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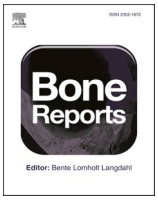

Case Report

# X-linked hypophosphatemia due to a de novo novel splice-site variant in a 7-year-old girl with scaphocephaly, Chiari syndrome type I and syringomyelia

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ABSTRACT

X-linked hypophosphatemia (XLH) is a rare X-linked dominant inherited disorder caused by loss-of-function variants in the PHEX gene and characterized by renal phosphate wasting, hypophosphatemia, abnormal vitamin D metabolism, growth retardation and lower limb deformities. We describe a case of XLH-rickets in a 7-year-old girl with scaphocephaly, Chiari syndrome type I and syringomyelia, with a de novo non-canonical splice variant (c.1080-3C > G) in intron 9 of the PHEX gene, that has not been previously described.

## 1. Introduction

X-linked hypophosphatemia (XLH, OMIM 307800), also known as vitamin D-resistant rickets, is a rare X-linked dominant inherited disorder caused by mutations in the PHEX gene (Phosphate regulating gene with Homology to Endopeptidases on the X Chromosome), located on chromosome Xp22.1–22.2. Accounting for >80 % of hypophosphatemic rickets cases and with a prevalence of 1 in 20,000, XLH is characterized by inadequate handling of phosphatemia in the kidney due to Fibroblast Growth Factor 23 (FGF 23) excess, causing hypophosphatemia, abnormal vitamin D metabolism, growth retardation and bone malformations [Ma et al., 2015].

The association of craniosynostosis with rickets is well known, with XLH being the most common metabolic cause of craniosynostosis [Rothenbuhler et al., 2019]. The sagittal suture is most commonly affected in XLH, resulting in dolichocephaly or scaphocephaly (Greek: scaphe = boat), a cranial deformity characterized by increase of the anterior-posterior diameter of the skull [Jaszczuk et al., 2016]. In children with XLH, scaphocephaly occurs in ≈ 60 % and a Chiari type I malformation in 25 % - 50 %, which causes the cerebellar tonsils to herniate through the foramen magnum [Yamamoto et al., 2020].

We describe here a case of a 7-year-old girl with scaphocephaly noted since the age of 8 months, who was referred to our pediatric department at the age of 15 months and received the clinical diagnosis of hypophosphatemic rickets. Brain imaging studies at the age of 4 years revealed Chiari syndrome with pathological ectopy of the cerebellar tonsils and syringomyelia in the cervicothoracic cord. Molecular genetic analysis confirmed the diagnosis of XLH, revealing an acceptor splice-site variant at −3 position (c.1080-3C > G) in the intron 9 of the PHEX gene. This is a novel pathogenic variant in the PHEX gene that has not been previously reported.

## 2. Case presentation

The patient, a 7-year-old girl today, is the first child of consanguineous parents of Greek Roma origin with the maternal grandfather and

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paternal grandmother (father's side) being first cousins. She has a healthy younger sister and there is no family history of hypophosphatemic rickets.

She was born by vaginal delivery at 38 weeks of gestation. At birth, her length and weight were at the 50th centile and her head circumference at the 90th centile. At the age of 8 months her head circumference surpassed 97th centile, while her length and weight were fallen at the 5th centile A brain ultrasound and a CT scan at 8 months of age revealed premature sagittal synostosis. Subsequently, with the diagnosis of scaphocephaly due to sagittal synostosis, the infant was referred for neurosurgical follow up.

At the age of 15 months the child was admitted to the Pediatric Nephrology Clinic of our department for further evaluation, due to hypophosphatemia detected after clinical examination that showed genu varum ("bow legs").

Upon admission, in addition to the scaphocephaly she manifested failure to thrive (weight and height at the 3rd centile), frontal bossing and leg bowing. There were no signs of psychomotor retardation. Laboratory investigation revealed hypophosphatemia (P: 2.3–2.8 mg/dl, normal values 3.5–6.5 mg/dl) with low renal phosphorus reabsorption (fractional reabsorption: 75 %) and normal PTH, 25(OH)D and 1,25 (OH)2D. Her bone age was lower than the chronological age. Radiological examination of the lower limbs revealed bilateral fraying and cupping in the distal femur and proximal tibia, widening of the growth plate and bowing deformities of the femur and tibia (Fig. 1). The joint line of the hip, knee and ankle remained parallel in the standing position. The clinical diagnosis of hypophosphatemic rickets was made and treatment with phosphate and alfacalcidol was initiated. The patient remained under the care of a multidisciplinary team consisting of pediatric nephrology and neurology, neurosurgery, orthopaedics and radiology. Her growth gradually improved, and the skeletal deformities remained stable.

At the age of 4 years, she underwent genetic testing (Next Generation Sequencing - NGS) with a panel of 17 genes causing hypophosphatemia. The patient was found to carry a novel variant c.1080-3C > G in the intron 9 of PHEX gene which was not identified in her parents and had presumably arisen de novo.

Head CT at the age of 4 years demonstrated scaphocephaly due to premature closure of the sagittal suture (Fig. 2), while a brain MRI revealed a 5-mm descent of the cerebellar tonsils below the level of the foramen magnum (Chiari syndrome type I), with no findings of increased intracranial pressure. The imaging evaluation of Chiari syndrome was completed with spinal cord MRI that revealed syringomyelia in the cervicothoracic cord (C5-C7, T5-T10), with the lesion descending to the conus medullaris (T11-T12) (Fig. 3).

At the age of six years, the treatment with phosphate and alfacalcidol was replaced by administration of burosumab, an IgG1 antibody that binds to the FGF23 and inhibits its activity. This treatment achieved

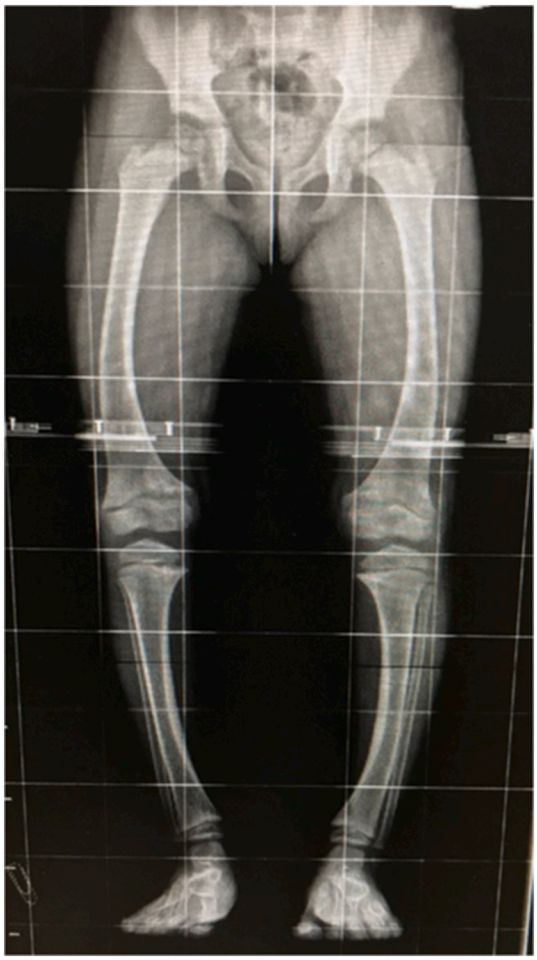

**Fig. 1.** Anteroposterior radiograph of the femur and tibia, shows increased axial height of the physis. The metaphyseal area is widened and there is bowing of the axis of the femur and tibia. The joint line of the hips, knees, and ankles remains parallel to the ground.

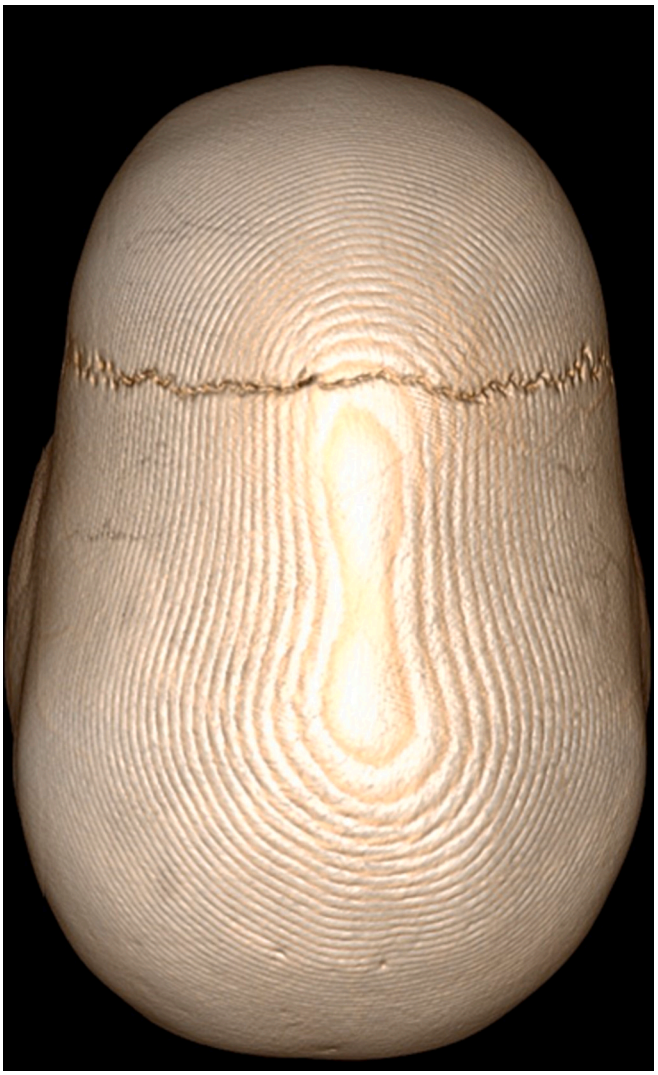

**Fig. 2.** Head CT (3D reconstruction) at the age of 4 years, showing evident elongation of the anteroposterior axis of the skull (scaphocephaly) as a result of the premature closure of the sagittal suture.

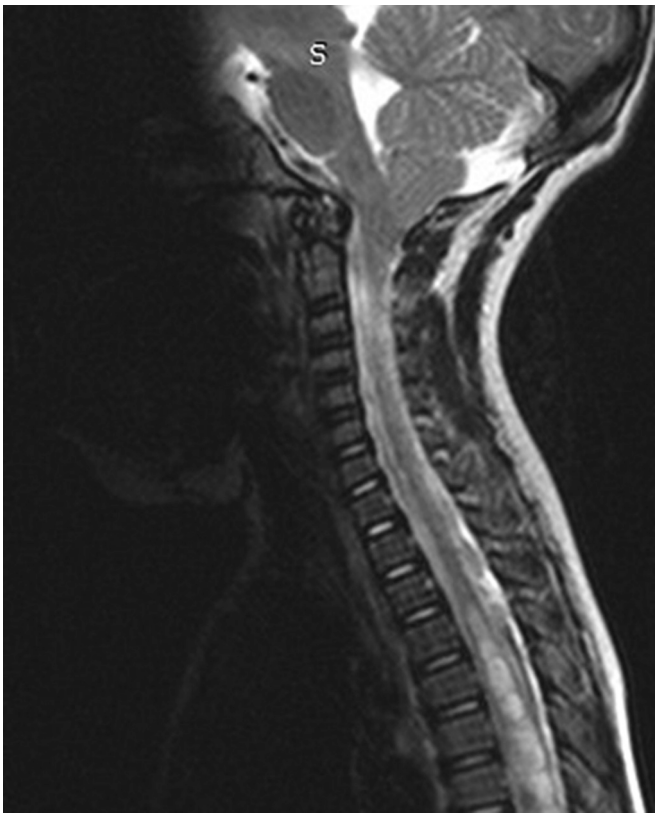


**Fig. 3.** Midline sagittal T2 MRI of the craniovertebral junction, cervical and upper thoracic spine at the age of 4 years. There is crowding at the level of the foramen magnum with altered CSF flow (not shown here) and syringomyelia from the T3/T4 level and caudally.

serum phosphorus concentrations >3.5 mg/dl and normal values of renal phosphorus reabsorption (fractional reabsorption: 81 %).

On the most recent follow up visit at the age of 7 years, the child remains at stable condition, free of any neurological symptoms, and is regularly followed up by orthopedic surgeon and neurosurgeon.

## 3. Discussion

Herein, we describe a case of a 7-year-old girl diagnosed with scaphocephaly at the age of 8 months and X-linked hypophosphatemic rickets (XLH) at the age of 15 months when she was referred to Pediatric Nephrology Clinic for further evaluation of hypophosphatemia and leg bowing (genu varum). During the 6-year follow up in our clinic the imaging studies showed displacement of cerebellar tonsils below the level of the foramen magnum (Chiari syndrome type I) and syringomyelia in the cervicothoracic cord.

Genetic analysis in our patient revealed a non-canonical novel variant at position −3 in intron 9 (c.1080-3C > G) in the PHEX gene. The variant c.1080-3C > G was not identified in the patient's parents and had therefore arisen de novo in her, it is not present in healthy population databases (https://gnomad.broadinstitute.org/) and has not been previously reported in the literature [gnomAD, 2023]. Multiple in silico tools predict that this variant detected in our patient has a damaging effect on splicing.

Another variant in the same position −3 in intron 9 (c.1080–3) has been previously described as pathogenic, but differently from our variant, the pyrimidine cytosine is substituted by the purine adenine (C > A). This variant (c.1080-3C > A) was described in a mother and her two sons affected with XLH and segregated with disease in the family [Ma et al., 2015]. Functional studies (RNA analysis in patients' peripheral blood lymphocytes) showed that the variant leads to exon 10 skipping, suggesting that nucleotide position c.1080-3C is clinically significant, and variants disrupting it are likely to be disease-causing [Ma et al., 2015; Rothenbuhler et al., 2019]. Based on the above lines of evidence, in addition to the patient's highly specific phenotype, the variant c.1080-3C > A was classified as pathogenic, according to the classification criteria of the American College of Medical Genetics & Genomics [Richards et al., 2015].

The ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar) includes 819 PHEX gene variants classified as pathogenic, including the index variant (RCV001914236.2) which was submitted after completion of our patient's and her parents' testing [ClinVar Database, 2023]. Among the above pathogenic variants, 136 affect a splice site. In addition, the new PHEX gene LSDB (locus-specific database, https://www.rarediseasegenes.com/) included 1022 unique variants at its last update on Feb 2, 2022 [PHEX Locus Specific Database, 2023]. The variants included have been either identified in the literature or shared from genetic testing programs [Sarafrazi et al., 2022]. A significant proportion (21 % corresponding to 214 variants) of the reported variants affect a splice site.

The LOVD database (https://databases.lovd.nl/shared/genes/PHEX) includes three variants affecting the position −3 of the acceptor splice site, with substitution of pyrimidine (Y) cytosine to guanine (Y > G). These variants are in introns 4, 7 and 21 and two of them are classified as pathogenic (Table 1) [BinEssa et al., 2019; Gaucher et al., 2009; Sarafrazi et al., 2022; The PHEX gene homepage - Global Variome shared LOVD, 2023].

The PHEX gene (OMIM # 300550) that is responsible for XLH, spans ≈243 kb and consists of 22 exons and 21 introns. Intronic mutations may occur at the beginning of an intron (5′ splice site or donor site) or at the end of an intron (3′ splice site or acceptor site). Typically, the consensus sequence at the 3′ splice site includes the nucleotides A and G at positions −2 and − 1 respectively, as well as a pyrimidine (Y) at position −3. Interestingly, in the −3 splice acceptor position of all acceptor sites of human genes, the pyrimidine cytosine is the most frequent nucleotide (64 %) followed by thymidine (29 %). The frequencies of the purines (R) adenine and guanine are significantly lower, with adenine recorded at a frequency of 6 % and guanine (which was found in our patient) at a frequency of 0.8 %. As a result, single nucleotide variants at position −3 of an intron, which substitute a pyrimidine (Y) by a purine (R), and particularly pyrimidine to guanine, are rare, indicating a potential splice defect [Ma et al., 2015]. This variant noticed in our patient, which leads to substitution of a pyrimidine by guanine (Y > G) at the acceptor site of intron 9, has not been previously reported in the literature.

Increased secretion of the phosphaturic hormone (phosphatonin)

**Table 1**
Review of reported mutations in 4 cases (including our case) at the position −3 of the acceptor splice site in different introns, substituting pyrimidine (Y) cytosine to guanine (Y > G) in the PHEX gene.

| Case (#) | Intronic position (c.) | Intron (IVS) | Functional studies confirming pathogenicity | Classification reported in LOVD database | References |
|---|---|---|---|---|---|
| 1 | c.437–3 | IVS 4 | Yes | VUS/ pathogenic | BinEssa et al., 2019 Gaucher et al., 2009 Sarafrazi et al., 2022 |
| 2 | c.850–3 | IVS 7 | Yes | Likely pathogenic /pathogenic | BinEssa et al., 2019 Sarafrazi et al., 2022 |
| 3 | c.2148–3 | IVS 21 | No | VUS | Sarafrazi et al., 2022 |
| 4 | c.1080–3 | IVS 9 | No | | Our case |

IVS: Intervening Sequencing, VUS: Variant of unknown significance.

fibroblast growth factor 23 (FGF23) in XLH seems to be the hallmark of pathophysiologic mechanism of disease [Haffner et al., 2019]. FGF23 inhibits sodium-dependent phosphate uptake in the renal proximal tubule and its action explains the characteristic features including renal phosphate wasting of phosphate, consequent hypophosphatemia, diminished synthesis of active vitamin D, rickets, short stature, tooth abscesses, enthesopathy and lower-extremity deformities [Haffner et al., 2019; Brame et al., 2004].

Craniosynostosis is another important clinical feature in XLH and can be observed in about one-third of patients with hypophosphatemia, but only a minority of them require surgery [Baroncelli and Mora, 2021]. The interactions among PHEX, fibroblast growth factor 23 (FGF23), and matrix extracellular phosphoglycoprotein (MEPE) have been proposed as mechanisms responsible for craniosynostosis in XLH [Murthy, 2009]. According to Murthy, PHEX gene defects lead to increased levels of fibroblast growth factor (FGF23) that activate the FGFR pathway. In turn, the cross binding of FGF23 to FGF receptors 2 and 3 results in fusion of cranial sutures (craniosynostosis) [Murthy, 2009].

Arnold-Chiari I malformation, otherwise known as the Chiari 1 malformation (CM1), can have a genetic basis or can be secondary to different conditions involving alterations in the basal skull, such as craniosynostosis and bone metabolic disorders. In 30 % to 70 % of CM1, syringomyelia has been reported [Arnautovic et al., 2015]. Based on several lines of evidence, in addition to that CM1 is not the result of neural tissue malformation, it has been recently proposed to define the Chiari type I malformation as "Chiari syndrome," while the term malformation should be reserved for Chiari types II-III [Frič and Eide, 2020].

Chiari syndrome may be associated with severe headache and vertigo, which may require neurosurgery. Routine ophthalmologic examination in patients with XLH and Chiari syndrome has been advocated to identify papilledema [Watts and Wordsworth, 2015]. Vega et al. emphasize that children with XLH who develop head shape abnormalities should be promptly referred to a craniofacial specialist [Vega et al., 2016]. Cranial vault remodeling (CVR) may be required to prevent or relieve elevated intracranial pressure and abnormalities of the cranial vault. In our case, the absence of papilledema in serial ophthalmological examinations, the absence of clinical manifestations from the Chiari I syndrome or from the syringomyelia and the stability of these two in serial MRI imaging, guided towards a "watch and wait" approach instead of a neurosurgical intervention.

Treatment of XLH includes conventional treatment which consists of multiple daily doses of oral phosphate salts associated with vitamin D active analogues that increase serum phosphate concentration without notable changes in the maximum tubular reabsorption of phosphate normalized to the glomerular filtration rate (TmP/GFR). Recent studies showed significant improvement in serum phosphate concentration and TmP/GFR by using burosumab, a recombinant human IgG1 monoclonal antibody that targets FGF23 [Mughal et al., 2023]. Our case had been under treatment with phosphate and alfacalcidol since the XLH diagnosis at the 15 months of age. Over the last 12 months she has been receiving only burosumab. With this new treatment, serum phosphorus concentrations are normal and normal values of renal phosphorus reabsorption have been achieved.

In summary, we herein describe a 7-year-old girl with XLH rickets, scaphocephaly, Chiari syndrome and syringomyelia. With regular follow up by orthopedic surgeon and neurosurgeon the child remains at stable condition and no neurological symptoms related to Chiari syndrome or syringomyelia have been noticed. The variant that was detected by genetic testing in our patient is a de novo splice-site variant at −3 position in intron 9 (c.1080-3C > G). This rare variant has not been previously reported and is the fourth case with substitution of pyrimidine (Y) to guanine (Y > G) at the position −3 throughout the introns in PHEX gene. Our case presents a novel genetic variant related to an unusual phenotype of XLH rickets and highlights the importance of collaboration between clinicians and genetic scientists for the diagnosis and holistic care of a patient with such a rare disease.

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## Informed consent

Written informed consent was obtained from the patient's parents.

## CRediT authorship contribution statement

**Maria Fourikou:** Writing – review & editing, Writing – original draft, Visualization. **Aristea Karipiadou:** Writing – review & editing, Writing – original draft. **Athina Ververi:** Writing – review & editing, Writing – original draft. **Parthena Savvidou:** Writing – review & editing, Writing – original draft. **Nikolaos Laliotis:** Writing – original draft, Visualization. **Vassilios Tsitouras:** Writing – original draft, Visualization. **Stella Stabouli:** Writing – review & editing, Supervision. **Emmanuel Roilides:** Writing – review & editing, Supervision. **Konstantinos Kollios:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

## Declaration of competing interest

The authors certify that they have no conflict of interest to declare.

## Data availability

No data was used for the research described in the article.

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