic variants associated with OPPG.
- These variants may cause a phenotype that is different from the classically described OPPG.

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Contributors

A.M. and A.D. were involved in the clinical evaluation and diagnosis of this patient. A.D., A.M., and N.V. were involved in the management and follow-up of the patient. A.D. and N.V. were involved in drafting the manuscript. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

References

1. Rozenberg S, Bruyère O, Bergmann P, *et al*. How to manage osteoporosis before the age of 50. *Maturitas*. 2020;138:14-25.
2. Collet C, Ostertag A, Ricquebourg M, *et al*. Primary osteoporosis in young adults: genetic basis and identification of novel variants in causal genes. *JBMR Plus*. 2017;2(1):12-21.
3. Gong Y, Slee RB, Fukai N, *et al*. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. *Cell*. 2001;107(4):513-523.
4. Yadav VK, Ryu JH, Suda N, *et al*. Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. *Cell*. 2008;135(5):825-837.
5. Ai M, Heeger S, Bartels CF, Schelling DK; Osteoporosis-Pseudoglioma Collaborative Group. Clinical and molecular findings in osteoporosis-pseudoglioma syndrome. *Am J Hum Genet*. 2005;77(5):741-753.
6. Laine CM, Chung BD, Susic M, *et al*. Novel mutations affecting *LRP5* splicing in patients with osteoporosis-pseudoglioma syndrome (OPPG). *Eur J Hum Genet*. 2011;19(8):875-881.
7. Cheung WM, Jin LY, Smith DK, *et al*. A family with osteoporosis pseudoglioma syndrome due to compound heterozygosity of two novel mutations in the *LRP5 gene*. *Bone*. 2006;39(3):470-476.
8. Stürznickel J, Rolvien T, Delsmann A, *et al*. Clinical phenotype and relevance of LRP5 and LRP6 variants in patients with Early-Onset Osteoporosis (EOOP). *J Bone Miner Res*. 2021;36(2):271-282.
9. Ren Q, Chen J, Liu Y. LRP5 and LRP6 in Wnt signaling: similarity and divergence. *Front Cell Dev Biol*. 2021;9:670960.
10. Deng HW, Mahaney MC, Williams JT, *et al*. Relevance of the genes for bone mass variation to susceptibility to osteoporotic fractures and its implications to gene search for complex human diseases. *Genet Epidemiol*. 2002;22(1):12-25.