Paediatric patients with heterozygous *ALPL* mutation show a broad clinical phenotype

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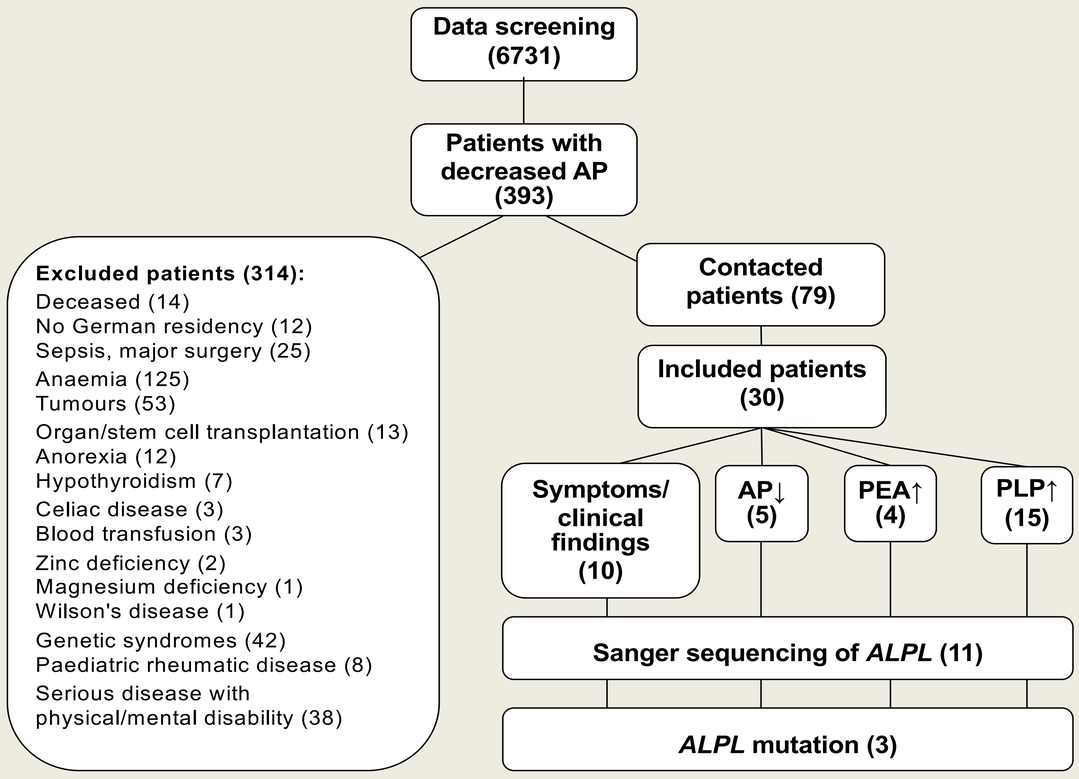
Background

Hypophosphatasia (HPP) is a congenital disorder of bone metabolism. It is caused by mutations in the *ALPL* gene, which codes for tissue-nonspecific alkaline phosphatase (TNSAP). Patients with disease manifestation in later childhood or adulthood often have mild and less pathognomonic symptoms. Childhood and adult HPP can be inherited recessively or dominantly. Dominant HPP is believed to result from the dominant negative effect of loss of function mutations. Among patients with heterozygous *ALPL* mutation, patients with dominant negative effect mutations (class 1 mutations) appear to be more affected. A single nucleotide polymorphism (SNP) in *COL1A2* seems to act as modifier of the phenotype of HPP. The heterozygous genotype G/C is statistically associated with a more severe phenotype [1].

An enzyme replacement therapy has been approved for HPP patients with manifestation of the disease during infancy or childhood.

Our goal was to identify patients with mild forms of HPP by laboratory data screening for decreased alkaline phosphatase (AP) (hypophosphatasemia) within a paediatric population.

Methods



We assessed a total of 6731 alkaline phosphatase (AP) measurements of the center for pediatrics and adolescent medicine at university of Freiburg between January 2011 and January 2016 for AP values below the defined age- and gender specific limits:

girls: ≤ 12 years: AP <125 IU/l; > 12 years: AP <50 IU/l;
boys: ≤ 14 years: AP <125 IU/l; > 14 years: AP <70 IU/l.

We identified 393 patients with decreased AP. By reviewing the medical history and available laboratory findings, 288 patients were excluded due to their underlying disease or acute conditions. 79 patients were contacted and 30 patients were included. These patients underwent a detailed anamnesis regarding HPP-specific symptoms, a physical examination and HPP-specific laboratory diagnostics (AP, pyridoxal phosphate (PLP), phosphoethanolamin (PEA) and anorganic pyrophosphate (PPi)). 11 patients had clinical and/or laboratory abnormalities which were suspicious for HPP, therefore a sequencing of the *ALPL* gene was performed. 3 patients with heterozygous *ALPL* mutation were identified. These 3 patients received further diagnostics depending on their symptoms.

Conclusion: A diagnostic algorithm based on a decreased AP is able to identify patients with *ALPL* mutation after exclusion of differential diagnoses of hypophosphatemia and additional detection of elevated substrates of AP. The diagnostic triad of decreased AP, increased PLP and increased PEA is hightly suggestive for the presence of an *ALPL* mutation. Patients with heterozygous *ALPL* mutation can show a HPP phenotype due to mutations with dominant negative effect or be asymptomatic carriers. *COL1A2* seems to modulate the phenotype of patients heterozygous for *ALPL* mutations [1].

Case reports of three patients with heterozygous *ALPL* mutation

	Patient 1	Patient 2	Patient 3
General characteristics			
Age; sex	11 years; male	12 years; male	13 years; female
Family history	Dental problems (father)	Negative	Negative
Symptoms	Short statue (Height-SDS -3.07)	None	Chronic pain syndrome: musculo-skeletal pain
Laboratory findings			
AP IU/l (reference 3rd-97th percentile)	126 (152-396)	139 (159-405)	80 (104-385)
PEA in urine mmol/mol creatinine reference 0-15 mmol	14.4	23.8	14.4
PLP in serum µg/l reference 5-30	> 100 (intake of a multivitamin supplement)	62	> 100
PPi in urine mmol/mol creatinine	74.71	26.37	23.60
Examinations			
Renal ultrasound	No nephrocalcinosis	No nephrocalcinosis	No nephrocalcinosis
Osteodensitometry (lumbar spine)	z -1,0	Not done	Not done
X-ray (spine, pelvis, knee, hand)	No skeletal abnormalities	Not done	No skeletal abnormalities
MRI lower limbs	Not done	Not done	No (micro)calcifications
Genetics			
ALPL	c.1451[T>G];[T=]	c.1204[delC];[C=]	c.1471[G>A];[G=]
COL1A2: rs42524	c.1645[C>G];[C>G]	c.1645[C=];[C=]	c.1645[C>G];[C=]
Risk for disease phenotype [1]	Class 1 G/G	Class 2 C/C	Class 2 G/C
Therapy with Asfotase alfa	Intended	No	No

References: [1] Taillandier et al. Genetic analysis of adults heterozygous for ALPL mutations. J Bone Miner Metab. 2018 Nov;36(6):723-733
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