

## Osteoporosis-pseudoglioma syndrome: Description of 9 new cases and beneficial response to bisphosphonates

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### ABSTRACT

Osteoporosis-pseudoglioma syndrome (OPPG) is a rare autosomal recessive disorder of severe juvenile osteoporosis and congenital blindness, due to mutations in the low-density lipoprotein receptor-related protein 5 (*LRP5*) gene. Approximately fifty cases of OPPG have been reported. We report 9 new cases of OPPG, in three related nuclear families of Conservative Mennonites in Pennsylvania. All 9 children with OPPG were blind and had osteoporosis. Four of six parents had low bone mineral density (BMD) or osteoporosis; 2 were normal. Sequence analysis from genomic DNA revealed homozygosity for a nonsense mutation of exon 6 of *LRP5* (W425X) in four OPPG cases tested in families A and C. In family B, OPPG cases were compound heterozygotes for the exon 6 W425X *LRP5* mutation and a second exon 6 mutation (T409A); bone phenotype was milder than in family A. Neither of these mutations was present in an unrelated normal. The four treated OPPG patients all responded to bisphosphonates (duration 1.5–6.5 years) with improvement in Z-scores. One patient had a negligible response to teriparatide. In summary, we report 9 new cases of OPPG due to two novel *LRP5* mutations, note a milder bone phenotype but similar ocular phenotype in *LRP5* W425X/T409A compound heterozygotes than in W425X homozygotes and describe positive response to bisphosphonate treatment in four cases.

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### Introduction

Osteoporosis-pseudoglioma syndrome (OPPG) is a rare autosomal recessive syndrome of juvenile-onset osteoporosis and ocular abnormalities described first by Saraux in 1967 [1]. To date, approximately 50 cases have been reported [1–14], most with onset of fractures after age 2 years [2], and congenital blindness, the latter due to persistence of the fetal ocular fibrovascular system and failure of retinal development [2,3]. OPPG is caused by inactivating mutations in the low-density lipoprotein receptor-related protein 5 gene (*LRP5*) [4]. *LRP5* is a membrane co-receptor in the canonical *Wnt* signaling pathway. *LRP5* mutations that prevent *Wnt* from binding to *LRP5* lead to pathway inactivation and OPPG, while mutations that prevent *LRP5* from binding to co-factor Dkkopf lead to pathway activation and excessive bone formation [15]. At least 12 different homozygous [2,4] and 15 compound heterozygous [2,5] *LRP5* mutations have been described in OPPG, most in the second or third of its four beta-propeller domains, which are high affinity *Wnt* binding domains that are highly conserved [2]. No phenotypic distinctions have been reported in compound heterozygotes compared

to homozygotes [2]. Obligate heterozygotes have been found to have modest degrees of low bone mass but no eye pathology [4,16].

Inactivating mutations in *LRP5* can also cause familial exudative vitreoretinopathy (FEVR), a disease characterized by premature arrest of the retinal vasculature [17]. The resulting retinal avascularity leads to complications including folding and neovascularization of the retina, which in turn leads to retinal detachment and blindness in most [18,19]. FEVR has been classically described without an osteoporotic phenotype (fractures, bone deformity) [18,20]. However, when bone mineral density testing has been routinely performed, most with FEVR have reduced bone mass or osteoporosis, leading to the suggestion that OPPG and FEVR are in a single phenotypic spectrum [20]. FEVR is heterogeneous, with 20% having *LRP5* mutations, 20–40% with mutations in the *LRP5* co-receptor Frizzled 4 (*FZD4*) and 40–75% idiopathic but reduced bone mass has been seen only in those with *LRP5* mutations [20].

Activating mutations in *LRP5* cause Familial High Bone Mass Syndrome (HBM), an autosomal dominant syndrome associated with non-pathologic high bone mass and have also been detected in some pathological bone sclerosing disorders [21–23], providing evidence that this gene is an important regulator of bone production. In familial HBM, activating *LRP5* mutations have been confined to the first beta-propeller domain [20–23]. No obvious ocular pathology has been reported in association with activating *LRP5* mutations.

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Scanty information is available on the treatment of osteoporosis in OPPG. We are aware of only two reports of bisphosphonate treatment in OPPG, a 21 year-old woman treated for 3 years with pamidronate [13] and 3 children aged 9–11 [14], treated with pamidronate for 2 years; all had improvement in bone mineral density. We report 9 new cases of OPPG in related members of 3 nuclear families from a Conservative Mennonite population in Pennsylvania. We describe 2 novel mutations in *LRP5*, note a milder bone phenotype in W425X/T409A compound heterozygotes than in W425X homozygotes and report response to treatment. Four patients were treated with bisphosphonates (1.5–6.5 years in duration); in one of these cases, bisphosphonate treatment was followed by teriparatide (total treatment duration 7.5 years).

**Materials and methods**

*Patients*

Patients were evaluated at the Amish Research Clinic in Strasburg, PA. The protocol was approved by the University of Maryland Institutional Review Board and signed informed consent from adults and assent from children was obtained. A history including fractures was obtained. A general physical examination included height, weight, and musculoskeletal exam in those with OPPG (shown in Fig. 1 as shaded symbols). Ophthalmology exams were conducted on all with OPPG and in their parents.

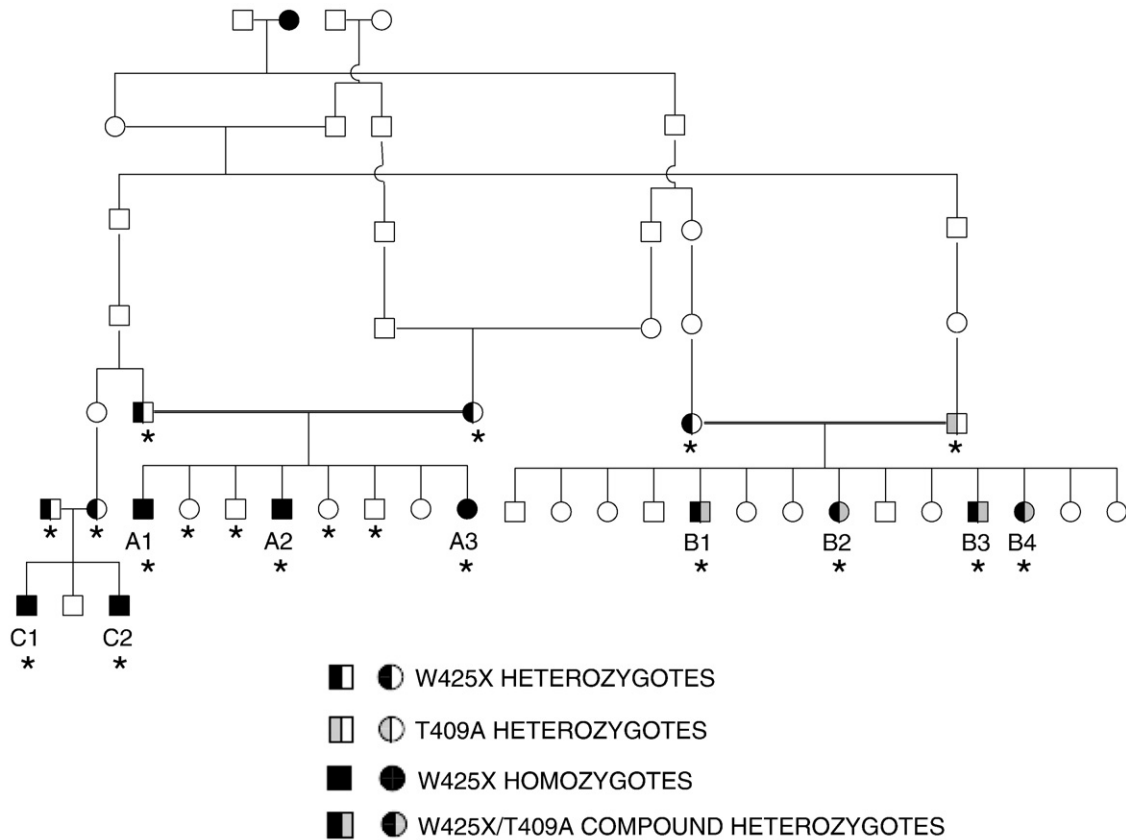
*Bone mineral density*

Bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DXA), using a Hologic 4500W (Bedford, MA), at the lumbar spine and hip in children and adults by a registered nurse

certified in bone densitometry. In children, premenopausal women and men under age 50, the Z-score, standard deviation (SD) from age and gender-matched controls, were used to assess normalcy of BMD. A Z-score above –2.0 was considered to be normal. For individuals under age 20 years, Hologic pediatric software was used to analyze scans. Pediatric Z-scores are not available for the spine under age 3 years or for the hip under age 5 years. For DXA scans done under age 3 years, we have used estimated Z-scores extrapolated from Hologic adult data. Because of the lack of pediatric Z-scores for the hip under age 3 years, we do not report the hip results here. In postmenopausal women and men over age 50, the T-score, (standard deviation from young adults at peak BMD) was used to assess BMD. According to the World Health Organization criteria [24], a T-score of –1.0 to –2.5 was considered “low bone mass” or “osteopenia” and lower than –2.5, osteoporosis. The coefficient of variation for BMD measurements, determined annually by 3 sequential measures on 1 day for each of 15 individuals, was 0.90% for total hip and 0.71% for the spine (L1–L4). The student’s Student’s *t* test was used to calculate the difference between Z-scores in W425X homozygotes and W425X/T409A compound heterozygotes.

*Mutation detection*

Genomic DNA was extracted from peripheral blood leukocytes from OPPG cases and their parents. Reference genomic DNA sequence for *LRP5* (accession ID NM\_002335) and exon information (accession ID-s AF283320 for exons 1–9 and AF283321 for exons 10–23) were obtained from GenBank. This information was used to design intronic PCR primers that flanked each of the 23 exons in *LRP5*. PCR products were generated from genomic DNA obtained from the OPPG patients and their parents and an unrelated individual and sequenced on an



**Fig. 1.** OPPG pedigree. The affected members are labeled A1 to C2. W425X homozygotes are shown in black symbols, compound heterozygous affecteds and W425X/T409A are shown in two tone symbols. Heterozygotes are shown with half shaded symbols, W425X in black and T409A in gray.

**Table 1**  
Clinical characteristics of individuals with OPPG and their families and protein change resulting from DNA mutations (age=at time of initial evaluation, min LP=minimal light perception)

	Sex	Age (years)	Eye phenotype	Bone phenotype			Protein change
				Fractures	Z-score	T-score	
<i>Family A</i>							
OPPG A1	M	8	Retinal detachment (7 weeks)	Multiple femur, spine (6 years)	-6.4		W425X homozygote
A2	M	4	Retinal detachment (birth)	Clavicle (7 years) Femur (10 1/2)	-4.7		W425X homozygote
A3	F	2	Retinal detachment (birth)	None	-2.9		W425X homozygote
Parents	F	32	Normal exam	None	-1.2	-1.2	W425X heterozygote
	M	33	Normal exam	None	-0.5	-0.5	W425X heterozygote
Siblings	F	11	Normal vision	None	-0.7		
	F	6	Normal vision	None	-0.4		
	M	4	Normal vision	None	-0.9		
	F	3	Normal vision	None	-1.5		
<i>Family B</i>							
OPPG B1	M	16	<sup>a</sup> Retinal detachment, vitreoretinal dysplasia	None	-2.5		W425X, T409A compound heterozygote
B2	F	11	Retinal detachment, cataract vitreoretinal dysplasia	Wrist (5 years old)	-2.7		W425X, T409A compound heterozygote
B3	M	6	<sup>b</sup> Exudative retinopathy (7 months)	None	-0.8		W425X, T409A compound heterozygote
B4	F	4	Retinal folds (2 months), retinal detachment	None	-1.5		W425X, T409A compound heterozygote
Parents	F	41	Normal vision	None	-1.2	-1.5	T409A heterozygote
	M	44	Normal vision	None	-1.4	-1.6	W425X heterozygote
<i>Family C</i>							
OPPG C1	M	2	Retinal detachment (birth)	Femur (2 1/2 years)	-4.2		W425X homozygote
OPPG C2	M	3mos	Retinal detachment (birth)	None			
Parents	F	22	Normal vision	None	-3.1	-3.0	W425X heterozygote
	M	24	Normal vision	None	-0.4	-0.4	W425X heterozygote

T-scores and Z-scores are shown of the spine.

<sup>a</sup> Reduced vision noted by parents in infancy. Eye report available from age 15, with light perception only in right eye, none in left.

<sup>b</sup> Eye enucleated (right) for pain at age 7. Pathology revealed phthisis bulbi with corneal and iris neovascularization, retinal disorganization with extensive fibrosis and osseous metaplasia of retinal pigment epithelium.

ABI3730 (Applied Biosystems, Foster City, CA). PCR products were sequenced in both directions. The obtained sequences were analyzed using Sequencher (GeneCodes, Ann Arbor, MI).

## Results

### Clinical and BMD findings

The pedigree is shown in Fig. 1. Individuals who were evaluated are noted by an asterisk. In this 6-generation Conservative Mennonite family, there were at least 3 consanguineous marriages, the closest of which were second-degree relatives. Clinical characteristics and DXA Z-scores are shown in Table 1 (one child with OPPG did not have a DXA due to age under 1 year). In families A and C, all OPPG patients were blind since birth (minimal light perception at birth in some that was lost after the first year); in family B light perception was present at birth and was lost by age 10 years. Eye pain was noted in A1 in early childhood but resolved; in C1 and C2 mild eye pain was still present at the time of this report (ages 4 years and 6 months). All had grossly normal intelligence, white sclerae and normal joint mobility. Height was normal in all except for A1 and A2, both below 5th percentile. One of nine with OPPG, C1, had a behavioral disorder characterized by excessive aggression (e.g. biting others) and he was noted to be mildly hypotonic as an infant. C1 was seen by a child psychiatrist (Kennedy Institute at Johns Hopkins) who noted aggressive behavior, expressive language delay and social delay and diagnosed "autism spectrum disorder". He had no improvement in behavior to risperidone but benadryl (used as needed) has had a beneficial effect on his aggressive behavior. The mother in family C (age 22 years) had a Z-score in the osteoporosis range (because she was premenopausal, the T-score is not appropriate to use for her) but had no history of fracture. Her vision and eye exam were normal. Affecteds in families A and C had typical changes seen in OPPG; in family B, eye findings were more typical of FEVR. Pathology findings from an eye removed (because of pain) in OPPG B1 are shown in Table 1. Biochemical data on patients with OPPG is shown in Table 2.

### Mutations in patients with OPPG

We sequenced each of the 23 exons of *LRP5* in affected subjects and their parents. Homozygosity for a novel nonsense mutation in exon 6 (substitution of a stop codon for tryptophan, W425X) was found in affected individuals in families A and C. In both families A and C, both parents were heterozygous for the mutation. This mutation would be expected to lead to a truncated protein of 425 amino acids as compared to the normal protein of 1615 amino acids. In family B, the mother was heterozygous for the same W425X mutation found in families A and C while the father was heterozygous for a different mutation in exon 6, a novel missense mutation leading to the substitution of alanine for threonine (T409A). The children with OPPG in family B were compound heterozygotes for the two exon 6 mutations (W425X, T409A).

### Treatment response

OPPG A1, A2, A3 and C1 were treated with bisphosphonates for 6, 4.5, 1.5, and 1.5 years respectively. The BMD treatment responses are shown in Fig. 2; biochemical responses in Table 2. In addition, all were treated with calcium 1000 mg daily and vitamin D<sub>3</sub> 400–800 IU daily, with vitamin D dose titrated to a target 25-hydroxyvitamin D level of >30 ng/ml. Initially, risedronate was used in A1 and A2 for cost reasons (no have health insurance). However, the BMD response to risedronate was minimal, so both were changed to IV pamidronate after 2 (A1) and 1 (A2) years, using the dosing used in children with osteogenesis imperfecta [25], 1 mg/kg over 3 h on 3 successive weeks, repeated every 3 months. As shown in Fig. 2, both A1 and A2 had good responses to pamidronate, with improved Z-scores. Pamidronate was stopped after 3.5 years in A1 and changed to teriparatide because he had a femur fracture while on treatment with pamidronate, and his Z-score after an initial good response to pamidronate (Z-score -4.0 improved to -2.2), did not improve from age 13 (Z-score -2.2) to 14 (Z-score -2.2). After a 6 month period of bisphosphonate treatment, he was started on teriparatide, initially at 20 mg subcutaneously every

**Table 2**  
Biochemical data and treatment for 4 treated OPPG patients (A1, A2, A3, and C1)

A1 (DOB 7/8/91)									
Date	Serum Ca (8.4–10.2 mg/dl)	Albumin (3.1–4.8 g/dl)	Calcium corrected for albumin (mg/dl)	Phosphate (mg/dl)	Alk phos (U/l)	Ur NTX (nM BCE/mM Cr) <sup>c</sup>	25(OH)D (ng/ml)	IPTH (12–65 pg/ml)	Cr (Mg/dl)
1/18/00 <sup>a</sup>	9.5	4.6	9.1	5.1	263		39	12	0.4
1/9/01					180				
5/1/01						643			
8/20/02	10.5				191	330	20.3		
9/20/02	8.9					47			
1/11/03	10.7				153	213			
4/22/03	9.9	4.4	9.6		144	253	15.9		0.4
8/19/03	9.8				162	265	31.7		
11/17/03	10.1	4.3	9.9		145	189	17		0.4
2/26/04	9.9	4.4	9.6		150	213	31		0.4
6/21/04	10.2				181		29		
11/22/04	9.2				120	84			
2/4/05							25		
4/12/05	10.3	4.8	9.7		168	125			0.7
6/3/05	9.6	4.4	9.3	4.1	144			30	
8/1/05 <sup>b</sup>						157	24	14	
11/24/05	9.5				133				
2/28/06	9.6			4.2		192	28	22	0.5
6/8/06	9.5				132	118			
8/15/06						86			
11/17/06	9.4	4			133		23		0.6
7/17/07	9.6				106	89	22		
1/08/08	9.6	4.6	9.2		86	35			0.6
A2 (DOB 4/13/96)									
Date	Calcium	Albumin	Calcium corrected for albumin	Phosphate	Alk phos	Ur NTX	25(OH)D	IPTH	Cr
1/9/01					152				
1/15/02						376			
1/14/03						204			
11/17/03	10.1	4.4	9.8	4.8	149	166	30		
11/29/04					110	150	38		
4/12/05	10.7	4.9	10.0		153	118			0.3
6/14/05	9.6	4.4	9.3		125	93		7	
11/1/05	10.3				133	86			
2/26/06	10.5	5.0	8.7		143	82	26		0.4
6/8/06	9.8				132	74			
8/15/06						120			
7/17/07	10.2	4.9	9.5		145	114	33		
1/08/08	10.3				125	129			0.4
A3 (DOB 4/9/02)									
Date	Calcium (mg/dl)	Albumin	Calcium corrected for albumin	Phosphate	Alk pho	Ur NTX <sup>c</sup>	25(OH)D	IPTH	Cr
1/08/08	10.1	5.1	9.2		159	162			0.4
7/17/07	10.0				156				
12/12/06									
8/15/06	10.3	4.9	9.6		221	452	25		0.4
C1 (DOB 6/18/03)									
Date	Calcium (mg/dl)	Albumin	Calcium corrected for albumin	Phosphate	Alk phos	Ur NTX	25(OH)D	IPTH	Cr
8/24/07	9.8	4.7	9.3		143	148	69		0.5
8/29/06						98			
3/10/06						325			
2/28/06	9.9			5.7	218			25	0.6
12/19/05							49	8	
11/22/05	10.0				233	266	40		

DOB = date of birth.

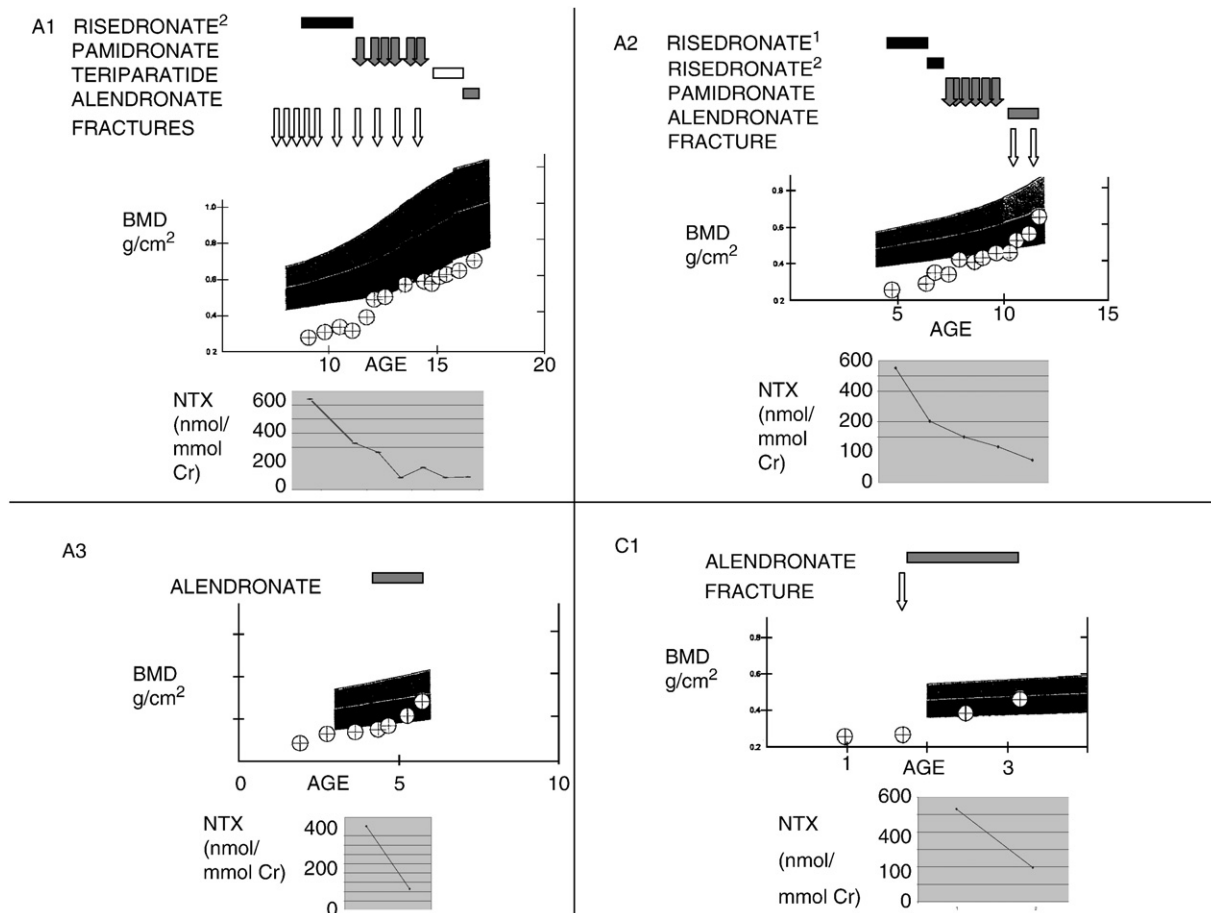
<sup>a</sup> Other tests on this date: 1,25-dihydroxyvitamin D 29 pg/ml (normal 18–62).

<sup>b</sup> Other tests on this date: testosterone 231, IGF-1-244 (both normal).

<sup>c</sup> Normal range for Urine NTX: males – Tanner I 55–508, females – Tanner I 6–662 nM BCE/mM creatinine. A1 was Tanner I at baseline in 1/00 (Mora et al., 1998, Calcif Tissue Int, 63(5):369–74).

other day. After 4 months to confirm lack of hypercalcemia, the dose was increased to 20 mg daily for the next 11 months. After 15 months of teriparatide, the Z-score did not change significantly from –2.5 to –2.6,

so it was stopped. After discontinuing teriparatide, alendronate 1 mg/kg/day (70 mg 4 times a week) was started and after 6 months, his Z-score improved from –2.6 to –2.4 and his urine N-telopeptide



**Fig. 2.** Bone mineral density, treatment, fractures and urine N-telopeptide (NTX) for patients A1, A2, A3 and C1. Risedronate<sup>1</sup> 35 mg per week, Risedronate<sup>2</sup> 25 mg twice a week.

decreased. In A1, his initial spine Z-score improved from  $-6.4$  (age 8 years) to  $-2.4$  (age 16 years). In A2, after 1.5 years of pamidronate, he was changed to oral alendronate 1 mg/kg/day [26]; his initial Z-score of  $-4.7$  (age 4 years) improved to  $-0.4$  (age 11.5 years).

Patient A3 was started on oral alendronate 1 mg/kg/day at age 4 years and after 1.5 years, her Z-score improved from an estimated  $-2.9$  (age 2 years) to  $-0.5$  (age 5.5 years). She has had no fractures. Patient C1 was started on the same alendronate regimen at age 2 8/12 years after a femur fracture. After 17 months of treatment, his Z-score improved from an estimated  $-4.2$  (age 2 8/12 years) to  $-0.3$  (age 4 years) and he had no further fractures. In family B, bisphosphonate therapy and follow up DXA were declined.

## Discussion

We report 9 new cases of osteoporosis-pseudoglioma (OPPG) syndrome in three related nuclear families. All OPPG patients had a severe ocular phenotype, characterized by congenital blindness, regardless of genotype. By contrast, the bone phenotype was more severe in those with a homozygous W425X genotype than in W425X/T409A compound heterozygotes. The two novel mutations in *LRP5* described here were both in the second beta-propeller structure. Four of the six adult obligate heterozygotes studied (parents of affected individuals) had mild osteopenia or osteoporosis, as has been shown in other families [4,16], and another one was normal. Improvement was seen in bone mineral density Z-score from treatment with bisphosphonates in the four treated OPPG patients (from baseline to most recent: A1  $-6.4$  to  $-2.4$ , A2  $-4.7$  to  $-0.4$ , A3  $-2.9$  to  $-0.5$ , C2  $-4.2$  to  $-0.3$ ).

The clinical features described in our OPPG patients A1–3 and C1–2 were similar to those described previously, with congenital blindness,

severe osteoporosis, short stature (in 2/9) and fractures occurring in early childhood [2]. Our patient A1 had the most severe bone disease with multiple fractures and bone deformity leading to wheelchair confinement since age 7. Although he also had propionic academia, this condition has not been associated with bony fragility [27]. As found in previous reports [2,16], most of our obligate heterozygotes had reduced bone mineral density, but none had eye pathology.

The homozygous W425X mutation predicts a stop codon and a severely truncated form of the *LRP5* protein containing 425 instead of the normal 1615 amino acids, likely resulting in complete absence of functional protein. The clinical result was classic OPPG syndrome in the 4 affected children homozygous for this genotype, with mean spine Z-scores of  $-4.6$ , similar to the reported mean in OPPG of  $-4.7 \pm 0.9$  [4]. The homozygous W425X phenotype was similar to a previously reported case of OPPG caused by a homozygous R428X mutation [4]. It is noteworthy that we found a milder bone phenotype in compound heterozygotes (cases B1–4, W425X/T409A) consisting of normal stature and a mean Z-score of  $-1.9$  vs  $-4.6$  for W425X homozygotes ( $p=0.02$ ). These compound heterozygotes, however, had similarly severe blindness to W425X homozygotes.

We are unaware of any previous reports of a mild bone phenotype with a compound heterozygous genotype that combines a stop codon and a missense mutation. We speculate that the missense T409A mutation might result in partially functional *LRP5*, adequate to stimulate slightly reduced bone production through the Wnt pathway, yet inadequate for normal eye development. *LRP5* expression constructs studies [2] designed to assess Wnt signal transduction have demonstrated variable  $\beta$ -catenin-mediated signal transduction. Interestingly, mutant constructs G404R and D434N that flank T409A and R425X had  $<50\%$  of wild type activity, while the majority of other

constructs were unable to transduce Wnt1 or Wnt10b signal. Despite this *in vitro* result demonstrating some Wnt signal transduction capability, the clinical result of the construct mutations in patients was OPPG. The function of LRP5 in eye development is complex and involves varied mechanisms, including direct stabilization of  $\beta$ -catenin (through Axin binding) [42] and transduction of Norrin signaling [2]. We speculate that our T409A mutation, as found in other OPPG missense mutations [2], resulted in reduced Norrin transduction, disrupting eye development but resulted in enough Wnt signaling to disrupt bone formation less severely. However, the mechanism of mutational effect in the compound heterozygotes must await functional studies of the mutant proteins.

Bone turnover markers, urine N-telopeptide (NTX) and alkaline phosphatase were normal for age in our OPPG patients. In the two previous reports of treatment in OPPG, one did not report markers of bone resorption [14]; in the other, one of three patients had minimally elevated urinary deoxypyridinoline [13]. We also found that vitamin D deficiency [25(OH)D < 20] and insufficiency [25(OH)D < 30 ng/ml] were common in our OPPG patients. Because of the importance of vitamin D to bone health [29], we recommend following 25(OH)D levels in OPPG patients.

The most robust treatment responses were seen in the youngest patients treated with alendronate (1 mg/kg/day). Possible explanations include a reduced response with age or more likely a better response with alendronate because it is a more potent antiresorptive agent than pamidronate and risedronate used previously. In our patient with the most severe osteoporosis and the oldest of those treated, OPPG A1, bisphosphonates appeared to lose efficacy over time. Because of ongoing fractures, he was given a trial of teriparatide, synthetic parathyroid hormone (PTH), the only anabolic bone agent available for treatment of osteoporosis [30–32]. PTH treatment is known to stimulate the Wnt signaling pathway, by decreasing DKK-1 [33] and sclerostin [34], both of which bind to LRP5 and decrease Wnt signaling. In studies on Lrp5 knock out mice, PTH treatment increased bone formation similarly to that seen in wild type mice [28], with the predominant increase seen in cortical bone [30,35]. Therefore, studies in mice have predicted a beneficial response to PTH in human OPPG. However, the human response to PTH is somewhat different from that in mice in that the BMD increase is seen in trabecular bone in humans [31] and in cortical bone in mice [28]. This raises the possibility that the mouse response to PTH might not be a perfect predictor of the human response.

Our OPPG patient treated with PTH (teriparatide) did not appear to have a definitive response to it in that his Z-score did not improve after 15 months of treatment. This could be explained by his prior longterm treatment with bisphosphonates, which are known to blunt the effect of teriparatide [36]. The 6 month gap between bisphosphonate and teriparatide treatment may have been inadequate to reduce the bisphosphonate effect of suppressing bone turnover. In this patient, we observed what appeared to be a paradoxical decrease in urine NTX (bone resorption marker) while on teriparatide, opposite to the increase in NTX expected [24,31]. We do not have an explanation for this. After discontinuing teriparatide, this patient was started on alendronate, with subsequent improvement in Z-score and further reduction in NTX. A controlled trial of teriparatide as the first line treatment in humans with OPPG could help to determine whether this drug is effective in this condition.

OPPG is a rare genetic syndrome. However, LRP5 has been shown to be important in the attainment of peak bone mass and skeletal response to loading [37] and to be a determinant for normal bone density [38,39]. LRP5 mutations have been reported in several cases of idiopathic juvenile osteoporosis [40]. In addition, common polymorphisms of LRP5 have been associated with variations in BMD, fracture risk and height in youth and old age ([41] for review). Therefore, learning more about OPPG could potentially help our understanding of the pathophysiology of common osteoporosis.

In summary, we report 9 new cases of OPPG and describe a milder bone phenotype in individuals who were W425X/T409A compound

heterozygotes than in W425X homozygotes. We report a beneficial response to bisphosphonates in four patients and a lack of definitive response to teriparatide in one. We recommend starting treatment with bisphosphonates in OPPG patients within the first few years of life.

## References

- [1] Saraux H, Frezal J, Foy C, Aron JJ, Hayat B, Lamy M. Pseudo-gliome et fragilité osseuse héréditaire à transmission autosomale récessive. *Ann Oculair (Paris)* 1967;200:1241–52.
- [2] Ai M, Heeger S, Bartels CF, Schelling DK, the Osteoporosis-Pseudoglioma Collaborative Group. Clinical and molecular findings in osteoporosis-pseudoglioma syndrome. *Am J Hum Genet* 2005;77:741–53.
- [3] Steichen-Gersdorf E, Gassner I, Unsinn K, Sperl W. Persistent hyperplastic primary vitreous in a family with osteoporosis-pseudoglioma syndrome. *Clin Dystrophol Apr* 1997;6(2):171–6.
- [4] Gong Y, Slee RB, Fukai N, et al. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. *Cell* 2001;107(4):513–23.
- [5] Cheung WM, Jin LY, Smith DK, Cheung PT, Swan EY, Low L, et al. A family with osteoporosis pseudoglioma syndrome due to compound heterozygosity of two novel mutations in the LRP5 gene. *Bone* 2006;39(3):470–6.
- [6] Swoboda W, Grill F. The osteoporosis pseudoglioma syndrome. Update and report on two affected siblings. *Pediatr Radiol* 1988;18(5):399–404.
- [7] Teebi AS, al-Awadi SA, marafie MJ, Gushnaq RA, Satyanath S. Osteoporosis-pseudoglioma syndrome with congenital heart disease: a new association. *J Med Genet* Jan 1988;25(1):32–6.
- [8] Somer H, Palotie A, Somer M, Hiokka V, Peltonen L. Osteoporosis-pseudoglioma syndrome: clinical, morphological and biochemical studies. *J Med Genet* Aug 1988;25(8):543–9.
- [9] McDowell CL, Moore JD. Multiple fractures in a child: the osteoporosis-pseudoglioma syndrome: case report. *J Bone Joint Surg Am* 1992;74(8):1247–9.
- [10] DePaepe A, Leroy JG, Nuytinck L, Meire F, Capoen J. Osteoporosis-pseudoglioma syndrome. *Am J Med Genet* 1993;45(1):30–7.
- [11] Shaharao V, Shah I, Mishra P, Muranjan M, Bharucha B. Osteoporosis pseudoglioma syndrome. *Indian Pediatr* 1999;36(3):313–5.
- [12] Bartsocas CS, Zeis PM, Eliz M, papadatos CJ. Syndrome of osteoporosis with pseudoglioma. *Ann Genet* 1982;25(1):61–2.
- [13] Frontali M, Stomeo C, Dallapiccola B. Osteoporosis-pseudoglioma syndrome: report of three affected sibs and overview. *Am J Med Genet* 1982;22(1):35–47.
- [14] Bayram F, Tanriverdi F, Kurtoglu S, Atabek ME, Kula M, Kaynar L, et al. Effects of 3 years of intravenous pamidronate treatment on bone markers and bone mineral density in a patient with osteoporosis-pseudoglioma syndrome (OPPG). *J Pediatr Endocrinol Metab* 2006;19(3):275–9.
- [15] Zacarin M, Cundy T. Osteoporosis pseudoglioma syndrome: treatment of spinal osteoporosis with intravenous bisphosphonates. *J Pediatr* 2000;137(3):410–5.
- [16] Levasseur R, Lacombe D, de Vernejoul MC. LRP5 mutations in osteoporosis-pseudoglioma syndrome and high-bone-mass disorders. *Joint Bone Spine* 2005;72:207–14.
- [17] Lev D, Binson I, Foldes AJ, Watemberg N, Lerman-Sagie T. Decreased bone density in carriers and patients of an Israeli family with osteoporosis-pseudoglioma syndrome. *Isr Med Assoc J* Jun 2003;5(6):419–21.
- [18] Criswick VG, Schepens CL. Familial exudative vitreo-retinopathy. *Am J Ophthalmol* 1969;68:578–94.
- [19] Jiao X, Ventruito V, Trese MT, Shastry BS, Hejtmanck JF. Autosomal recessive familial exudative vitreoretinopathy is associated with mutations in LRP5. *Am J Hum Genet* 2004;75:878–84.
- [20] Toomes C, Bottomley HM, Jackson RM, Towns KV, Scott S, Mackey DA, et al. Mutations in LRP5 or FZD4 underlie the common familial exudative vitreoretinopathy locus on chromosome 11q. *Am J Hum Genet* 2004;74:721–30.
- [21] Qin M, Hayashi H, Oshima K, Tahira T, Hayashi K, Kondo H. Complexity of the genotype-phenotype correlation in familial exudative vitreoretinopathy with mutations in the LRP5 and/or FZD4 genes. *Hum Mutat* 2005;26(2):104–12.
- [22] Johnson ML, Gong G, Kimberling W, Recker SM, Kimmel DB, Recker RB. Linkage of a gene causing high bone mass to human chromosome 11 (11q12–13). *Am J Hum Genet* 1997;60:1326–32.
- [23] Boyd LM, Mao JM, Belsky J, Mitzner L, Farhi A, Mitnick MA, et al. High bone density due to a mutation in LDL-receptor-related protein 5. *N Engl J Med* 2002;346:1513–21.
- [24] van Wesenbeeck L, Cleiren E, Gram J, Beals RK, Benichou O, Scopelliti D, et al. Six novel missense mutations in the LDL Receptor-related protein 5 (LRP5) gene in different conditions with an increased bone density. *Am J Hum Genet* 2003;72:763–71.
- [25] WHO criteria.
- [26] Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck-Gibis J, Travers R, et al. Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab* 2000;85:1846–50.
- [27] DiMeglio LA, Peacock M. Two-year clinical trial of oral alendronate versus intravenous pamidronate in children with osteogenesis imperfecta. *J Bone Miner Res* 2006;21(1):132–40.
- [28] Desviat LR, Perez B, Perez-Cerda C, Rodriguez-Pombo P, Clavero S, Ugarte M. Propionic academia: mutation update and functional and structural effects of the variant alleles. *Mol Genet Metab* 2004;83:28–37.
- [29] Iwaniec W, Wronski TJ, Liu J, Rivera MF, Arzaga RR, Hansen G, et al. PTH stimulates bone formation in mice deficient in Lrp5. *J Bone Miner Res* 2007;22(3):394–402.

- [29] Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–81.
- [30] Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis with osteoporosis. *Lancet* 1997;350(9077):550–5.
- [31] Bilezikian JP, Rubin MR, Finkelstein JS. Parathyroid hormone as an anabolic therapy for women and men. *J Endocrinol Invest* 2005;28(8 Suppl):41–9.
- [32] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster J-Y, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434–41.
- [33] Kulkarni NH, Halladay DL, Miles RR, Gilbert LM, Frolik CA, Galvin RJS, et al. Effects of parathyroid hormone on Wnt signaling pathway in bone. *J Cell Biochem* 2005;95:1178–90.
- [34] Bellido T, Ali AA, Gubrij I, Plotkin LI, Fu Q, O'Biren CA, et al. Chronic elevation of parathyroid hormone in mice reduces expression of sclerostin by osteocytes: A novel mechanism for hormonal control of osteoblastogenesis. *Endocrinology* 2005;146:4577–83.
- [35] Sawakami K, Robling AG, Ai M, Pitner ND, Liu D, Warden SJ, et al. The Wnt Co-receptor LRP5 is essential for skeletal mechanotransduction but not for the anabolic bone response to parathyroid hormone treatment. *J Biol Chem* 2006;281(33):23698–711.
- [36] Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J Bone Miner Res* 2004;19: 745–51.
- [37] Koller DL, Ichikawa S, Johnson ML, Lai D, Xuei X, Edenberg HJ, et al. Contribution of the LRP5 gene to normal variation in peak bone mineral density in women. *J Bone Miner Res* 2005;20(1):75–80.
- [38] Mizuguchi T, Furuta I, Watanabe Y, Tsukamoto K, Tomita H, Tsujihata M, et al. LRP5, low-density-lipoprotein-receptor-related protein 5, is a determinant for bone mineral density. *J Hum Genet* 2004;49:80–6.
- [39] Koay MA, Woon PY, Zhang Y, Miles LJ, Duncan EL, Ralston SH, et al. Influence of LRP5 polymorphisms on normal variation in BMD. *J Bone Miner Res* 2004;19: 1619–27.
- [40] Hartikka H, Makitie O, Mannikko M, Doria AS, Daneman A, Cole WG, et al. Heterozygous mutations in the LDL receptor-related protein 5 (LRP5) gene are associated with primary osteoporosis in children. *J Bone Miner Res* 2005;20: 783–9.
- [41] Ferrari SL, Deutsch S, Choudhury U, Chevalley T, Bonjour JP, Dermizakis ET, et al. Polymorphisms in the low-density lipoprotein receptor-related protein 5 (LRP5) gene are associated with variation in vertebral bone mass, vertebral bone size and stature in whites. *Am J Hum Genet* 2004;74:866–75.
- [42] Xia C-H, Liu H, Cheung D, Wang M, Cheng C, Du X, et al. A model for familial exudative vitreoretinopathy caused by LRP5 mutations. *Hum Mol Genet* 2008;17 (11):1605–12 (Jun 1).