



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

Gabriela Bastida^a, Flavia Ramírez^a, Georgina Exeni^a, Mailén Costa^a, Silvia A. Ávila^{a,b}

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*.

doi: <http://dx.doi.org/10.5546/aap.2022-02682.eng>

To cite: Bastida G, Ramírez F, Exeni G, Costa M, Ávila SA. First report in Argentina of a pathogenic *DMP1* variant associated with autosomal recessive hypophosphatemic rickets. *Arch Argent Pediatr* 2023;121(2):e202202682.

^a Hospital Provincial Neuquén, Neuquén, Argentina; ^b School of Medical Sciences, Universidad Nacional del Comahue, Río Negro, Argentina.

Correspondence to Silvia A. Ávila: silvia347@gmail.com

Funding: This article is part of a study that received a research grant from Ultragenyx Pharmaceutical Argentina, LATAM.

Conflict of interest: None.

Received: 4-11-2022

Accepted: 7-20-2022



This is an open access article under the Creative Commons Attribution–Noncommercial–Noderivatives license 4.0 International. Attribution - Allows reusers to copy and distribute the material in any medium or format so long as attribution is given to the creator. Noncommercial – Only noncommercial uses of the work are permitted. Noderivatives - No derivatives or adaptations of the work are permitted.

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.¹ 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.

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

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

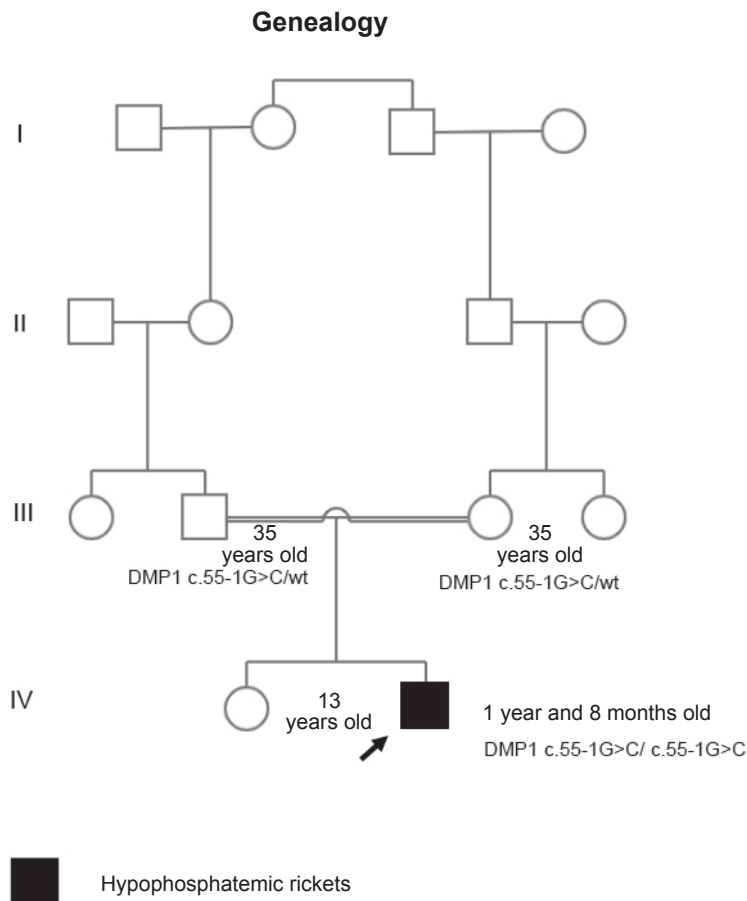
hypophosphatemic rickets.^{7,10}

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, Feng¹⁴ 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

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



form. 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

Hereditary autosomal dominant hypophosphatemic rickets is associated with activating mutations in *FGF23*. In these cases, a copy of an altered gene in each cell is sufficient to cause the disorder. The risk of recurrence is 50% for descendants of affected individuals.

CONCLUSION

HRR 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

- Misra M, Pacaud D, Petryk A, Collett-Solberg PF, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. 2008; 122(2):398-417.
- Gentile C, Chiarelli F. Rickets in Children: An Update. *Biomedicines*. 2021; 9(7):738.
- Acar S, Demir K, Shi Y. Genetic Causes of Rickets. *J Clin Res Pediatr Endocrinol*. 2017; 9(Suppl 2):88-105.
- MedlinePlus. Hereditary hypophosphatemic rickets. [Accessed on: April 12th, 2022]. Available at: <https://medlineplus.gov/genetics/condition/hereditary-hypophosphatemic-rickets/>
- Baker LR, Stamp TC. Autosomal recessive hypophosphataemia. *Arch Dis Child*. 1989; 64(8):1209.
- Chanchlani R, Nemer P, Sinha R, Nemer L, et al. An Overview of Rickets in Children. *Kidney Int Rep*. 2020; 5(7):980-90.
- Lorenz-Depiereux B, Bastepe M, Benet-Pages A, Amyere M, et al. DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. *Nature Genet*. 2006; 38(11): 1248-50.
- National Center for Biotechnology Information. DMP1 Dentin matrix acidic phosphoprotein 1 [*Homo sapiens* (human)] [Accessed on: April 12th, 2022]. Available at: <https://www.ncbi.nlm.nih.gov/gene/1758#gene-expression>
- Bacchetta J, Bardet C, Prié D. Physiology of FGF23 and overview of genetic diseases associated with renal phosphate wasting. *Metabolism*. 2020; 103S:153865.
- National Center for Biotechnology Information. ClinVar. [Accessed on: March 23rd, 2022]. Available at: <https://www.ncbi.nlm.nih.gov/clinvar/variation/8574/>
- George A, Sabsay B, Simonian PA, Veis A. Characterization of a novel dentin matrix acidic phosphoprotein. Implications for induction of biomineralization. *J Biol Chem*. 1993; 268(17):12624-30.
- Fisher LW, Torchia DA, Fohr B, Young MF, Fedarko NS. Flexible structures of SIBLING proteins, bone sialoprotein, and osteopontin. *Biochem Biophys Res Commun*. 2001; 280(2):460-5.
- He G, Dahl T, Veis A, George A. Nucleation of apatite crystals in vitro by self-assembled dentin matrix protein 1. *Nat Mater*. 2003; 2(8):552-8.
- Feng JQ, Ward LM, Liu S, Lu Y, et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. *Nat Genet*. 2006; 38(11):1310-5.
- MedlinePlus. Hereditary hypophosphatemic rickets: Causes. [Accessed on: April 12th, 2022]. Available at: <https://medlineplus.gov/genetics/condition/hereditary-hypophosphatemic-rickets/#causes>