CASE REPORT OLGU SUNUMU

A Novel PHEX Mutation in A Case Followed Up with A Diagnosis of X-linked Hypophosphatemic Rickets

X'e Bağlı Hipofosfatemik Raşitizm Tanısı ile Takip Edilen Bir Olguda Yeni Bir PHEX Mutasyonu

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Abstract

Introduction: X-linked hypophosphatemic is a result of a mutation which leads to loss of function in the *phosphate-regulating endopeptidase homolog X-linked (PHEX)* gene. The case is here presented of a patient followed up for XLH rickets, with the formation of a stop code through frame-shifting mutation in the PHEX gene.

Case Report: An 18-month old male infant presented at our clinic with the complaint of curvature in the legs. In the physical examination of the infant, height was measured as 78 cm (-1.67 SDS) and weight was 12.5 kg (0.52 SDS). Deformity was present in the frontal protusion, the wrist widths and the legs. Laboratory test results were determined as phosphorus: 2.3 mg/dL (n=3.5-4.7), calcium: 9.8 mg/dL (n=8.5-10.5) , alkaline phosphatase (ALP) 707 IU/L (n=40-150), 25(OH) D vitamin:18 µg/L (n=18-40), PTH: 79 pg/mL (n=15-68), and tubular phosphorus reabsorption was low (71%). Visualisation on wrist radiographs of collapse in the metaphyseal sections of the radus and ulna and metaphyseal irregularity. Conventional treatment was started. Next generation sequence analysis of the proband revealed the presence of a hemizygous c.281_288delTTCCCGAA (p.lle94ArgfsTER14) frameshift variant in *PHEX* gene. This novel variant is pathogenic according to the ACMG criteria, and not reported in any database before. While full-fill clinical recovery was not achieved with conventional treatment and some complications occured, Burosumab treatment was started.

Conclusion: Here presented of a patient who was diagnosed with XLH, and was then determined with a novel mutation in the *PHEX* gene. The current treatment options directed at the basic pathology render genetic diagnosis more important in cases of hypophosphatemic rickets.

Keywords
Hypophosphatemic rickets, *PHEX* gene, X-linked

Anahtar kelimeler
Hipofosfatemik rikets, *PHEX* geni, X'e bağlı kalıtım

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Öz

Giriş: X'e bağlı hipofosfatemik (XLH) rikets *fosfat düzenleyici endopeptidaz homolog X (PHEX)* geninde fonksiyon kaybına yol açan bir mutasyon sonucunda gelişmektedir. Burada, XLH tanısı ile izlenen ve PHEX geninde novel bir mutasyon saptanan olgu sunulmaktadır.

Olgu Sunumu: On sekiz aylık erkek bacaklarla eğrilik nedeniyle başvurdu. Fizik muayenesinde boyu 78 cm (-1,67 SDS) ve ağırlığı 12,5 kg (0,52 SDS) olarak ölçüldü. Frontal bölgede belirginleşme, bilekte genişleme ve bacaklarda o bind deformitesi mevcuttu. Laboratuvar incelemesinde fosfor: 2,3 mg/dL (n=3,5-4,7), kalsiyum: 9,8 mg/dL (n=8,5-10,5), alkalen fosfataz 707 IU/L (n=40-150)

idi. 25(OH) D vitamini: 18 µg/L (n=18-40), parathormonu 79 pg/mL (n=15-68) ve tübüler fosfor geri emilimi düşüktü (%71). Bilek grafisinde radius ve ulnanın metafiz bölümlerinde düzensizlik ve çanaklaşma vardı. Olguya hipofosfatemik rikets tanısı ile konvansiyonel tedavi başlandı. Yeni nesil dizi analizi ile *PHEX* geninde çerçeve kayması mutasyonuna yol açan hemizigot c.281_288delTTCCCGAA (p.lle94ArgfsTER14) varyantı tespit edildi. Bu yeni varyant, ACMG kriterlerine göre patojenik ve daha önce herhangi bir veri tabanında rapor edilmemiştir. Konvansiyonel tedavi ile tam klinik düzelme sağlanamayınca ve tedavi ile ilişkili komplikasyonlar oluşması üzerine olguya Burosumab tedavisi başlandı.

Sonuç: Burada *PHEX* geninde yeni bir mutasyon saptanan bir olgu sunulmuştur. Burosumab gibi temel patolojiye yönelik mevcut tedavi seçenekleri, hipofosfatemik raşitizm olgularında genetik tanıyı daha önemli hale getirmektedir.

Introduction

As XLH causes the loss of phosphorus from the kidneys, it is the most frequently seen form of rickets characterised by hypophosphatemia, with a frequency of 1/20,000. The disease forms as a result of mutation in the *PHEX* gene localised on XP22.1 (1). The *PHEX* gene encodes a protein named phosphate-regulating neutral endopeptidase (2). This protein suppresses serum levels of the phosphatonin, fibroblast growth factor 23 (FGF-23). Inactivating mutations in *PHEX* result in an upregulation of FGF-23 expression. Elevated levels of serum FGF-23 downregulates renal sodium-phosphate transporters and increase urinary phosphorus excretion. It also reduces the absorption of phosphorus from the intestine by restricting the synthesis of active vitamin D (3). While phosphate salts and active vitamin D metabolites have been used in treatment for many years, it is currently known that differentiation of XLH from other hypophosphatemic rickets types can change the treatment approach (4).

The case is here presented of a patient who presented at the rickets clinic, was diagnosed with XLH, and was then determined with a novel mutation in the *PHEX* gene.

Genomic DNA was isolated from peripheral blood nucleated cells. The amino acid coding regions of the relevant genes were amplified with the Osteo-GeneSGKit DensidadOsea-CE 57 Genes kit and sequenced in the Illumina MiSeQ system. The Genomized Database was used in the analysis of the data, and the IGV_2.3.6 program was used in the visual evaluation of the data.

Case Report

An 18-month old male infant presented at our clinic with the complaint of curvature in the legs. There had been no previous complaints in the patient history, and the curvature in the legs had been noticed as the infant started to walk. There was no parental consanguinity and the infant had been born at term as the first pregnancy. The mother was short in height, with curvature in the legs (Patient's pedigree is shown in Figure 1). In the physical examination of the infant, height was measured as 78 cm (-1.67 SDS) and weight was 12.5 kg (0.52 SDS). Deformity was present in the frontal protusion, the wrist widths and the legs. Laboratory test results were determined as phosphorus: 2.3 mg/dL (n=3.5-4.7), calcium: 9.8 mg/dL (n=8.5-10.5), alkaline phosphatase (ALP) 707 IU/L (n=40-150), 25(OH) D vitamin: 18 µg/L (n=18-40), PTH: 79 pg/mL (n=15-68) and tubular phosphorus reabsorption was low (71%). The diagnosis of hypophosphatemic rickets was made from the visualisation on wrist radiographs of collapse in the metaphyseal sections of the radius and ulna and metaphyseal irregularity.

Conventional treatment was started for the patient at the recommended doses of 30 mg/kg/day phosphate and 20 ng/kg/day calcitriol. In the 6th month of treatment, ALP and PTH levels returned to normal. In the second year of treatment, nephrocalcinosis developed. At the age of 5 years, the height of the patient was SDS -1.87 and rachitic findings continued, more evidently in the lower extremity bones. Next generation sequence analysis of the proband revealed the presence of a hemizygous c.281_288delTTCCCGAA

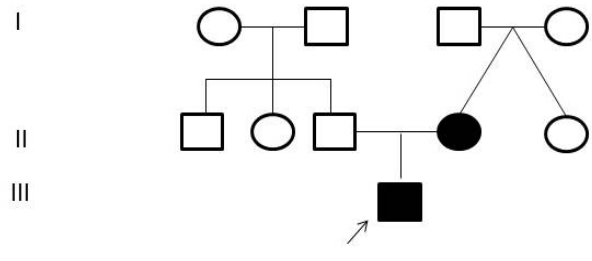

Figure 1. Pedigree of patient.

(p.Ile94ArgfsTER14) frameshift variant in *PHEX* gene (Figure 2). Sanger sequencing confirmed this variant in heterozygous manner in his mother demonstrating true hemizgosity. This novel variant is pathogenic according to the ACMG criteria and not reported in any database before. While full-fill clinical recovery was not achieved with conventional treatment and some complications occured, Burosumab was planned to use as a treatment option.

Discussion

The genetic basis of XLH disease is a mutation in the PHEX gene leading to function loss (1). Mutation result in increased synthesis and secretion of fibroblast growth factor 23 (FGF-23) (5). By leading to reduced gene expression of sodium-phosphate co-transporters (NaPi-IIa and NaPi-IIc) in the apical surface of proximal renal tubule cells, increased FGF-23 impairs proximal renal tubular re-absorption of phosphate (6). In addition, increased FGF-23 activates CYP24A1 enzyme by inhibiting CYP27B1 enzyme and decreases the level of 1.25-dihydroxyvitamin D (1.25(OH)2D), which is the active metabolite of vitamin D in the circulation (7).

Chronic hypophosphatemia leads to reduced bone mineral density and the weighting of clinical symptoms varies in each case. Patients most frequently present with the complaint of curvature in the legs, as in the current case. In growing children, the main skeletal findings are progressive bowing in the extremities, anteromedial torsion in the tibia and short height. These findings improve with medical treatment but the majority are not completely eliminated. The main finding of rickets on radiographs is metaphyseal irregularity. Typical laboratory findings are hypophosphatemia and low/normal 1.25 (OH)2D vitamin level. The serum alkaline phosphatase level increases and serum calcium and 25 OH D vitamin levels usually are normal (8). Conventional XLH treatment consists of phosphate salts and active vitamin D preparates (9). Higher treatment doses are associated with nefrocalsinozis and could improve bone deformities (10). In recent years, a treatment option has come to the fore which targets the main pathogenesis of XLH rickets. Excessive action of FGF-23 is causing XLH, therefore the inhibition of FGF-23 activities to be new candidate for treatment (11,12). Burosumab is a recombinant human IgG1 monoclonal

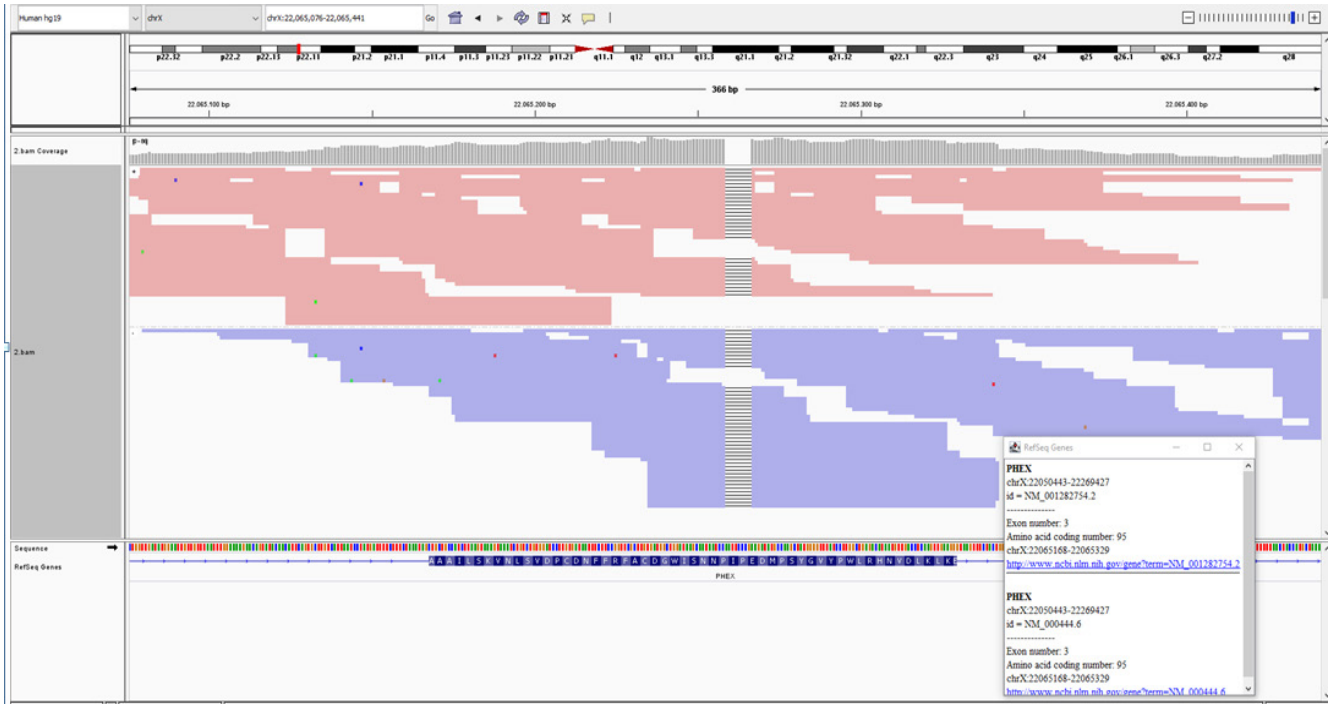

Figure 2. Integrative genomic view of c.281_288delTTCCCGAA (p.Ile94ArgfsTER14) hemizygous change in *PHEX* gene in exon 3.

antibody that inhibits FGF-23 activity. In phase 1 and phase 2 studies including adults diagnosed with XLH, treatment with Burosumab has been shown to correct phosphate re-absorption and thus normal levels of serum phosphorus and 1.25 $(OH)_2D$ are recovered (13). In a phase 2 study of children, Burosumab was shown to improve phosphorus metabolism and reduce the severity of rickets (4,14).

Burosumab treatment is superior to conventional management of the condition in both adults and children and has been transformative for the treatment of XLH (15). The current treatment options directed at the basic pathology render genetic diagnosis more important in cases of hypophosphatemic rickets. The case has been presented here of a patient determined with a novel mutation in the PHEX gene.

Ethics

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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