Two siblings with hypophosphatemic rickets: SLC34A3 gene mutations with different clinical phenotypes

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BACKGROUND:

- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH; OMIM: 241530) is a rare autosomal recessive disorder, which is the result of loss-of-function mutations in the sodium-phosphate co-transporter NPT2c.
- This disorder is characterized by renal phosphate (Pi) wasting, hypercalciuria, increased 1,25 $(OH)_2$ D levels, and decreased parathyroid hormone (PTH) levels.
- Here we report the clinical features of two siblings with HHRH, confirmed with molecular diagnosis.

CASE REPORT:

Two siblings born to first-degree consanguineous parents,

- *Sibling 1* is a 16-year 9-month old boy
- *Sibling 2* is a 8-year 8-month old girl

- They were both referred to our outpatient clinic due to bowing legs and difficulty in walking
- In addition, *Case 1* suffered fracture on his right femur, which was the fourth fracture on his leg
- Birth histories and developmental milestones were normal in both of them
- All clinical and laboratory findings of the patients are given in Table 1.
- Genetic analysis revealed homozygous mutation in SLC34A3 c.756G>A (pGln252=) and c.1335+2T>A p.? (splice donor variant)
- After oral phosphorus treatment clinical and biochemical improvements were observed in both cases. In Sibling 1, no fractures were detected after therapy.
- No side effects were seen during the treatment.

Table 1:Clinical and laboratory features of the patients

	Sibling 1	Sibling 2
At presentation		
Age (yrs)	16.4	8.7
Weight kg (SDS)	48 **(-2.6)**	24.7 **(-0.7)**
Height cm(SDS)	155.3 **(-3.0)**	129.9 **(-0.1)**
BMI kg/m²(SDS)	19.9 **(-1.0)**	14.6 **(-0.9)**
PubertyTanner	5	1
Clinical Findings	• Severe deformity on the lower extremity • Multiple long bone fractures • Bounded to the wheelchair	• Genu valgum deformity
Laboratory (normal ranges)		
Ca, mg/dl (9.2-11)	9.7	10.1
P, mg/dl (2.5-5.0)	1.7	3.3
ALP, U/L (142-335)	360	435
PTH, pg/ml (15-65)	8.2	14.5
25 OH D vitamin, ng/ml	9.2	13.4
1-25 OH D vitamin, pg/ml (26-95)	88	-
TPR	88%	88%
Imaging		
Renal USG	Hypercalciuria Bilateral renal calculi	Hypercalciuria Grade 1 nephrocalcinosis
L1-L4 z-score (DXA)	-3.9	-2.0
Genetic	*SLC34A3* c.756G>A (pGln252=) and c.1335+2T>A p.? (splice donor variant)	
Treatment	Oral phosphate (50 mg/kg/gün)	Oral phosphate (20 mg/kg/gün)
Duration of Treatment	0.5	0.5

Yrs: Years, BMI: Body mass index, Ca: Calcium, P: Phosphate, ALP: Alkalen phosphatase, PTH: Parathormone, TPR: Tubular phosphate reabsorption, USG: Ultrasound, DXA: Dual energy X absorptiometry

CONCLUSION:

- HHHR is a rare cause of hypophosphatemic rickets
- The clinical phenotype due to mutations in the SLC34A3 gene may vary even among effected siblings regarding to
  - severity of hypophosphatemia,
  - short stature,
  - deformity of extremities and also frequency of fractures.