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PHEX Gene Mutations and Genotype-Phenotype Analysis of Korean Patients with Hypophosphatemic Rickets

X-linked hypophosphatemic rickets (XLH) results from mutations in the *PHEX* gene. Mutational analysis of the *PHEX* gene in 15 unrelated Korean patients with hypophosphatemic rickets revealed eight mutations, including five novel mutations, in nine patients: two nonsense mutations, two missense mutations, one insertion, and three splicing acceptor/donor site mutations. Of these, c.64G>T, c.1699C>T, c.466_467 insAC, c.1174-1G>A, and c.1768+5G>A were novel mutations. To analyze the correlation between genotype and phenotype, phenotypes were compared between groups with and without a mutation, in terms of mutation location, mutation type, and sex. Skeletal disease tended to be more severe in the group with a mutation in the C-terminal half of the *PHEX* gene, but no genotype-phenotype correlation was detected in other comparisons. Further extensive studies of the *PHEX* gene mutations and analyses of the genotype-phenotype relationships are required to understand PHEX function and the pathogenesis of XLH.

Key Words : *Hypophosphatemic Rickets, X-linked Dominant; PHEX; Mutation; Genotype; Phenotype*

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INTRODUCTION

Familial hypophosphatemic rickets (FHR) is defined as a group of disorders caused by a defect in renal phosphate transport, leading to phosphate wasting and hypophosphatemia. FHR is also characterized by the abnormal regulation of vitamin D metabolism, resulting in inappropriately normal 1, 25-dihydroxyvitamin D concentrations despite hypophosphatemia (1). X-linked hypophosphatemic rickets (XLH; MIM 307800), the most common form of FHR, is characterized by rickets and osteomalacia, lower-extremity deformities, short stature, bone pain, dental abnormalities, and abnormal vitamin D metabolism (2). Other less common forms of FHR include autosomal dominant hypophosphatemic rickets (ADHR), hereditary hypophosphatemic rickets with hypercalciuria, and tumor-induced osteomalacia.

XLH results from loss-of-function mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), located on Xp22.1 (3). PHEX is a member of the M13 family of type II cell-surface-membrane zinc-dependent proteases, which include neprilysin (NEP), two endothelin-converting enzymes (ECE-1 and -2), the KELL antigen, and damage-induced neuronal endopeptidase/X-converting enzyme (4). *PHEX* cDNA has been cloned (5) and consists of 22 exons spanning 2,247 bp of genomic sequence. Seventeen of the 22 exons are less than 130 bp long (2). *PHEX* and *NEP* share conserved genomic structures. Like NEP, PHEX includes a short N-terminal tail, a single N-terminal hydrophobic region corresponding to a transmembrane domain, a highly conserved zinc-binding domain in exons 17 and 19, and several conserved cysteine residues and amino acids that, in NEP, are involved in its catalytic activity (1).

Several studies have identified mutations in the *PHEX* gene in individuals with XLH. Recently, we studied the clinical and molecular characteristics of Korean patients with XLH. In this report, we describe eight different *PHEX* mutations identified in 15 unrelated Korean patients with hypophosphatemic rickets, including five novel mutations.

MATERIALS AND METHODS

Subjects

This study included 15 patients and five of their family members, aged from 20 months to 60 yr (average, 22 yr). Of the 15 patients, five had a family history of XLH, four were sporadic cases, and the other six were unknown. Diagnoses were made based on clinical, radiological, and laboratory findings by specialists at the Korea University Guro Hospital. Of the

15 patients, four were male and 11 were female. Overall, there were five male and 15 female individuals (including family members). Five patients were young children. Of the five family members evaluated, three were related to patient 1-1 (mother, maternal aunt, and cousin) and two to patient 7-1 (mother and maternal aunt) (Fig. 1).

For phenotypic analyses, the medical records and histories of the patients were reviewed retrospectively. The severity of the skeletal disease was assessed by orthopedic surgeons and was classified as mild, moderate, or severe (Table 1) (1). Osteotomies were performed in patients who complained of gait disturbance caused by either pain or fatigue. For the two patients with affected family members, the families were analyzed as a unit. They were classified as having mild disease if all members had mild disease, as having moderate disease if at least one member had moderate disease, or as having severe disease if at least one member had severe disease.

Although there are no widely accepted criteria with which to describe the severity of dental disease manifestations in patients with rickets, we simplified the assessment of dental disease severity by describing it in terms of the number of dental abscess lesions and the treatments performed for these abscesses (Table 1). The data on dental diseases were collected based on the histories of the patients.

Mutation analysis

Informed consent for DNA analysis was obtained from the patients or their parents, depending on the patient's age. Genomic DNA was extracted from the peripheral blood using the G-DEX™, II Genomic DNA Extraction Kit (Intron, Seongnam, Korea), according to the manufacturer's protocol. Screening for mutations was performed with PCR amplification and direct sequencing. All 22 exons of the *PHEX* gene, including at least 40 bp of the exon-intron flanking regions, were amplified by PCR. Sequencing was performed with a Dynamic™, ET Dye Terminator Kit (GE Healthcare, Buckinghamshire, U.K.) and a MegaBACE 500 Genetic Analyzer (GE Healthcare), according to the manufacturer's instructions. Base calling of the sample files was performed with Cimarron Base Caller version 3.12 software (GE Healthcare).

The *PHEX* genes of 50 normal female individuals were also analyzed to confirm that the sequence variations in the *PHEX* gene identified in this study were not polymorphisms but real pathogenic mutations. Novel mutations were defined by their absence from the Human Gene Mutation Database (http://www.uwcm.ac.uk/uwcm/mg/hgmd0.html) and from mutations previously reported in PubMed (http://www.ncbi.nlm.nih.gov/PubMed/). The functional consequences of novel splice variants were predicted with the Automated Splice Site Analyses program on the web (https://splice.cmh.edu/) (6).

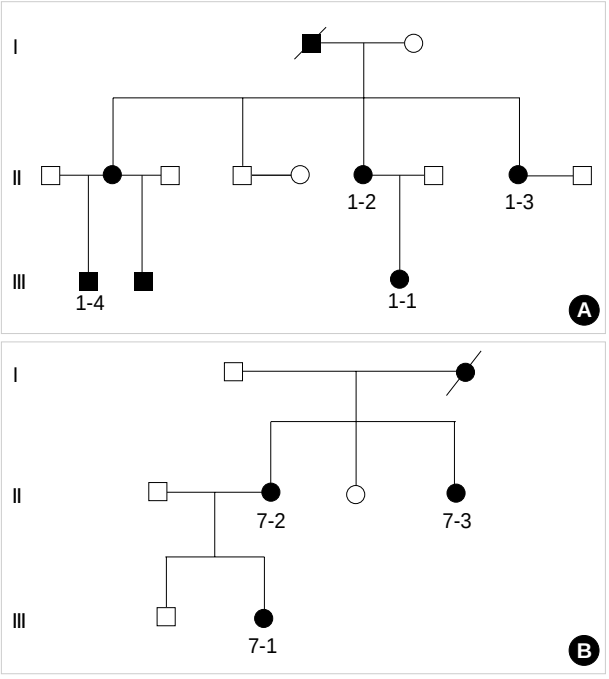

Fig. 1. Pedigrees of patients 1 (A) and 7 (B) with X-linked hypophosphatemic rickets.

Statistical analysis

The Wilcoxon rank-sum test and the two-tailed Fisher's exact test were used to calculate p values and to determine whether the differences between the phenotypes of the genotype groups were statistically significant. We used a significance level of $p<0.10$ because the sample size was small, in accordance with previously published analyses of small samples (1, 7).

RESULTS

In a total of 15 patients, the average ages at onset and diagnosis were 31 months and 90 months, respectively. The male: female ratio among the patients was 4:11 (Table 2, 3). Laboratory findings were available for 10 patients: seven patients

Table 1. Classification of phenotypic severity of skeletal and dental diseases

Classification	Skeletal disease	Dental disease
None	N/A	No dental abscess
Mild	No or mild bowing and no history of osteotomy	Less than two dental abscess lesions
Moderate	Moderate bowing and/or a history of osteotomy	More than three dental abscess lesions and/or extraction
Severe	Severe bowing and/or a history of osteotomy	Severely malpositioned teeth with orthodontic treatment

N/A, not applicable.

Table 2. Genotype and phenotype data for patients and family members with a *PHEX* gene mutation

No.	Familial relationship	Family history	Sex/age (yr)	Age at onset	Age at diagnosis (yr)	Mutation*	Predicted amino acid change	Exon/intron	Bowing	Osteotomy	Dental severity	Treatment	
												Phosphate	Vitamin D
1-1	Proband	Y	F/18	5 yr	14	c.1363G>T	p.Glu455X	12	Severe	Y	Mild	Y	Y
1-2	Mother	Y	F/40	5 yr	37	c.1363G>T	p.Glu455X	12	Severe	Y	Mild	Y	Y
1-3	Maternal aunt	Y	F/32	6 yr	28	c.1363G>T	p.Glu455X	12	Mild	Y	Severe	Y	N
1-4	Cousin	Y	M/22	2 yr	17	c.1363G>T	p.Glu455X	12	Mild	Y	Moderate	Y	Y
2-1	Proband	N	F/18	birth	4	c.1601C>T	p.Pro534Leu	15	Moderate	Y	None	N	Y
3-1	Proband	U	F/34	3 yr	32	c.466_467 insAC†	Frameshift	5	Mild	Y	Moderate	Y	Y
4-1	Proband	U	F/39	1-2 yr	2	c.1174-1G>A†	Splicing variant	IVS10	Severe	Y	Severe	Y	Y
5-1	Proband	U	F/16	3 yr	3	c.1174-1G>A†	Splicing variant	IVS10	Moderate	Y	Moderate	Y	Y
6-1	Proband	U	F/3	2 yr	2	c. 64G>T†	p.Ala22Ser	1	Mild	N	Moderate	N	Y
7-1	Proband	Y	F/33	<1 yr	30	c.1699C>T†	p.Arg567X	16	Severe	Y	Severe	Y	Y
7-2	Mother	Y	F/60	38 yr	44	c.1699C>T†	p.Arg567X	16	Moderate	Y	Mild	N/A	N/A
7-3	Maternal aunt	Y	F/47	U	11	c.1699C>T†	p.Arg567X	16	Mild	N	Mild	N/A	N/A
8-1	Proband	U	F/20	5 yr	5	c.1768+5†	Splicing variant	IVS17	Mild	N	None	N/A	N/A
9-1	Proband	Y	M/15	10 yr	10	c.1965+1G>A	Splicing variant	IVS19	Severe	Y	Moderate	N	Y

*Reference sequences for *PHEX*, gDNA U82907, cDNA NM_000444. Mutation numbering is based on cDNA sequences. +1 corresponds to the first base of the translation initiation codon. †Novel mutations identified in this study. N/A, not applicable. U, unknown.

Table 3. Genotype and phenotype information for patients without a *PHEX* gene mutation

No.	Family history	Sex/age	Age at onset	Age at diagnosis	Bowing	Osteotomy	Dental severity	Treatment	
								Phosphate	Vitamin D
10-1	N	M/4 yr	2 yr	3 yr	Severe	Y	Moderate	Y	Y
11-1	N	M/4 yr	2 yr	2 yr	Severe	Y	Mild	Y	Y
12-1	Y	F/5 yr	2 yr	2 yr	Mild	N	Mild	N	N
13-1	U	F/20 mo	16 mo	16 mo	Mild	N	None	N	N
14-1	N	F/5 yr	Birth	1 yr	Mild	N	None	Y	Y
15-1	Y	M/14 yr	13 mo	13 mo	Severe	Y	Severe	Y	Y

U, unknown.

Table 4. Genotype-phenotype correlations in patients with and without a *PHEX* gene mutation

	Mutation (+) (n=9)	Mutation (-) (n=6)	*p* value
Sex ratio (M:F)	1:8	3:3	> 0.1
Family history (+:-)	3:1	2:3	> 0.1
Age at onset (months)	64±71.2	17±9.5	0.049
Skeletal disease			> 0.1
Mild	3	3	
Moderate to severe	6	3	
Dental disease			> 0.1
None to mild	2	4	
Moderate to severe	7	2	

with a *PHEX* gene mutation and three patients without a *PHEX* gene mutation. The mean total serum calcium and phosphorus levels for those 10 patients were 9.2±0.4 mg/dL and 2.2±0.8 mg/dL, respectively.

Eight different mutations in the *PHEX* gene were detected in nine patients of the 15 unrelated Korean patients (60%). Of these, c.64G>T, c.1699C>T, c.466_467insAC, c.1174-1G>A, and c.1768+5G>A were novel mutations identified in this study (Fig. 2).

Inspection of the mutations revealed that c.1363G>T (p.Glu455X) and c.1699C>T (p.Arg567X) were nonsense mutations, and that c.1601C>T (p.Pro534Leu) and c.64G>T (p.Ala22Ser) were missense mutations. One mutation, c.466_467insAC, was an insertion that causes a frameshift leading to a downstream stop codon at amino acid 222. Three mutations, c.1174-1G>A (IVS10-1G>A), c.1768+5G>A (IVS17+5G>A), and c.1965+1G>A (IVS19+1G>A), occur at splicing acceptor/donor sites; c.1174-1G>A was detected in two unre-

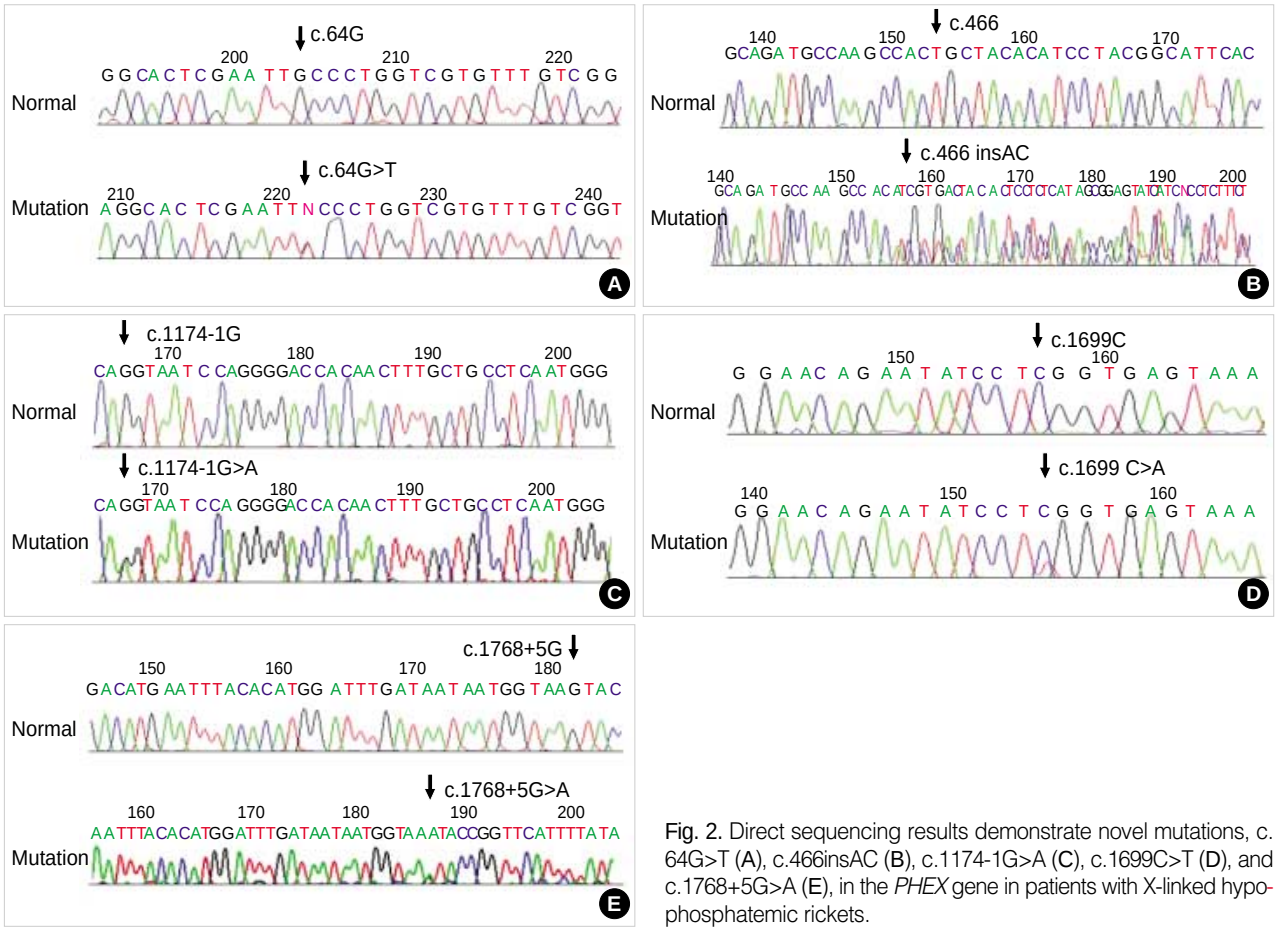

Fig. 2. Direct sequencing results demonstrate novel mutations, c.64G>T (A), c.466insAC (B), c.1174-1G>A (C), c.1699C>T (D), and c.1768+5G>A (E), in the *PHEX* gene in patients with X-linked hypophosphatemic rickets.

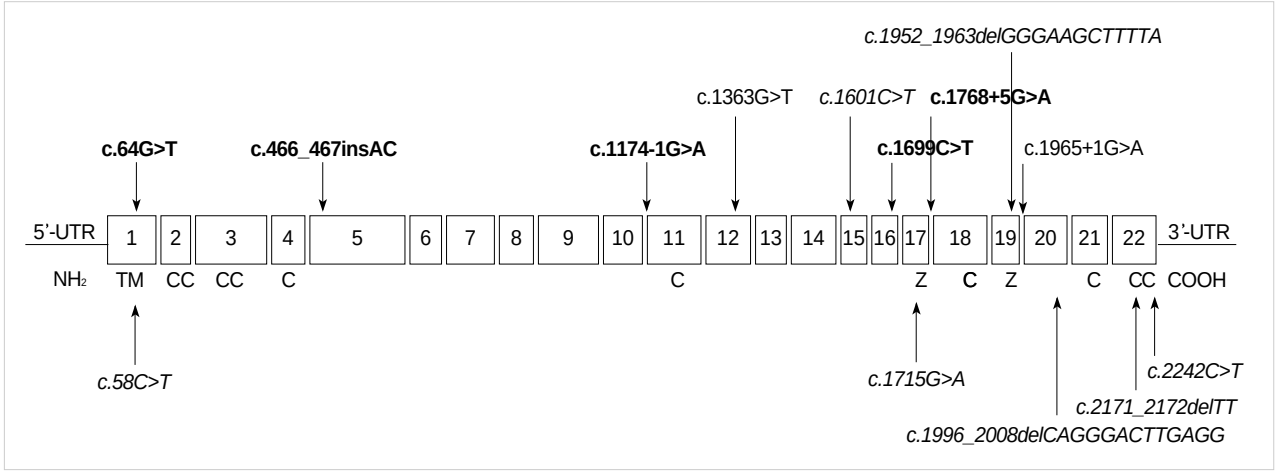

Fig. 3. Mutations of the *PHEX* gene identified in Korean patients with X-linked hypophosphatemic rickets. The putative transmembrane domain (TM), cysteine residues (C), and zinc-binding domains (Z) are shown below the boxes of the 22 exons. Novel mutations found in this study are shown in bold.

lated Korean patients. Two mutations, c.64G>T and c.466_467insAC, are located in the N-terminal half and the other six mutations are in the C-terminal half of the PHEX protein (Fig. 3). For novel splice variants, automated splicing mutation analysis predicted that the c.1174-1G>A variation decreases the binding energy of the natural splice acceptor site to 0.5% and thus abolishes the site, and that the c.1768+5G>A variation decreases the binding energy of the natural splice site to 8.7% of its initial energy and thus weakens the original donor splice site.

Table 5. Genotype-phenotype correlations in patients with a *PHEX* gene mutation in terms of mutation type

Mutation	Types		Locations	
	Truncating (n=3)	Nontruncating (n=6)	N-terminal half (n=2)	C-terminal half (n=7)
Sex ratio (M:F)	0:3	1:5	0:2	1:6
Family history (+:–)	2:0	1:1	0:0	3:1
Age at onset (months)	107±107.8	43±42.7	30±6.0	74±29.8
Skeletal disease				
Mild	2	1	2	1
Moderate to severe	4	2	0	6*
Dental disease				
None to mild	2	0	0	2
Moderate to severe	4	3	2	5

*$p<0.1$ (0.083); $p>0.1$ for other parameters.

The phenotypes of the 15 patients and of all available family members (including five family members of two patients) were analyzed. The average age at onset was 64 months in the group with a *PHEX* mutation and 17 months in the group without a *PHEX* mutation ($p=0.049$; Table 4). No significant correlation was found between the severity of the skeletal or dental disease and the mutation type (Table 5). Skeletal disease was more severe in the group with a mutation in the C-terminal half of the protein ($p=0.083$) (Table 5).

DISCUSSION

XLH is the most common form of FHR and results from a mutation in the *PHEX* gene. In our study, the mutation detection rates in the *PHEX* gene were 60% in familial cases and 25% in sporadic cases among patients with XLH. These are similar to the results of previous studies: 51-86% in familial cases and 22-57% in sporadic cases (1, 2, 8-10), except for one Finnish study, in which the mutation detection rate was 100% for familial cases and 93% for sporadic cases (11). The lower mutation detection rate in sporadic cases might be explained by the fact that the sporadic disease can be caused by other types of hypophosphatemic rickets, such as ADHR (1). Thus, patients without a *PHEX* gene mutation should be screened for mutations in fibroblast growth factor 23 (4, 12). Because only the 22 exons were screened for mutations in our study, mutations in the promoter, introns, 5′-untranslated region, 3′-untranslated region, and target sequences of miRNAs might have been overlooked (10, 13).

The c.1601C>T mutation has been observed in many studies (1, 2, 8-10, 14). This region may be prone to mutation, as suggested by Dixon et al. (9). Pro534 is encoded by one of 47 CpGs in the *PHEX* gene (15). The p.Pro534Leu mutation seems to affect the local hydrophobicity of the gene product, because leucine is aliphatic (2), and the substituted proline is conserved in ECE-1 and the KELL antigen (8). The c.64G>T mutation, a new mutation detected in this study, occurs at the site of the putative transmembrane domain. No mutation was identified in the putative transmembrane domain in a previous study (9).

The marked difference in the average age at onset between the groups with and without a *PHEX* mutation may be the result of the small sample size and the late age at onset of one family member, subject 7-2 in Table 2. Severe phenotypes usually begin to manifest at an earlier age than do mild phenotypes. However, early mean age of onset and disease severity were not correlated in this study. Furthermore, the difference in the average age at onset between the groups with and without a *PHEX* gene mutation was not statistically significant in a previous study (10). A larger sample size is required to confirm these data.

The number of mutations in the C-terminal half of PHEX was 3.5 times greater than the number in the N-terminal half in this study, and 1.7 times greater than that reported by Filisetti et al. (15). Patients with a mutation in the C-terminal half of the protein had more severe skeletal disease in this study. The N-terminal region contains the cytoplasmic domain, transmembrane domain, and five conserved cysteine residues, whereas the C-terminal region contains two zinc-binding motifs in exons 17 and 19, five conserved cysteine residues, and the catalytic site (2, 5, 15, 16). No agreement has yet been reached regarding the correlation between the disease phenotypes and *PHEX* mutation locations, including those in this study (1, 8, 17). Holm et al. (1) identified a trend between truncating mutations and more severe skeletal disease in a familial group ($p=0.072$). However, Cho et al. (10) reported no correlation between phenotype and mutation type, consistent with the results of this study.

The gene dosage effect was also analyzed in the nine patients with *PHEX* mutations, but no significant correlation was found (data not shown). Because the sample was small, we did not divide the group into prepubertal and postpubertal age groups. However, Holm et al. (1) reported a trend towards an association between male sex and more severe dental disease. Because XLH is inherited as an X-linked dominant trait, females should usually be less severely affected than males. However, no gene dosage effect was observed in this study or in a

previous study (10), although our sample was too small to allow any conclusion to be drawn. Previous studies have indicated that the *PHEX* gene is subject to random inactivation, but it has also been reported that some alleles escape inactivation (18, 19).

Hypophosphatemic rickets often exhibit high pulp horns, large pulp chambers, and dentinal clefts. Although odontoblast function is normal, hypophosphatemia leads to dysplastic and poorly mineralized areas of the interglobular dentin (20). We classified dental diseases according to the number of dental abscess lesions and the treatments performed for these abscesses. However, no genotype-phenotype correlation was detected in comparisons of dental disease severity.

In this study, although skeletal disease tended to be more severe in the group with a mutation in the C-terminal half of PHEX, the sample size was too small to draw a definitive conclusion. Therefore, identification of the mutation in the *PHEX* gene may have a limited prognostic value in patients with XLH. Other factors may exist that determine the phenotypes of patients with XLH.

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