A mosaic mutation of phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) in X-linked hypophosphatemic rickets with mild bone phenotypes

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Abstract. X-linked hypophosphatemic rickets (XLH) is primarily characterized by renal phosphate wasting with hypophosphatemia, short stature, and bone deformity of the leg. Here we present a male case of XLH with relatively mild bone deformity caused by a mosaic mutation of the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*). Polymerase chain reaction (PCR) direct sequencing revealed a novel in-frame deletion, NM-000444.6:c.671-685del p.Gln224-Ser228del, at exon 6 in *PHEX* as a mosaic pattern. This mutation was not found in any database and may result in a significant change in higher-order protein structure and function. TA cloning of the PCR product and clone sequencing estimated the mutation allele frequency at 21%. Literature review of the previously reported three cases with novel mosaic mutations in *PHEX*, together with the present case, suggests that the rates of the mutation allele correlate with phenotype severity to some extent. We initially treated him with nutritional vitamin D supplements and phosphate salts. However, to avoid the development of secondary/tertiary hyperparathyroidism, we had switched nutritional to active vitamin D supplementation with reduced phosphorus salts. The present report contributes to understanding the relationship between the mosaic rate, in addition to the mutation locus, of the *PHEX* gene, and clinical features of XLH.

Key words: X-linked hypophosphatemic rickets, Phosphate-regulating gene with homologies to endopeptidases on the X chromosome, Rickets, Mosaicism

X-LINKED HYPOPHOSPHATEMIC RICKETS (XLH) is the most common form of hereditary rickets, with a prevalence of 1/20,000 [1]. Affected individuals have lifelong hypophosphatemia that results from loss-of-function mutations of the gene encoding phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) that cause excess circulating levels of fibroblast growth factor 23 (FGF23). FGF23, which comprises 251 amino acids, is a hormone produced mainly by osteoblasts and osteocytes and regulates phosphate homeostasis and vitamin D metabolism via a specific FGF receptor- α -klotho-complex in tubular

kidney cells. Excess FGF23 impairs renal phosphate reabsorption and decreases the synthesis of the active metabolite of vitamin D, 1,25-dihydroxyvitamin D3 (1,25-[OH]₂D₃), leading to hypophosphatemia [2]. As a result, extraskeletal ossification, osteoarthritis, joint mobility limitations, and occasionally spinal cord compression may develop.

The human *PHEX* gene comprises 22 exons that encode a 749-amino-acid protein and is strongly expressed in osteoblasts and osteocytes [3]. Since the *PHEX* gene mutation was first identified in 1995, at least 407 mutations, including nonsense mutations, have been registered in the Human Gene Mutation Database (<http://www.hgmd.cf.ac.uk/ac/index.php>). However, how *PHEX* gene mutations increase FGF23 levels and the relationship between mutation locus, type of mutation, and heterogeneous clinical features of XLH remain unknown.

Submitted Dec. 22, 2020; Accepted Apr. 1, 2021 as EJ20-0809

Released online in J-STAGE as advance publication Apr. 28, 2021

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Case Report

A 61-year-old Japanese man presented to our hospital for a detailed examination of his coxodynia. He was unmarried and had no children. He had short stature (150 cm), bow legs, and scoliosis. He had never experienced any low-trauma fracture and lacked a family history of short stature, pathological fractures, and any congenital diseases. He was born at full term by normal vaginal delivery. He had been short in stature since his childhood. He was diagnosed with rickets at 5 years of age and received treatment with active vitamin D by age 10. During his growth spurt, he grew 30 cm to reach 150 cm tall. He had suffered from coxodynia since he was in his 40s. During the same period, he developed multiple caries.

The patient's laboratory test data on admission (Table 1) revealed hypophosphatemia, slightly elevated bone-specific alkaline phosphatase, reduced renal function, reduced 25-hydroxyvitamin D3 (25-[OH]D3), elevated parathyroid hormone (PTH) level, reduced renal tubular phosphorus reabsorption, and elevated FGF23 (assayed

using the FGF-23 ELISA Kit, Kainos Laboratories, Tokyo). X-ray examinations revealed curvature of the spine (Fig. 1A), Looser's zones in the femurs, and ectopic ossification in the pelvis (Fig. 1B). The space of both hip joints was narrow with irregular margins (Fig. 1B). Based on the findings of bone changes, hypophosphatemia, and elevated FGF23 levels, FGF23-related hypophosphatemic rickets was suspected.

Because the patient's bone pain symptom was mild and because his 25-(OH)D3 level was as low as 10.6 ng/mL, we initially treated him with nutritional vitamin D supplements (25 µg/day) and phosphate salts (600 mg/day). Nutritional vitamin D supplementation normalized his 25-(OH)D3 and 1,25-(OH)2D3 levels from 10.6 to 34.2 ng/mL (>20 ng/mL) and from 42.3 to 69.4 pg/mL (20–60 pg/mL), respectively (Table 1). However, considering that FGF23 suppresses the activity of 1α-hydroxylase, the conversion of 25-(OH)D3 to 1,25-(OH)2D3 may be relatively insufficient. Indeed, PTH levels were elevated from 102 to 239 pg/mL during the course. To avoid the development of secondary/tertiary hyperparathyroidism, we thereafter had treated him with

Table 1 Laboratory data of the patient on admission

	Before	After treatment with nutritional vitamin D and phosphate salts	After treatment with active vitamin D and phosphate salts	Reference range
Phosphate (mg/dL)	1.8	3.2	2.5	2.3–4.5
Calcium (mg/dL)	9.3	8.5	8.6	8.2–10.2
Alkaline phosphatase (IU/L)	373	417	450	110–330
BAP (µg/L)	24.7	24.8		3.7–20.9
AST (IU/L)	20	18	15	12–31
ALT (IU/L)	24	19	14	8–40
γ-GTP (IU/L)	29	25	18	11–73
Albumin (g/dL)	4.5	3.9	4	3.8–5.3
UN (mg/dL)	17	18	22	8–22
Creatinin (mg/dL)	1.21	1.38	1.3	0.6–1.1
estimated GFR cr (mL/min per 1.73 m ²)	48.4	39.16	44.13	≥90
cystatin C (mg/L)		1.47		
estimated GFR cys (mL/min per 1.73 m ²)		46.3		
25-(OH)D3 (ng/mL)	10.6	34.2		>20
1,25-(OH)2D3 (pg/mL)	42.3	69.4		20–60
PTH (pg/mL)	102.2	248	168	10.3–65.9
FGF23 (pg/mL)	104	239		<30
TmP/GFR (mg/mL)	1.2	1.42	1.17	2.3–4.3
TRP (%)	66.72	44.46	46.7	81–90

BAP, bone specific alkaline phosphatase; GFR, glomerular filtration rate; UN, urea nitrogen; 25-(OH)D3, 25-hydroxyvitamin D3; 1,25-(OH)D3, 1,25-dihydroxyvitamin D3; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; TmP, tubular maximum phosphate reabsorption; TRP, tubular reabsorption of phosphate.

Fig. 1 X-ray examinations of the spine (A) and pelvis/femoral heads (B)

A: Spine curvature.

B: Looser's zones in the femurs (thin arrow). Ectopic ossification (thick arrow) in the pelvis. The space of both hip joints was narrow with irregular margins.

active vitamin D and phosphate salts, which reduced his PTH level to 168 pg/mL after 3 months (Table 1).

Materials and Methods

Genomic DNA was extracted from whole blood using a rapid extraction method [4]. The mutation was screened by CHIPS (CEL nuclease mediated heteroduplex incision with polyacrylamide gel electrophoresis and silver staining) assay, a highly sensitive enzyme mismatch cleavage assay described elsewhere [5, 6]. Subsequently, the mutation was confirmed by Sanger sequencing using the BigDye Terminator v3.1 Cycle Sequencing Kit on a 3100XL Genetic Analyzer (Thermo Fisher Scientific). PCR primers used in the CHIPS and direct sequencing were shown in Table 2. To distinguish the shorter fragment of the mutation allele from the wild-

type allele, we set PCR primers as forward primer PHEX-6F: 5'-AATATGGCTGGGATGCAGAC-3' and reverse primer PHEX-6AS: 5'-GAGTAAACTTACAGACTTGGCTTC-3' as shown in Fig. 2A. TA cloning of this PCR product was performed with pT7 Blue T-vector (Novagen). The mutation allele frequency was estimated by colony direct PCR and 12% polyacrylamide gel electrophoresis for 100 colonies.

Written informed consent was obtained from the patient after he received courteous genetic counseling and an explanation of the genetic testing, as approved by the institutional review board (No. G111).

Genetic Analyses

We performed a genetic analysis for the candidate genes involved in FGF23-related hypophosphatemic rickets. We identified a shorter PCR fragment derived from the *PHEX* gene at exon 6 (Fig. 2A) in the patient. Sanger sequencing revealed a *PHEX* in-frame deletion NM_000444.6:c.671_685del p.Gln224_Ser228del as a mosaic pattern. Clone PCR of 100 colonies estimated the mutation allele frequency 21% (Fig. 2B), suggesting the mosaic mutation. This mutation was not found in any database, including the Genome Aggregation Database (<http://gnomad.broadinstitute.org>), the Exome Aggregation Consortium (<http://exac.broadinstitute.org>), and the Human Gene Mutation Database, suggesting that this mutation is a novel and not a normal variant.

The deleted region of the *PHEX* gene (Gln224_Ser228) in this patient is completely conserved among mammalian species, for example, human, mouse, and bat. Using the software tool Sequence to Function Annotation Server (<http://citeseerx.ist.psu.edu>), we could see that in the high-order structure of the DNA around the mutation, the deletion exists between the β -sheet structure and α -helix structure. The deletion causes the shortage of the β -sheet structure and makes the protein structure unstable. Using the software tool PROVEAN (<http://provean.jcvi.org/index.php>), we also predicted the impact of this novel mutation on protein structure by *in silico* analyses. These *in silico* prediction engines resulted in a score of -21.52, which suggests deleterious damage in *PHEX* function. These results suggest that this region is critical for the function of the protein and is causal for XLH. From these results, we diagnosed the patient's illness as XLH caused by a mosaic novel *PHEX* mutation.

Discussion

We report a novel *PHEX* in-frame deletion mutation as a mosaic pattern in a sporadic male case of XLH with

Table 2 *PHEX* each exon PCR primer for CHIPS and direct sequencing

Exon*	Primer Name	Primer Seq	Product size (bp)
1	PHEX-1F	5'-GAGCAAGAAAGCCTTGGATG-3'	334
	PHEX-1R	5'-ACCTATGAACGCAGGCAAAC-3'	
2	PHEX-2F	5'-TGTTTCCGAGGGTGGTTTAC-3'	266
	PHEX-2R	5'-CAAAATTGCATTTCGTACTTGG-3'	
3	PHEX-3F	5'-GGGGAAATATAAATGCCAAGG-3'	345
	PHEX-3R	5'-TGTTTTTCTGTCAAATATTGCTC-3'	
4	PHEX-4F	5'-TTTCTGGAGGTTGGAATTGTG-3'	324
	PHEX-4R	5'-CTTTCACAATCATTCCTTTAACACC-3'	
5	PHEX-5F	5'-CTAGTGTGCTGATCCAGTTTGC-3'	371
	PHEX-5R	5'-GGCAGCATGAGTCTCTTCC-3'	
6	PHEX-6F	5'-AATATGGCTGGGATGCAGAC-3'	293
	PHEX-6R	5'-CCTGCATTGGGAATATGGTC-3'	
7	PHEX-7F	5'-TTCTGCTCTCCATGTCTCTCA-3'	298
	PHEX-7R	5'-ATTTTCATTGAGGATATACTGCCTTT-3'	
8	PHEX-8F	5'-CAGATGTTTTGGCACATGTAGG-3'	278
	PHEX-8R	5'-ACCAAGACTGAGAGCAGGTTTTAC-3'	
9	PHEX-9F	5'-GATTCTCTCATTCTGTTTGTCTCTC-3'	260
	PHEX-9R	5'-AAAGGATGTGAGAAGGGAAGC-3'	
10	PHEX-10F	5'-GGAGCTTTGCCAACTGTTTC-3'	294
	PHEX-10R	5'-CCCCTGTCTAATCCCTAAAGATG-3'	
11	PHEX-11F	5'-TTCAGCCATGGGTTTTATCC-3'	282
	PHEX-11R	5'-CTACCACCTGGAAGGCTGAC-3'	
12	PHEX-12F	5'-GCTTCTTGGCTTTGACGTTTC-3'	263
	PHEX-12R	5'-GGGGTCATTGAGTCAACAG-3'	
13	PHEX-13F	5'-GAAGGGCGCATTTCTACATC-3'	273
	PHEX-13R	5'-TTGGTGTTTCTGGCATCAC-3'	
14	PHEX-14F	5'-TTGCTCCTTCCATGCTGAAG-3'	300
	PHEX-14R	5'-AACTGGCAAGCCAGCTACTC-3'	
15	PHEX-15F	5'-GTCCAACATCCCCATTGTTC-3'	297
	PHEX-15R	5'-AGCATACCCTGCCACTTTTG-3'	
16	PHEX-16F	5'-GAGGAGTGCCTTTCAGATGG-3'	276
	PHEX-16R	5'-CCATGGCTTCTTTCTGCTG-3'	
17	PHEX-17F	5'-CAGTTTATCTTGGCTTTCCATTG-3'	264
	PHEX-17R	5'-AAGCTATGATGCTGCTGCTATG-3'	
18	PHEX-18F	5'-CTTGTGCGAGGTGAGGAAAG-3'	287
	PHEX-18R	5'-TGGTTTAAAGCAAGCTAATGTCC-3'	
19	PHEX-19F	5'-GCCTACCTCTGATTTATTGAATGTG-3'	297
	PHEX-19R	5'-AAGAACATGGCTATGGTATGAATTG-3'	
20	PHEX-20F	5'-TTTGCTATTCTGTGCTAGCTG-3'	240
	PHEX-20R	5'-GGGAGCAAACCAAGTCCTG-3'	
21	PHEX-21F	5'-ATTTGGAGCAGTTAAACAGCAG-3'	239
	PHEX-21R	5'-TCTGGTAGAGCCCTTGGATG-3'	
22	PHEX-22F	5'-AGAATGCCAACCTTCTTTCTAGC-3'	299
	PHEX-22R	5'-TCTCCAGGCCTAAAGCAATG-3'	

* Exon number is according to Genbank NM_000444.5, transcript variant 1 (https://www.ncbi.nlm.nih.gov/nuccore/NM_000444.5)

Fig. 2 Mosaic mutation in the *PHEX* gene

A: The 3% agarose (top) and 12% polyacrylamide gel electrophoresis identified a shorter fragment derived from the *PHEX* gene at exon 6 (arrow).

B: PCR-direct Sanger sequencing detected low mosaic peaks. Cloning the PCR product and clone sequencing revealed the *PHEX* in-frame deletion mutation. Clone PCR of 100 colonies revealed 79 wild-type and 21 mutant alleles (allele frequency 21%).

relatively mild bone deformity. We found it difficult to diagnose this patient as XLH because of his relatively mild symptoms and absence of family history. Of note, frequency of sporadic XLH are as high as 30% [7], 53% [8], and 54% [9]. *PHEX* mutation frequencies are less common in sporadic cases (28%–73%) than familial cases (52%–91%) with XLH [8].

Some studies have reported genotype-phenotype correlations in XLH; however, there has been no definite relationship found between disease severity and type of mutation [7, 10]. The mosaic mutation in *PHEX* appears to be rare. Indeed, there have been only three cases with novel mosaic mutations in *PHEX* reported in males [11–13]. Table 3 summarizes the clinical features of these

cases. Among these cases, the Chinese boy [11] and the Japanese man [12] with a higher mutation rate seem to present relatively severer phenotypes. On the other hand, the Korean man [13] and the present patient with a lower mutation rate present a relatively milder phenotype. This trend in findings suggests that, in these cases, the rates of the mutation allele correlate with phenotype severity to some extent. Therefore, in patients with mild phenotypes, genetic analyses are strongly recommended to determine the mosaic somatic mutation of *PHEX*. However, we must keep in mind that mutation rates may vary among organs.

In the XLH subjects without impaired kidney function, serum FGF23 level negatively correlates with serum phosphate. However, FGF23 increases exponentially as eGFR declines [14]. Also, in the present patient, moderately impaired renal function is attributable to his elevated FGF23 levels. In this setting, elevated FGF23 levels are no longer consistent with his mild symptoms and the mosaic mutation of *PHEX*. Unfortunately, besides the present case, FGF23 levels were not reported in other cases with the *PHEX* mosaic mutation (Table 3). Accumulating similar cases will clarify the regulatory mechanisms of FGF23 production independently of the *PHEX* function as well as the role FGF23 plays in the disease severity of XLH.

Unfortunately, he had initially been treated with nutritional vitamin D supplements and phosphate salts. The majority of patients with XLH (83.3%) were reported to have evidence of secondary hyperparathyroidism [15]. Transient increase in serum phosphorus after phosphate doses is expected to stimulate PTH production due to unidentified mechanism in XLH patients [16]. Indeed, prolonged use of high-dose phosphate therapy has been identified as a risk factor for PTH elevation [17]. Active vitamin D supplementation reduces elevated PTH levels. Of note, FGF23 suppresses 25-hydroxyvitamin D-1 α -hydroxylase and activates 25-hydroxyvitamin D-24-hydroxylase in the kidney [2]. In patients with XLH whose FGF23 levels are elevated, the nutritional vitamin D supplementation insufficiently elevates 1,25-(OH) $_2$ D $_3$ levels. In addition, serum 1,25-(OH) $_2$ D $_3$ levels represent 1,25-(OH) $_2$ D $_3$ production in the renal tubule, which correlates with PTH levels, while actual action of 1,25-(OH) $_2$ D $_3$ in the intestine is only associated with 1,25-(OH) $_2$ D $_3$ production in the intestine by local 1 α -hydroxylase and irrelevant to serum 1,25-(OH) $_2$ D $_3$ levels. Therefore, his elevated serum 1,25-(OH) $_2$ D $_3$ level after nutritional vitamin D supplementation may be attributable to the elevated PTH levels and does not represent his actual local 1,25-(OH) $_2$ D $_3$ activity in the intestine. The treatment with phosphate under insufficient active vitamin D supplementation may aggravate

Table 3 Summary of the clinical features of previously reported cases of X-linked hypophosphatemic rickets with a mosaic mutation of *PHEX*

	Case reference number			
	11	12	13	Present case
Age (year)/Gender/ Nationality	4.5/M/China	35/M /Japan	26/M/Korea	61/M/Japan
Family history	—	Proband's daughter	—	—
Bone phenotypes	Caput quadratum Bow legs	Bow legs	Mild osteoarthritis in both joint Multiple old fractures	Bow legs Curvature of his spine
Serum FGF23 level	N.D.	N.D.	N.D.	104 pg/mL
Serum phosphate level	2.0 mg/dL	1.7 mg/dL	2.0 mg/dL	1.8 mg/dL
Serum alkaline phosphatase level	616 IU/L	215 IU/L	99 IU/L	373 IU/L
Mutation in <i>PHEX</i> *	c.1769-1G>A p.Gly590GlufsTer28	c.1669C>T p.Arg567Ter	c.589C>T p.Gln197Ter	c.671_685del p.Gln224_Ser228del
Mosaic rate	42%	60%	38%	21%

N.D., not determined; * mRNA reference number is NM_000444.5

his secondary hyperparathyroidism. Therefore, we had switched nutritional to active vitamin D supplementation with reduced phosphorus salts to prevent the development of secondary/tertiary hyperparathyroidism according to the clinician's guide to XLH [16], resulting in a reduction in his PTH level.

Recently, burosumab, a human anti-FGF23 antibody, was developed as a potential treatment for XLH. In children with XLH, treatment with burosumab increased renal tubular phosphate reabsorption, serum phosphorus levels, linear growth, and physical function and reduced the pain and severity of rickets [18]. In adults with XLH, the treatment increased serum phosphorus levels and mobility and reduced pain and the severity of rickets [19]. Therefore, to improve patients' quality of life, early definite diagnosis is of great importance in XLH, although the indication for burosumab treatment in adults with XLH should be carefully discussed.

In summary, we found a novel *PHEX* in-frame deletion NM_000444.6:c.671_685del p.Gln224_Ser228del

mutation as a mosaic pattern in a sporadic male case of XLH with relatively mild bone deformity. The mutation may result in a significant change in higher-order protein structure and function and might, through an increase in the production of FGF23, cause XLH. Mild symptoms of rickets may be associated with the *PHEX* mutation presented as a mosaic pattern. We believe the present report contributes to understanding the relationship between the mosaic rate, in addition to the mutation locus, of the *PHEX* gene, and clinical features of XLH.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

Disclosure Statement

The authors have nothing to disclose.

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