Diversity in phenotype of 2 siblings with X-linked hypophosphatemic rickets due to *PHEX* mutation

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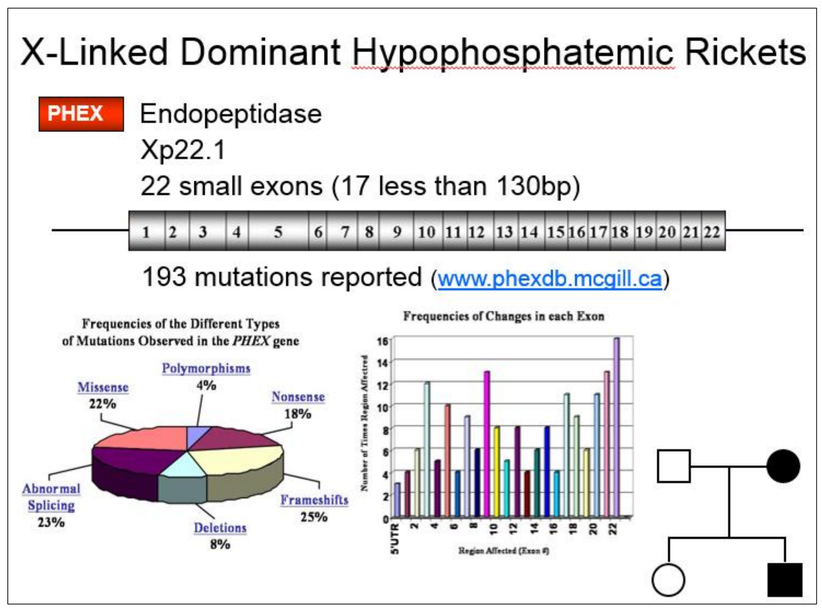
OBJECTIVES

Hypophosphatemic rickets (HR) belongs to a heterogeneous group of rare diseases which are caused by phosphate deregulation due to excessive renal phosphate wasting. The most common form is X-linked hypophosphatemic rickets (XLH, X-linked dominant, OMIM #307800), caused by mutations in *PHEX* gene (OMIM *300550, Phosphate regulating gene with homology to neutral endopeptidases on the X chromosome) located on the X chromosome, and encoding for a transmembrane endopeptidase involved in phosphate metabolism and bone mineralization. There is also, among others, autosomal dominant hypophosphatemic rickets (ADHR, OMIM #193100) caused by mutations in the gene encoding fibroblast growth factor 23 - *FGF23* (OMIM *605380) and autosomal recessive hypophosphatemic rickets caused by mutations in *DMP1* gene. XLHR phenotype is characterized mainly by rickets with bone deformities, short stature, dental anomalies. The typical laboratory findings include hypophosphatemia, low renal phosphate reabsorption, normal serum calcium level, hypocalciuria, normal/low serum level of vitamin D (1,25(OH)2D3), normal serum level of PTH, and increased activity of serum alkaline phosphatase.

The aim of the study was to investigate the clinical phenotype and molecular background of HR in a family in which XLHR was suspected.



CASE PRESENTATION

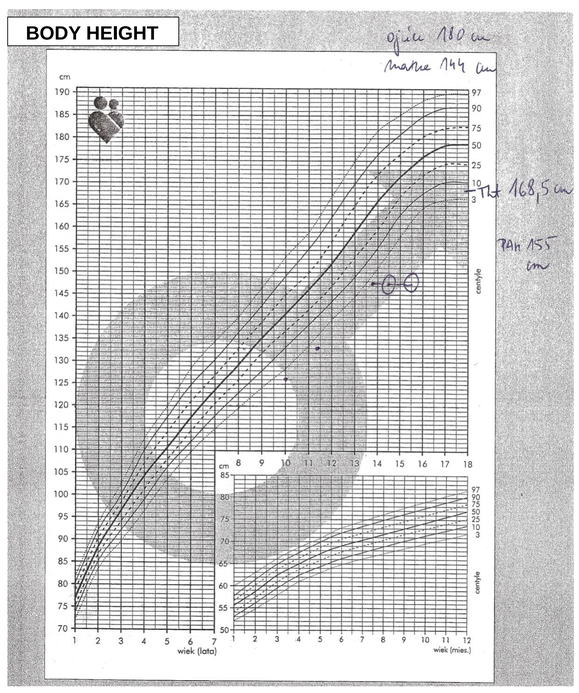
Two siblings, an older brother aged 14 years and 1 month and his younger sister aged 12 years and 10 months were diagnosed with HR due to clinical and biochemical picture.

PATIENT	SEX	AGE	AGE AT DIAGNOSIS	CLINICAL SYMPTOMS	EAR PROBLEMS	DENTAL PROBLEMS	OTHER CLINICAL FEATURES
1	MALE A2 P4, testes 12 ml	14y 1m	11 months	Genu varum (as in the mother), short stature, lumbar hyperlordosis	no	no	Chronic rhinitis, obesity, low level of cholesterol and triglicerides (as in the father)
2	FEMALE Menarche: 11y 5m A3 P5 Th5	12y 10m	3 months (therapy was started before clinical symptomes occured)	Genu valgus, lumbar hyperlordosis	no	no	low level of cholesterol and triglicerides (as in the father)

PATIENT	S-Ca (N 2,2-2,7 mmol/l)	S-P (N 4-7 mg/dl)	S-ALP (N 93-309 IU/L)	S-PTH (N 15-68,3 pg/ml)	S-25(OH)D3 (N 9,4-59,1; opt. 30-50 ng/ml)	U-Ca (N <4 mg/kg/d)	U-P (N16-20 mg/kg/d)	TRP1 % (N>80%) At the diagnosis	TRP2 % (N>80%) During therapy
1	2,50	↓3,00	↑ 482	37,6	20,0	0,59	↓ 13,9	85,4	-
2	↓1,89	↓2,61	129	↓14,2	33,7	1,9	18,9	82	-

S – serum U – urine ALP – alkaline phosphatase TRP - Tubular reabsorption of phosphate

BODY HEIGHT



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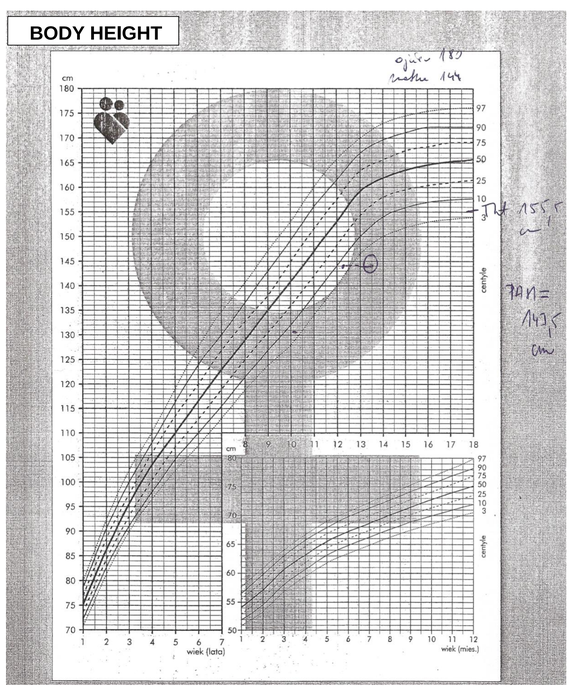

METHODS AND RESULTS

DNA was isolated from fresh blood and all exons of *PHEX* gene were amplified using PCR and directly sequenced.

The dominant clinical sign in both patients was bowing of legs (genu varum in a boy and genu valgum in a girl). Short stature, predominantly affecting the brother, and lumbar hyperlordosis were also observed. Short stature and genu varum were also seen in affected mother. The difference in height was probably due to the time of treatment introduction, as it was initiated in the girl in the infantile period before the clinical signs appeared. In both patients a novel c.1483-1G>A mutation in intron 13 was identified. This mutation was also present in the affected mother leading to changes in the transcription of the RNA.

CONCLUSIONS

The early diagnosis of XLHR is very important for proper treatment and to prevent severe bone deformities and improve final height.

Early treatment with vitamin D and phosphorus is not alwasy effective, safe for the patients and helps reducing of progression of bone deformities.

Genu varum is likely to be involved in worsening height prognosis.

Whether earlier ortopedic intervention could improve the height prognosis recquires further investigation.

Molecular confirmation of hypophosphatemic rickets may be crucial in patients in whom laboratory results are inconclusive.

The molecular analysis of *PHEX* gene is very important for the confirmation of clinical diagnosis of hypophosphatemic rickets and highlights the role of further genetic counselling in families with HR patients.

References

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