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, PMD.
- BMD metabolism propeller 1', a region in LRP.
- Bilateral congenital retinal folds caused him progressive irreversible vision loss and acquired microphthalmal.
- 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 g/L; PTH 34 pg/ml; 25OH vitamin D 24 ng/ml; CTX 1231 pg/ml; urine Calcium/Creatinine ratio 0.2, PTE 93%.
- 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.

### Case Report

- **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 vertebrae slightly reshaped
  - No new fractures
  - Started puberty at 11.2 years

### DIAGNOSIS: Primary Osteoporosis + congenital retinal folds

- 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).

### Study strategy & results

1. **SNP array (RSOH, Illumina)**
   - Loss of heterozygosity in 11p15.1-11q13.3

2. **Skeletal dysplasia NGS panel**
   - **Novel homozygous nonsense variant**
     - NM_002335.3 (LRP5)-c.-441G>A,
     - (p.Trp147Ter)
     - Both parents are heterozygous for this variant.
     - Contains low-density lipoprotein receptor-related protein-5 gene LRP5 is expressed in fetal ocular macrophages & osteoblasts, thus, our first candidate gene.

### 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 OPGP 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.