P1-P036

Novel *LRP5* loss-of-function mutation causes Osteoporosis-Pseudoglioma Syndrome

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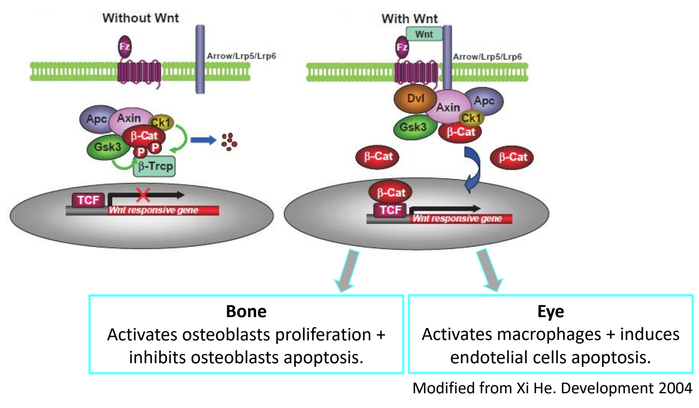
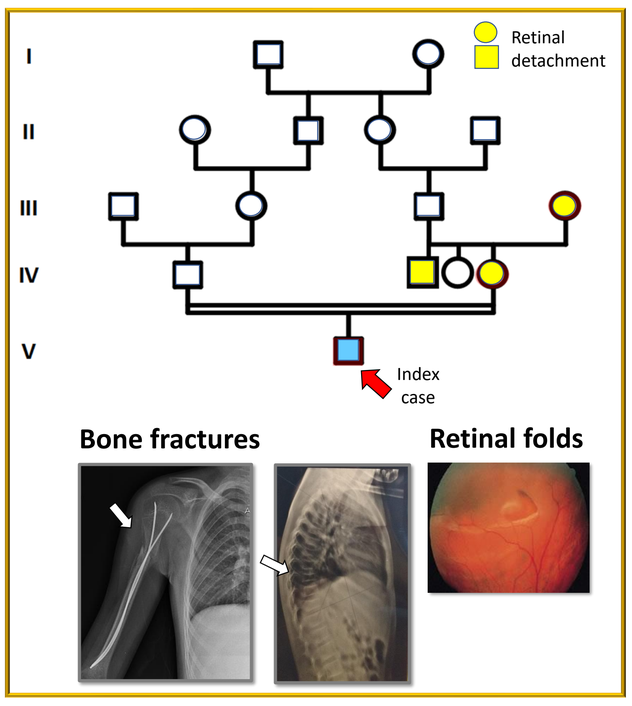
Background

- ✓ Osteoporosis is a complex disorder, characterised by low bone mass and microarchitectural bone deterioration, influenced by both environmental and genetic factors.
- ✓ Primary osteoporosis in children is a rare early onset disorder with high morbidity and mortality.
- ✓ The treatment currently available is symptomatic, with a variable response from child to child.
- ✓ The knowledge of the underlying pathophysiological mechanisms enables the development of new therapies.
- ✓ Wnt signaling pathway has been shown to be involved in the regulation of bone remodeling.
- ✓ LRP5 is a single-span transmembrane protein required for Wnt/βcatenin signaling pathway, relevant for fetal and postnatal osteogenesis.



Modified from Xi He. Development 2004

Case Report

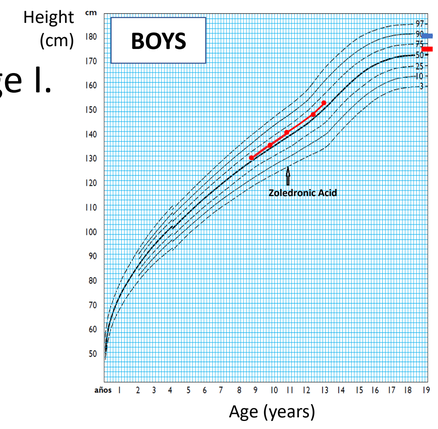


- Native Argentinean boy born from a consanguineous family.
- Delivered at term, birth weight 2900 g (-0.95 SDS), birth length 50.5 cm (0.06 SDS), microcephaly (-1.93 SDS).
- **Bilateral congenital retinal folds** caused him progressive irreversible vision loss and acquired microphthalmy.
- Since the age of 5 y he suffered four low trauma **long bone fractures** and two **vertebral fractures**.
- **Physical examination** when referred at 8.6 y:

  Weight 27kg (50th Pc), height 129 cm (50th Pc), normal growth velocity, Tanner stage I.

  Microcephaly, bulky vision, white sclera, normal teeth, absence of hyperlaxity, slight kyphosis and adequate neurodevelopment were observed.
- **Bone metabolism markers fell within normal range** calcium 10.3 mg/dL; phosphate 4.9 mg/dL; magnesium 1.9 mg/dL; ALP 195 IU/L; bone ALP 61.5 ng/L; PTH 54 pg/ml; 25OH vitamin D 24 ng/ml; CTX 1231 pg/ml; urine Calcium/Creatinine ratio 0.2; PTR 91%.

Known secondary causes of osteoporosis were ruled out.

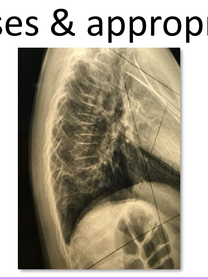


- **Dual-energy X-ray absorptiometry (DXA)** Total body -3.9 SDS.
- **Family History**: No history of fractures, parents have normal BMD. Retinal detachment in maternal line.

DIAGNOSIS: Primary Osteoporosis + congenital retinal folds

- **Treatment:** Zoledronic acid 0.0125 mg/kg/dose every six months for 2 years, then 0.05 mg/kg/dose once/year, exercises & appropriate nutrition
- **Follow-up** after 3 years:
  - ✓ BMD has improved 2.1 SDS
  - ✓ Affected vertebras slightly reshaped
  - ✓ No new fractures
  - ✓ Started puberty at 11.2 years

DXA (Lunar) L2-L4	Basal	1st year treatment	2nd year treatment	3rd year treatment
g/m2	0.370	0.495	0.522	0.570
Z-Score (SDS)	-3.9	-2.3	-2.2	-1.8

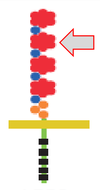


Study strategy & results

1. **SNP array (850k, Illumina)** → Loss of heterozygosity in 11p15.1-11q13.3 → Contains **low-density lipoprotein receptor-related protein-5 gene** *LRP5* is expressed in fetal ocular macrophages & osteoblasts, thus, our first candidate gene.
2. **Skeletal dysplasia NGS panel** SkeletalSeq.V7.

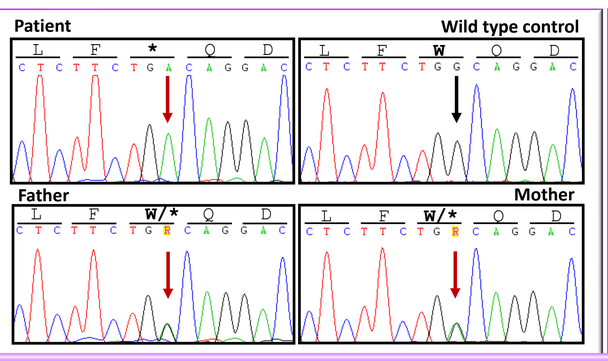
LRP-5
- ✓1615 aminoacid protein
- ✓Wnt ligand

Trp 47 located in the 2nd domain of the extracellular region of the receptor.



Novel homozygous nonsense variant
NM_002335.3 (*LRP5*):c.441G>A, (p.Trp147Ter)

Both parents are heterozygous for this variant.



Classified as Pathogenic according to the **ACMG** guidelines:
- ✓**PVS1** Null variant in a gene where LOF is a known mechanism of disease (OPPG)
- ✓**PM1** Located in 'Beta-propeller 1', a region in LRP-5 with 18 pathogenic out of 22 classified variants
- ✓**PM2** Absent from available databases (GnomAD).
- ✓**PP3** Predicted as pathogenic by different bioinformatic tools (CADD, DANN, GERP, Mutation taster).

Osteoporosis - Pseudoglioma Syndrome (OPPG)

Conclusions

- ✓ We identified a novel homozygous LRP5 loss-of-function mutation, which causes autosomal recessive Osteoporosis-pseudoglioma syndrome (OPPG, MIM 259770).
- ✓ Scarce information exists regarding the treatment of OPPG in children. Thus, understanding the molecular mechanisms underlying primary osteoporosis is important for improving screening for co-morbidities, genetic counselling and the development of novel therapies.

- ✓ Poster number: **P1-P036**
- ✓ Topic: **Bone, growth plate and mineral metabolism 2**
- ✓ First author: **Débora Braslavsky**

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