PHENOTYPE CHARACTERIZATION OF A *PHEX* NON-CANONICAL SPLICE-SITE MUTATION IN PEDIATRIC AND ADULT PATIENTS OF A FAMILY AFFECTED BY X LINKED HYPOPOSPHATEMIC RICKETS.

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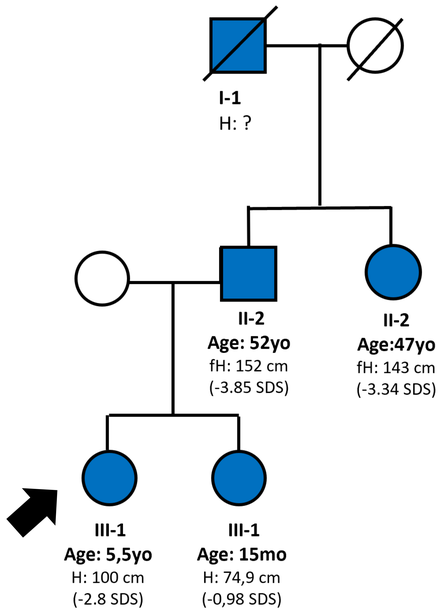
BACKGROUND

X-linked hypophosphatemia (XLH) is a rare hereditary condition caused by mutation in *PHEX* gene involved in phosphate homeostasis. PHEX disruption determine deficient skeletal mineralization, rickets, bone deformity, growth failure, dental problems, joint pain and impairment. More than 400 pathogenic or likely pathogenic variants have been reported, among them only 17% are splice-site mutations. This is the first report describing phenotypic features of a rare PHEX intron mutation, c.1586+6T>C.

FAMILIAL PEDIGREE



PEDIATRIC CASE REPORT

The proband (III-1) presented with a diagnosis of rickets. Clinical examination points out : asymmetric short stature, macro-dolichocephaly, frontal bossing, dental hypodiplasia, varus tibia and knee, waddling gait since the first year of life. Total body X-ray scan highlighted features of active rickets (RSS 6). Biochemistry on admission were consistent with hereditary hypophosphatemic rickets (Table 1, columns T0). Genetic analysis for XLH was performed and revealed *PHEX i*ntron mutation, c.1586+6T>C.

Proband's sister (III-2) received an early diagnosis of XLH at 15 months of age after testing positive for c.1586+6T>C mutation. On admission, rachitic rosary, thickened wrists and varus tibia and knee were present. Radiographic scans shows active rickets (RSS 8), while laboratory examination revealed hypophosphatemia with hyperphosphaturia (Table 1, columns T0).

Burosumab therapy (0,8mg/Kg/2w) demonstrated an excellent clinical and biochemical response at 6 months of follow-up (Table 1, columns T6) and no side effects.

	III-1		III-2	
	T0	**T6**	**T0**	**T6**
HEIGHT/LENGTH, SDS	-2.34	-2,26	-1.14	-1.09
Δ H/L-TARGET H , SDS	1,55	1,47	0,35	0.30
GROWTH VELOCITY, SDS	-3.09	**-1.19**	-1,73	**0.16**
OFC, SDS	>1,88	>1,88	0.47	1.09
Ca, mg/dL	9,7	10,2	9,8	10,1
P, mg/dL	2,4	**3,65**	3,2	**4,19**
PTH, pg/mL	24,4	59,1	24,9	37,2
25-(OH)D3, ng/mL	30,5	20,7	37	14,7
ALP, U/L	423	323	741	465
TRP %	72	91	80,4	84

Table.1 Anthropometric and laboratory data's periodic assessment

ADULT CASE REPORT

Both adult patients received a late diagnosis in adulthood only after XLH diagnosis in pediatric patients.

They both share a personal history of poor growth misdiagnosed with constitutional short stature, and multiple orthopaedic treatments for tibial varum.

Subject II-1 and II-2 shared severe asymmetric short stature, transmissive hypoacusis, tibia vara and reduced mobility due to severe bone and joint pain. Subject II-2 showed also dental enamel hypoplasia. Biochemistry on admission revealed evident hypophosphatemia and hyperphosphaturia (table 2, columns T0).

Skeletal survey demonstrated diffused osteomalacia and spondylarthrosis, coxosclerosis and dysmorphism of femoral epiphyses and fibula in both patients. In addition, subject II-1 presented hyperostosis in bone's III proximal, widespread osteoarthritis of the foot bones, while subject II-2 had dysmorphism of tibial epiphyses.

Compassionate use in adult patients (1 mg/Kg/4w), ameliorated Quality of life as shown by The Western Ontario and McMaster Universities Arthritis Index (WOMAC) despite non-significant biochemical improvement (table 2, columns T6).

	II-1		II-2	
	T0	**T6**	**T0**	**T6**
Ca, mg/dL	8,3	9.6	9.9	10.3
P, mg/dL	1.9	2.8	2.7	3.13
PTH, pg/mL	40	90.2	31.5	41.4
25-(OH)D3, ng/mL	18.2	13.8	33.3	10.6
ALP, U/L	111	n.a.	62	n.a.
TRP %	85	n.a.	81	n.a.
WOMAC, score	3,43	2,7	3,71	3,14

Table.2 Laboratory data's periodic assessment

CONCLUSIONS

Data inhere presented extend the phenotypic characterization of a non-canonical splice site mutation in the *PHEX* gene. In 2019, BinEssa H.A. et al. demonstrated that C to T substitution in position c.1586+6 causes partial exon 14 skipping with 40% of wild-type protein present and speculated this variant could determine a milder phenotype due to a certain percentage of normal transcript. On the contrary, this report points out this genetic defect has complete penetrance and severe expressivity. Non-canonical splice-site mutations should not be omitted in genetic screening as the correct and precocious diagnosis is mandatory to start timely the appropriate treatment.

We are confident that precocious therapy onset in infancy will positively address growth failure and major skeletal abnormalities in patients III-1 and III-2 as some preliminary data on Burosumab therapy suggested.

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