RANKL. All SNPs with genotyping rate <98%, with frequency of the minor allele <1% and those that were not in Hardy-Weinberg equilibrium, were excluded. In addition, among the SNPs in linkage disequilibrium, a representative one was chosen, so that only 159 were finally studied. The intensity of treatment, the activity of the disease measured by the DAS28 and HUPI indices, as well as having achieved at least low activity after 2 years of follow-up were chosen as surrogate severity variables. The association of each of the SNPs with these variables was analyzed by linear regression, and ordered logistic regression according to the variable, and adjusted for potentially confusing variables, such as age, sex and presence of anti-cyclic citrullinated peptide antibodies. We selected those SNPs that were consistently associated with ≥ 3 surrogate severity variables, and then, the relationship of the selected SNPs with BMD of the forearm, lumbar spine and hip (Hologic-4500 QDR) was analyzed by means of linear regression adjusted for age and sex.

Results: As shown in the attached table, 11 SNPs were associated with the severity of the disease; 7 of them were also associated with BMD, although only 3 confirmed the previously described relationship between severity of disease and BMD.

SNP	GENE	MOLECULE	DISEASE ACTIVITY	BMD
rs4355801	LOC441377/ TNFRSF11B	OPG	Decrease	No relationship
rs3134058	TNFRSF11B	OPG	Increase	No relationship
rs10505346	TNFRSF11B	OPG	Increase	No relationship
rs6469804	TNFRSF11B/ COLLECT10	OPG	Decrease	No relationship
rs1805034	TNFRSF11A	RANK	Decrease	Decrease
rs599323	TNFRSF11A/ZCCHC2	RANK	Increase	Increase
rs386283	AKAP11/TNFSF11	RANK-L	Increase	Increase
rs1324004	AKAP11/TNFSF11	RANK-L	Decrease	Increase
rs111900837	AKAP11/TNFSF11	RANK-L	Increase	Decrease
rs7142875	AKAP11/TNFSF11	RANK-L	Increase	Increase
rs7557277	AKAP11/TNFSF11	RANK-L	Increase	Decrease

Conclusion: This preliminary study highlights the relationship between gene variants of molecules involved in bone remodeling and the severity of early-onset arthritis. However, more studies are needed to confirm this relationship and validate it in other populations. This would confirm the involvement of these gene variants in disease activity and bone mass variation.

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EXON 5 DUPLICATION IN ALPL GENE AS THE GENETIC CAUSE OF HYPOPHOSPHATASIA IN A 3 YEAR OLD GIRL

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Background: Hypophosphatasia (HPP) (OMIM 146300, 241510, 241500) is an inborn error of metabolism caused by pathogenic variants in the gene *ALPL* that codifies for the tissue non-specific alkaline phosphatase (¹). The disease presents with different degrees of severity, from perinatal forms to mild adult phenotypes, including odontohypophosphatasia where only dental complications are described. Until now, more than 380 variants are described to cause HPP, and only 2,9% are large deletions or duplications (http://www.sesep.uvsg.fr/03_hypo_mutations.php).

Objectives: Identify the genetic cause of the disease in the girl with an infantile HPP.

Methods: The patient is a female child born by cesarean at week 37 of gestation. The child required reanimation. Weight, length and cranial perimeter were below percentile 10th (1735g, 42 cm, 31,5 cm respectively). She presented and obstetric femur fracture and normal to low alkaline phosphatase (AF) activity (158 U/L (reference 142-335 U/L)). After fracture, a second determination of AF (127U/L) and pyridoxal-5'-phosphate (PLP) concentration (240,41 mgc/L, reference 6,4-23) were measured. Skeletal interrogation revealed low bone mineralization, tongues of radiofluency in long bones and narrow ribs. A clinical diagnose of hypophosphatasia was done. At the three year-old revision she still presents weight and length below percentile 15th, a mild cardiac problem but had no fractures since birth. She presents lung malformation, and cannot eat solid food. She still has low AF activity (154 U/L) and high PLP (69,13 µg/L; references 150-350 U/L and 3,6-18 µg/L respectively). She is on school but has language delay. Genetic analysis: DNA was extracted from peripheral blood of patient and her mother. From patient's sample we performed Sanger sequencing of exons 1 to 12, CGH analysis using a customized whole genome CGH 4x44k Agilent array enriched in probes for *ALPL* gene (130 probes) and qPCR of exons 2 to 12.

Results: The study of copy number variants of *ALPL* gene by qPCR revealed a duplication in exon 5 in the patient and her mother.

Conclusion: Although gross deletions and duplications are a rare phenomenon in HPP, here we present a case of a 3 year old child and her mother that present a single exon duplication as a probable cause of the disease. Actually, the mother is under clinical evaluation. Part of the active site is codified in exon 5, suggesting that a duplication might alter the correct structure and/or function of the protein. So, including the screening of copy number variants during the genetic screening is important to reach the correct diagnosis of HPP.

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