

## Case Report

# Advances in Clinical Endocrinology and Metabolism

## Suppressible RANK-Ligand Levels in a Patient with Trichorhinophalangeal Syndrome Type II on Denosumab Therapy

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### Abstract

Trichorhinophalangeal Syndrome Type II (TRPS2) is a rare contiguous gene syndrome caused by deletion of *TRPS1* and *EXT1* genes, characterized by facial, hair and skeletal abnormalities. The prevalence of osteoporosis in TRPS, especially in TRPS2, is not well known. *OPG* gene, which is located between *TRPS1* and *EXT1* genes, blocks the Receptor Activator of Nuclear Factor- $\kappa$ B Ligand (RANKL), preventing osteoclast formation. Thus, we hypothesize that patients with loss of the Osteoprotegerin (*OPG*) gene will have osteoporosis in the setting of unopposed RANKL. Denosumab, a human monoclonal antibody against RANKL, may be beneficial in decreasing osteoclast differentiation and bone degradation. We describe now a 25-year-old woman with TRPS2 with osteoporosis and multiple osteochondromas. Gene testing revealed a large deletion on the long arm of chromosome 8, including *TRPS1*, *OPG* and *EXT1* genes. Her osteoporosis was refractory to bisphosphonate therapy; however, after Denosumab administration her bone RANKL levels decreased with marked clinical improvement. She had no adverse effects and no additional fractures after 2 years of therapy. Denosumab may be an effective treatment option in TRPS2-associated osteoporosis.

**Keywords:** Trichorhinophalangeal syndrome, RANK Ligand, Osteoporosis, *OPG* gene

### Introduction

The tricho-rhino-phalangeal syndromes are a series of three autosomal dominant syndromes, classified as type I, II, and III, that share distinctive facial features (large laterally protruding ears, bulbous nose and elongated upper lip), hair abnormalities (fine, sparse, depigmented and slow growing hair) and skeletal abnormalities (short stature, short feet, brachydactyly with ulnar and radial deviation) [1-3]. Type II (TRPS2) or Langer-Giedion syndrome (OMIM 150230), is a rare contiguous gene syndrome caused by the loss of function of *TRPS1* (8q23) and *EXT1* (8q24.13) on the long arm of the chromosome

8 [1]. TRPS2 is distinguished from Types I and III by the presence of multiple osteochondromas (exostoses) due to loss of the *EXT1* gene [4].

Previously reported cases of TRPS2 demonstrate its phenotypic skeletal variations. Hall and Cappuccio et al. reported patients with features of TRPS and multiple cartilaginous exostoses [1,5]. Schinzel et al. [6] reported patients with TRPS2 associated with mild scoliosis and exostoses of cervical spine. In 2014, Macchiaiolo et al. reported a case of TRPS1 with severe osteoporosis, improved after treatment with bisphosphonate [7],

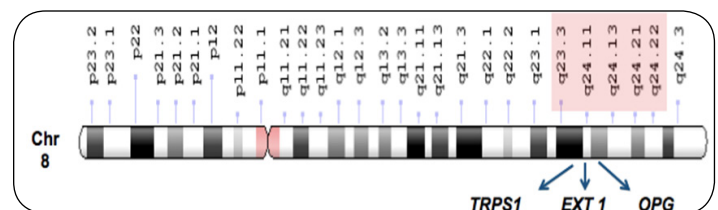
however to our knowledge, no previous cases of TRPS2 with severe osteoporosis have been reported. The exact rate of osteoporosis in TRPS patients is not well known due to the rarity of the disease. Mass et al. [8] described 103 patients with different types of TRPS, reporting a 25% prevalence of osteopenia in this cohort. Of the 8 patients with TRPS2 and radiographic evaluation, 5 of them had osteopenia. Two out of 10 TRPS2 patients had 1 fracture reported. It is likely the bony phenotype is dependent on the nature of the gene deletion. We hypothesize that patients with loss of the osteoprotegerin (*OPG*) gene, residing on the same arm of chromosome 8 (8q24.12), will have osteoporosis. *OPG* gene blocks receptor activator of nuclear factor- $\kappa$ B ligand (RANKL), preventing osteoclast formation [9]. Thus, the deletion of the *OPG* gene leads to unopposed RANKL and severe bone resorption. Currently, only symptomatic treatment is available for patients with TRPS2 and osteoporosis, highlighting the need for novel pharmacotherapies to improve quality of life and ambulation. Given the molecular mechanism of bone resorption, it can be postulated that *OPG* deletion with resultant elevated RANKL levels could have improved clinical sequelae with suppression of these RANKL levels. Denosumab is a human monoclonal antibody against RANKL, preventing the binding of RANKL to its cognate receptor [10,11]. This results in decreased osteoclast differentiation and bone degradation, with subsequent increase in cortical and trabecular bone mass. Peak onset is about 10 days with a half-life of 25-28 days. A recent meta-analysis revealed that Denosumab is a safe, well tolerated treatment for osteoporosis [12]. Therefore, it is possible that in a patient with TRPS2 and *OPG* deletion, targeted Denosumab treatment may suppress RANKL levels and result in improved clinical outcomes.

We report a patient with TRPS2 with deletion of the *OPG* gene resulting in elevated RANKL levels, and subsequent osteoporosis, who demonstrated suppressible RANKL levels and marked clinical improvement on Denosumab treatment.

## Case Presentation

Our patient is now a 25-year-old female with TRPS2 associated with osteoporosis and multiple osteochondromas. She had a history of multiple fractures in utero as well as after birth with a lifetime fracture rate of about 3 per year. Her fractures led to significant pain with ambulation and limited daily activity. She had severe physical discomfort preventing her from participating in school sports or leaving her house independently. Gene testing revealed a large deletion on the long arm

of chromosome 8 [del (8q23.3-q24.22)], expanding the *TRPS1*, *EXT 1*, and *OPG* gene regions (Figure 1). She failed 2 years of bisphosphonate therapy from 10-12 years of age with continued fractures. Her exam was significant for short stature, dysmorphic facies and bony abnormalities of her upper extremities. Initial CT bone densitometry showed a mean cancellous vertebral bone density of 183 mg/cm<sup>2</sup> (normal 285  $\pm$  45 mg/cm<sup>2</sup>). Free-soluble serum RANKL was measured before treatment, as well as at 6 and 18 months on Denosumab therapy using a sandwich ELISA (Biomedica Immunoassays BI 20462). Her initial RANKL level was elevated at 0.283 pmol/L (previously reported median RANKL level in healthy adult women was 0.18 pmol/L [13]). She was started on Denosumab at 60 mg per dose every 6 months for a total of 4 doses [14]. Her RANKL was undetectable two weeks after her second dose. Bone resorption markers decreased with baseline urine N-telopeptide of 27 nmol BCE/mmol creatinine and serum C-telopeptide of 336 pg/mL, compared to 14 nmol BCE/mmol creatinine and 103 pg/mL respectively after 6 months on Denosumab (Table 1).



**Figure 1:** Location of *TRPS1*, *EXT1* and *OPG* genes on the chromosome 8.

Just prior to her dose at 18 months, RANKL level as well as her bone resorption markers rose again (Table 1). Dual-energy X-ray Absorptiometry (DXA) scans were obtained at baseline and again 6 months on treatment. Her baseline DXA showed a lumbar spine T-score of -2.7 and hip T-score of -2.9. DXA scan 1 year on treatment showed 4.7% bone density increase in her lumbar spine compared to her prior study as well as 3.9% increase in her hip (Table 2). DXA scan 2 years off treatment showed overall decline in both lumbar and hip bone density. She had no adverse effects. Following 2 years of therapy, she had no additional fractures with significant improvement in quality of life. She now lives independently and can participate in sports and social activities. Per self-report her quality of life has improved significantly. She continues to take 1000 IU of cholecalciferol and 500 mg of calcium citrate daily.

## Discussion

To our knowledge, this is the first reported case of a

**Table 1:** Bone markers during treatment course .

	Reference range	Baseline	6 months on Denosumab	18 months on Denosumab
			(2 weeks after the 2nd dose)	(Prior to the 3rd dose)
RANKL (pmol/L)	*0.18	0.283	Undetectable	0.21
Urine N-Telopeptide (nmol BCE/mmol creatinine)	Apr-64	27	14	37
Serum C-Telopeptide (pg/mL)	64-640	336	103	284

\*Mean adult women (n = 154) reported by Kerschan-Schindl et al. [13]

**Table 2:** DXA evaluation over time.

DEXA T-score	Baseline	6 months on Denosumab	1 year on Denosumab	2 years on Denosumab	2 years Post Treatment
Lumbar Spine (L2-L4)	-2.7	-2.6	-2.3	-2.1	-2.6
Left Femoral Neck	-1.5	-1.9	-1.7	-2.4	-2.1
Left Total Hip	-2.9	-3	-2.9	---	-3.4

patient with TRPS2 with severe osteoporosis refractory to bisphosphonate therapy, who had profound clinical and biochemical improvement on Denosumab. Unfortunately, there are still no established diagnostic criteria or standard treatment for patients with TRPS. Symptomatic treatment includes vitamin D and calcium supplementation, physical therapy and surgical removal of exostoses. However, as demonstrated in our patient, these interventions often do not improve quality of life, ambulation or fracture rate and therefore further investigation for targeted therapy is required in this patient population.

Our case highlights that TRPS2 with large gene deletion extending to the OPG gene region can be associated with debilitating osteoporosis, resulting in decreased ambulation and poor quality of life. Deletion of the OPG gene led to elevated RANKL levels in our patient which was the likely etiology of her severe bone disease. We demonstrated the ability to suppress RANKL levels with targeted therapy with Denosumab. Furthermore, not only was the treatment associated with biochemical improvement, but she also had profound clinical improvement with no further fractures. To date, those improvements continue, suggesting that Denosumab may be a beneficial treatment for patients with TRPS2 and osteoporosis secondary to deletion of the OPG gene. Her RANKL and other bone resorption makers rose just prior to her 18-month dose, suggesting the possible need for on-going treatment in these patients. In addition, she had worsening DXA off treatment, further supporting need for continued therapy.

There is no optimal treatment duration defined for Denosumab at this time. In evaluating Denosumab use in women with osteoporosis compared to placebo, there was no significant difference in the overall incidence of cancer, cardiovascular events, or adverse and serious adverse events of infection [15]. However, since this article there have been reports of rebound-associated vertebral fractures, hypocalcemia following injections, and hypercalcemia in the setting of severe bone resorption following discontinuation of therapy [16-19]. Our patient is only two-years post-Denosumab therapy with on-going close follow-up. Long-term risks and benefits should be further discussed with the family prior to continuing treatment. Additional investigation is required to determine the appropriate dosing interval, length of treatment and long-term effects of Denosumab therapy in this patient population.

### Conclusion

Elevated RANKL levels were seen in our patient with TRPS2 with large chromosome deletion including *OPG*. Following Denosumab therapy, her RANKL level decreased significantly with dramatic clinical improvement, suggesting Denosumab may be an effective treatment option in TRPS2-associated osteoporosis.

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