First report in Argentina of a pathogenic DMP1 variant associated with autosomal recessive hypophosphatemic rickets

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ABSTRACT

Hereditary hypophosphatemic rickets is a genetic condition associated with impaired bone mineralization caused by phosphate deficiency. It results in skeletal deformity and growth retardation in early childhood. Different inheritance patterns have been described according to the locus involved. Given the phenotypic overlapping and the difficulty in analyzing reduced genealogies, molecular studies are important to establish the genetic cause and implement a family-centered approach. The autosomal recessive form of hypophosphatemic rickets (ARHR, OMIM 241520) is an extremely rare condition reported in families of European and Middle Eastern descent. Loss-of-function mutations in the DMP1 (dentin matrix acidic phosphoprotein 1) gene are associated with hereditary hypophosphatemic rickets type 1. In this article, we describe the first report of an Argentine family with hereditary hypophosphatemic rickets due to a mutation in the DMP1 gene.

Key words: hypophosphatemic rickets, DMP1.
INTRODUCTION

Rickets is a disease of growing bone seen in children and adolescents due to deficiency in calcium, phosphate and/or vitamin D, leading to inadequate mineralization of osteoid tissue in the growth plate and bone matrix. Although nutritional rickets remains a significant health problem in the world, the identification of hereditary forms of rickets has increased with the use of technology. Genetic conditions include vitamin D-dependent rickets and hereditary hypophosphatemic rickets (HHR).2,3

HHR induces skeletal deformity and growth retardation. Patients have lower limb deformities and dental defects. Some adult patients develop enthesopathy with calcification of tendons and ligaments which may involve the spinal ligaments with loss of trunk flexion and extension movements, neck rotation, and bone marrow compression.

HHR-associated genes are involved in the maintenance of adequate phosphate balance through the direct or indirect regulation of the FGF23 protein (encoded by the FGF23 gene). This protein generally inhibits renal reabsorption of phosphate. Different inheritance forms are described according to the locus involved.

X-linked hypophosphatemic rickets (XLHR, OMIM 307800) is the most common hereditary form. It has an estimated incidence of 1 in 20 000 live births and a prevalence of 1.7 per 100 000.2–4 It is associated with mutations in the PHEX gene.

The other hereditary forms of rickets have been described in few families and their prevalence has not been established.2,4

Autosomal recessive hypophosphatemic rickets (ARHR) is associated with mutations in the DMP1 gene (MIM 600980) and ENPP1 gene (MIM 173335). The first publications of ARHR were made in the 70s.3,5,6 In 2006, Lorenz-Depiereux et al.,7 described what is now known as autosomal recessive hypophosphatemic rickets type 1 associated with mutations in DMP1 (ARHR1, OMIM 241520).

The dentin matrix acidic phosphoprotein 1 (DMP1) gene encodes for DMP1 protein, an acidic phosphoprotein of the extracellular matrix and a member of the integrin-binding glycoprotein family. It is essential to the proper mineralization of bone and dentin.8 It interacts with PHEX to exert a negative effect on FGF23. Mutations leading to loss of function of DMP1 or PHEX cause, among other effects, an increase in FGF23 and the hypophosphatemia that characterizes HHR.6,9

In this article, we describe the first report of a case of autosomal recessive hypophosphatemic rickets type 1 in Argentina.

CASE REPORT

The index case is a boy aged 1 year and 8 months at the time of the first consultation, the second child of a couple of a 35-year-old woman and a 37-year-old man. Both referred to themselves as healthy and consanguineous (second-degree cousins). Sibship is completed by a 13-year-old girl with no phenotypic alterations and normal laboratory parameters. The family comes from a small town in an Argentine province that currently has a population of 3000 inhabitants and at least 4 past generations were born and lived there.

The patient was referred for consultation due to short stature, gait disorder, and frequent falls. The boy’s physical examination revealed the short stature already described (-3.42 SD) and genu varum (intercondylar distance of 4.9 cm). The rest of the anthropometry was within normal ranges for age and sex. The neurological development was normal.

The radiological exam showed the presence of genu varum and metaphyseal widening especially in the lower limbs, with epiphyseal irregularities and a frayed appearance of the metaphyses (Figure 1); bone age corresponded to 1 year and 6 months old.

The renal and urinary tract ultrasound showed no abnormalities. Laboratory tests showed the following results: serum calcium 8.2 mg/dL (RV: 9.4–10.8); phosphate 2.3 mg/dL (RV: 4.5–6.2); creatinine 0.45 mg/dL (RV: 0.30–0.60); alkaline phosphatase 630 IU/L (RV: 136–169); parathyroid hormone (PTH) 143 pg/mL (RV: 10–60); vitamin D2 28.6 ng/mL (sufficiency level: 31–80); calciuria/creatininuria ratio 0.05 (cutoff point to confirm hypercalciuria: 0.7); tubular reabsorption of phosphate 65% (RV greater than 85%); ratio of maximum tubular reabsorption of phosphate to glomerular filtration rate (TmP/GFR) 1.9 (RV: 3.6 to 7.6); pH 7.38; bicarbonate 23.9 mEq/L; base excess -1.1; sodium 140 mEq/L; potassium 4.8 mEq/L; chloride 101 mEq/L.

The hearing test was normal.

HHR was suspected based on clinical, radiological, and biochemical data, and treatment with phosphorus salts and calcitriol was initiated.
The next-generation sequencing (NGS) genetic study of a panel of genes linked to HHR (ALPL, CLCN5, CYP27B1, CYP2R1, DMP1, ENPP1, FAH, FGF23, KL, PHEX, SLC34A1, SLC34A3, VDR) showed the presence of a pathogenic variant of DMP1 in homozygosity: Chr4:88,578,183 G>C (or alternatively c.55-1G>C - ENST00000339673). The detection was confirmed by the Sanger technique. This variant contains a nucleotide change in a splicing acceptor site.

According to the American College of Medical Genetics rules for the classification of variants, the case qualifies for the following rules: PVS1 (loss-of-function variant), PM2 (extremely low frequency in healthy controls), and PP5 (reported in ClinVar with 1 star associated with ARHR1 by 2 subscribers).

This variant is the one originally described by Lorenz-Depiereux et al. segregating in 1 of the 3 families reported at the time of describing the association of DMP1 with the recessive form of hypophosphatemic rickets.\(^7,10\)

The study of both parents by the Sanger technique confirmed their mutation carrier status. The clinical and biochemical examination of both was within normal parameters.

**DISCUSSION**

DMP1 was originally identified as an extracellular matrix protein.\(^11\) It belongs to the SIBLING family, which includes bone sialoprotein (BSP), osteopontin (OPN), matrix extracellular phosphoglycoprotein (MEPE), and dentin sialophosphoprotein (DSPP).\(^12\) DMP1 contains acidic domains that play an important role in mineralization by nucleating the formation of hydroxyapatite crystals.\(^13\) In his study, Feng\(^14\) showed that mice lacking DMP1 had hypophosphatemic rickets. In human beings, the loss of function of both copies of DMP1 is associated with clinical, laboratory, and radiological findings similar to those that can be found in the X-linked or autosomal dominant

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**FIGURE 1. X-ray of the lower limbs with metaphyseal widening and a frayed appearance**

![X-ray of the lower limbs with metaphyseal widening and a frayed appearance](image-url)
Haploinsufficiency has been reported in heterozygous carriers: mild hypophosphatemia, low TRP, and focal osteomalacia, without skeletal deformities characteristic of rickets.

The phenotype of recessive forms of hypophosphatemic rickets overlaps with the X-linked form due to mutations in the PHEX gene. Genealogical profiling does not always reveal the mechanism of inheritance, as sometimes there is an index case with no family history. In recessive forms, both parents are carriers and the risk of recurrence is 25% for new children of the couple. The risk of disease for the offspring of those affected is extremely low as long as they do not conceive with another carrier.

When the condition results from mutations in the PHEX gene, inheritance is X-linked dominant. It affects both male and female patients, but greater variability is expected in the female. Affected males do not transmit the condition to their sons, while females can transmit it to both sons and daughters.15

Figure 2. Genealogy of the family. Note the parental consanguinity

**CONCLUSION**

HHR displays genetic heterogeneity and the transmission pattern described may correspond, depending on the locus involved, to dominant, recessive, or X-linked dominant forms.

We describe a family with a single affected individual and the detection in a homozygous individual of the pathogenic variant DMP c.55-1G>C. This diagnosis set the basis to perform genetic counseling corresponding to a recessive form of the condition.

This is the third family described with this mutation in the bibliography and this is the first report of ARHR1 in Argentina.
REFERENCES