Loss of functional Osteoprotegerin: more than a skeletal Problem

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Background

Juvenile Pagets disease (JPD) is an ultra-rare, debilitating bone disease, stemming from unopposed RANKL action due to loss of functional osteoprotegerin (OPG).
JPD-1 is caused by recessive mutations in TNFRSF11B. A genotype-phenotype correlation spanning from mild to very severe forms is described. It is unclear whether heterozygous mutations carriers are also affected.
Objective and hypotheses: To describe the complexity of the human phenotype of OPG deficiency in more detail and to investigate heterozygous mutation carriers for clinical signs of JPD.

Patients and Methods

Three children with JPD-1 from families of Turkish, German and Pakistani descent and 18 family members (13 heterozygous) were evaluated for signs of JPD.

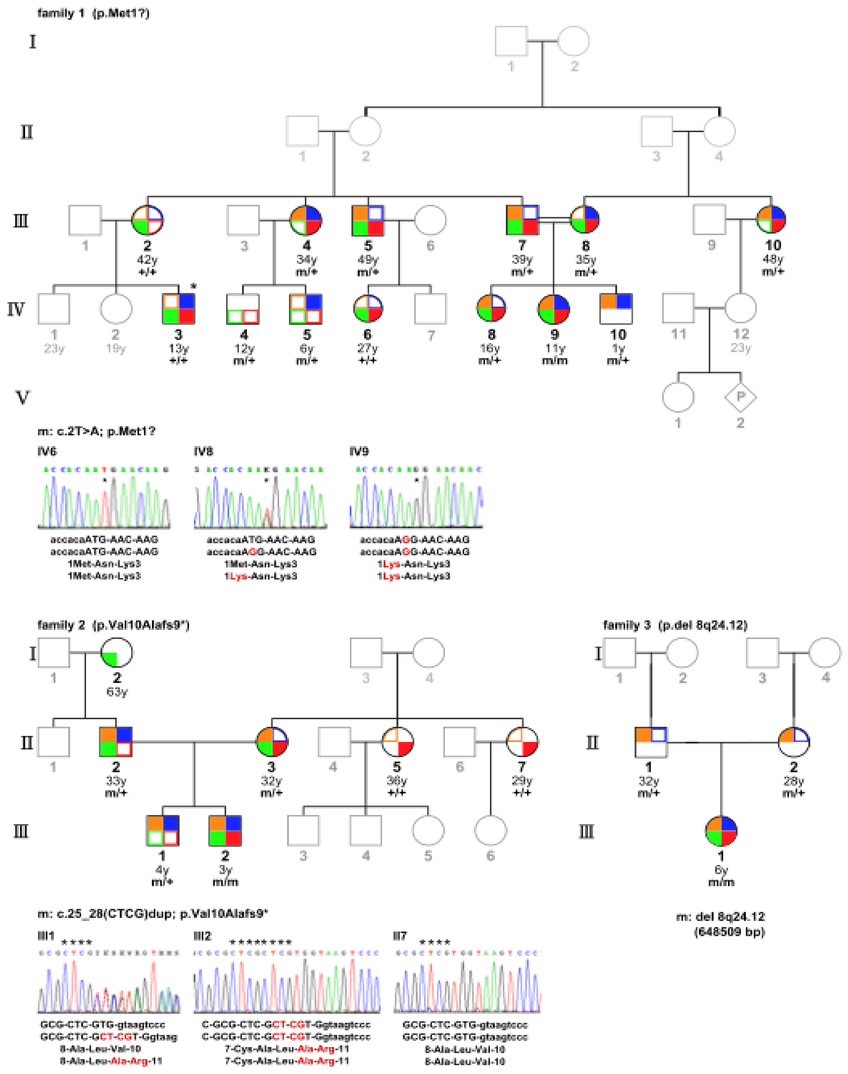

Figure 1: Pedigree of families: presence of bone pain (red), elevated TRAP 5b levels (blue), diminished OPG levels (brown) and osteopenia (green) are indicated by closed symbols.

A new disease-causing 4 bp-duplication: c.[25-28dup];[25-28dup] in exon 1 was detected in the German patient and a homozygous microdeletion including TNFRFSF11B in the Pakistani patient.

Results

Skeletal abnormalities in the affected children include bowing deformities and fractures, contractures, short stature and skull involvement (Chiari 1 Malformation). Two of the patients were found to be **growth hormone deficient** in 2 stimulation tests. However, treatment with hGH resulted in unsatisfactory growth in patient 1. (Figure 2)

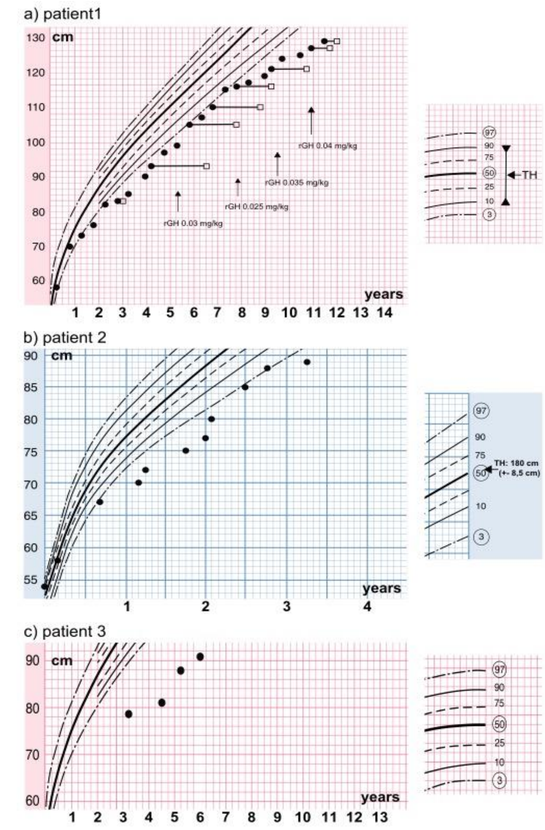

Figure 2: Growth charts of the 3 patients with JPD-1

Complex malformation of the inner ear and the vestibular structures resulted in early deafness in all three patients.

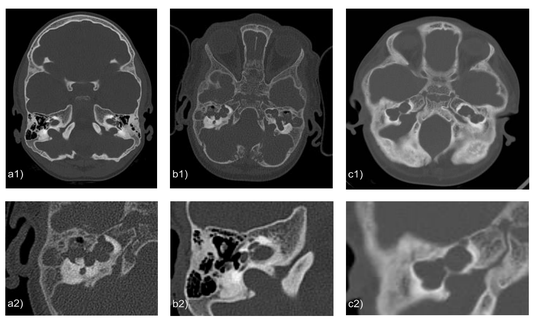

Figure 3: CT-scans inner ear

Heterozygous family members displayed low osteoprotegerin (OPG) and elevated RANKL levels (Figure 4). Elevated bone turnover markers (7) and osteopenia (6), bone pain (8), short stature (1), vision impairment (2) and hearing impairment (1) were also present.

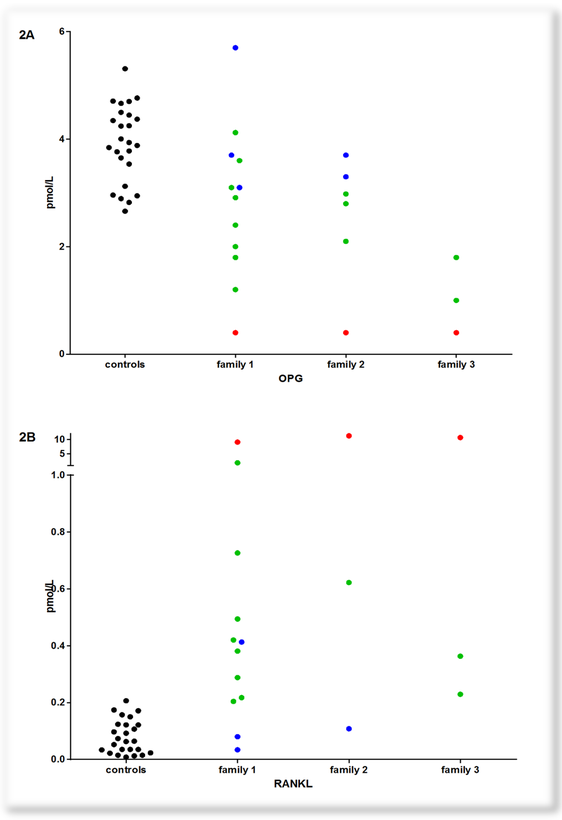

Figure 4: OPG and RANKL plasma levels in healthy controls (black), patients with JPD (red) heterozygous (green) and unaffected (blue) family members.

Conclusion

- JPD-1 is a complex disease affecting multiple organ systems. Growth hormone deficiency, Chiari Malformation and inner ear malformations are extra skeletal manifestations.
- Diminished osteoprotegerin levels are present in heterozygous family members and may result in osteopenia and bone pain.
- Diagnostic and therapeutic measures should aim to address the complex phenotype.

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