Poster P276

Genetic Characterization and Clinical Manifestations in Adults with Hypophosphatasia in the United States

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INTRODUCTION

- Hypophosphatasia (HPP) is a rare, chronic, and progressive metabolic disorder caused by deficient tissue-nonspecific alkaline phosphatase (ALP) activity.[1] This deficiency impairs bone and tooth mineralization and disrupts calcium and phosphate regulation, leading to a range of skeletal and non-skeletal symptoms.[1,2]
- HPP diagnosis is based on clinical manifestations accompanied by persistently low ALP activity.[3]
- HPP can be inherited in an autosomal dominant or autosomal recessive manner.[4] Many patients with HPP have one or two pathogenic variants of the *ALPL* gene; however, some patients carry variants of uncertain significance (VUS), while others have no identifiable *ALPL* variant.[4,5] Approximately 400 pathogenic variants of the ALPL gene have been identified to date.[6]
- Due to the rarity of HPP, limited information exists on the burden of HPP in patients with negative or uncertain genetic testing results.

OBJECTIVES

- This study aims to describe the genetic classification of adult patients with HPP and compare clinical manifestations of the condition based on *ALPL* genetic testing results (positive, negative, or VUS).
- Specific aims of the study were to:
  - Describe the genetic classification of HPP patients initiating treatment (positive, VUS, negative).
  - Compare burden of disease among patients with positive, negative, and VUS genetic testing results.
  - Assess how the classification of variants originally described as VUS have changed over time.

CONCLUSIONS

- We found that among treated adult HPP patients in the US, 16% presented with negative or VUS genetics.
- The clinical burden of the disease is multisystemic and substantial and does not differ significantly among patients with positive, negative, or VUS genetics.
- A majority of VUS were later reclassified as pathogenic or likely pathogenic, indicating that the presence of a VUS does not exclude a diagnosis of HPP. However, the proportions of reclassified VUS varied between databases.
- It is therefore crucial to educate payers, HCPs, and patients that HPP can be diagnosed in the absence of positive genetic testing and that genetic confirmation is not a mandatory criterion for diagnosis.

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Disclosures

Christina Peroutka has participated in advisory board meetings for Alexion and received research funding from Alexion to participate in the HPP Global Registry and Immune Substudy. Ashwin Anand, Michael Sicilia, and Anuja Panthari are employees of Forian, a consultancy that received funding from Alexion to conduct this analysis. Abigail Jastrab and Anastasia Abramson are employees of PANTHERx Rare, a company working in a partnership with Alexion. Genevieve Lyons, Jon Vlasnik, William R Mowrey, and Briana Sullivan are full-time employees of Alexion, AstraZeneca Rare Disease and hold stocks in the company.

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METHODS

- This retrospective, observational study analyzed *ALPL* genetic testing data of adult patients (aged ≥18 years) with HPP in the United States (US) who initiated treatment with asfotase alfa (AA).
- Data (11/1/2015 to 6/30/2025) were sourced from PANTHERx Rare's proprietary SWFT™ platform, which captures a large database of genetic and clinical data for HPP patients. PANTHERx Rare is a rare disease specialty pharmacy that dispenses almost all of AA prescription fills in the US, oversees patient intake, and coordinates the prior authorization process, supporting appropriate, timely access to therapy.
- Clinical manifestations and ALP enzyme levels prior to treatment were obtained from medical records.
- Included patients were required to have genetic testing data available. Testing was performed prior to treatment initiation.
- The results were classified as positive (≥1 pathogenic/ likely pathogenic variant), negative (benign/ likely benign variant(s) only or no variant reported), or uncertain (VUS variant(s) only), as reported by the testing laboratory. For patients with a VUS, the identified variant(s) were recorded.
- Chi-square tests were used for categorical variables and one-way ANOVA was used for continuous variables to compare across groups based on genetic testing results.
- To assess how variants originally classified as VUS have changed over time, each variant that was originally reported as VUS was researched using Human Genome Build hg38 and germline classifications in Franklin, Varsome, and *ALPL* Gene Variant databases to verify whether that variant is currently (as of November 2025) considered as Pathogenic/Likely Pathogenic, VUS, or Benign/Likely Benign.
  - For each variant originally classified as VUS, we reported the current classifications based on the three databases, as well as the concordance between them.

Figure 1: Patient Flow Diagram

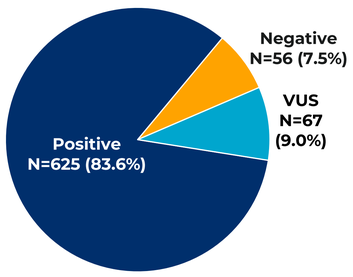
Note that all percentages were calculated using the total number of patients in the PANTHERx Rare database (N=2,281) as the denominator.

RESULTS AND INTERPRETATION

Patient Characteristics

- A total of 748 patients (mean age at referral of 46.3 years, 80% female) met the inclusion criteria (**Figure 1**).
- A majority of patients (83.6%) had positive genetic testing results, while 9.0% had VUS only, and 7.5% had negative results. (**Figure 2**).
- Patient demographics by genetic testing result are presented in **Table 1**.

Figure 2: Genetic Testing Results Among Adult HPP Patients (N=748)



VUS, variant of uncertain significance.

16% of adult patients with HPP initiated treatment in the absence of positive genetic testing

Table 1: Patient Demographic by Genetic Testing Results

	Positive (N=625)	Negative (N=56)	VUS (N=67)	P-Value
Age (Mean, SD), y	46.75 (15.29)	42.30 (12.09)	45.03 (15.97)	**<0.001**
Age (N, %)				**0.15864**
18-29 y	85 (13.6%)	7 (12.5%)	13 (19.4%)	
30-49 y	275 (44.0%)	31 (55.4%)	25 (37.3%)	
50-64 y	171 (27.4%)	16 (28.6%)	21 (31.3%)	
≥65 y	94 (15.0%)	2 (3.6%)	8 (11.9%)	
Sex (N,%)				
Male	126 (20.2%)	9 (16.1%)	12 (17.9%)	**0.70981**
Female	499 (79.8%)	47 (83.9%)	55 (82.1%)	

SD, standard deviation; VUS, variant of uncertain significance; y, years.

Symptom Burden

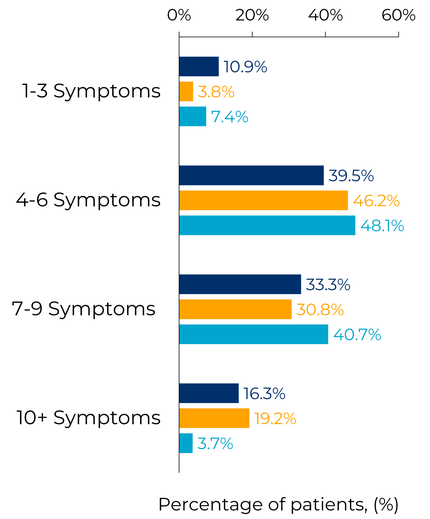
- Both genetic testing results and symptom data were available for 311 patients.
- There were no significant differences in most symptoms between patients with positive, negative, and VUS genetic test results (**Figure 3**).
  - Pain and weakness were the most common symptoms across all groups. Muscle/joint pain impacted 79.1%, 80.8%, and 77.8% of patients with positive, negative, and VUS results, respectively (p=0.96); bone pain occurred in 79.1%, 88.5%, and 74.1% (p=0.41).
  - Difficulty walking was reported by 43.0%, 34.6%, and 44.4% with positive, negative, and VUS results (p=0.69).
  - Fractures were common in all groups, affecting 72.1%, 69.2%, and 85.2% with positive, negative, and VUS results, respectively (p=0.31).

Number of Symptoms

- Patients experienced 6-7 HPP symptoms on average. The mean number of symptoms experienced did not vary significantly among patients with positive, negative, and VUS genetics (6.8, 6.9, and 6.1 symptoms per patient, respectively; p=0.51)
- A nominally higher proportion of patients with VUS experienced 4-6 and 7-9 symptoms, while more patients with positive and negative genetic testing results experienced ≥10 symptoms (**Figure 4**). However, these differences were not statistically significant (p=0.51).

Disease burden did not vary significantly among patients with positive, negative, or VUS genetic results

Figure 4: Number of Symptoms by Genetic Testing Results (N=311)



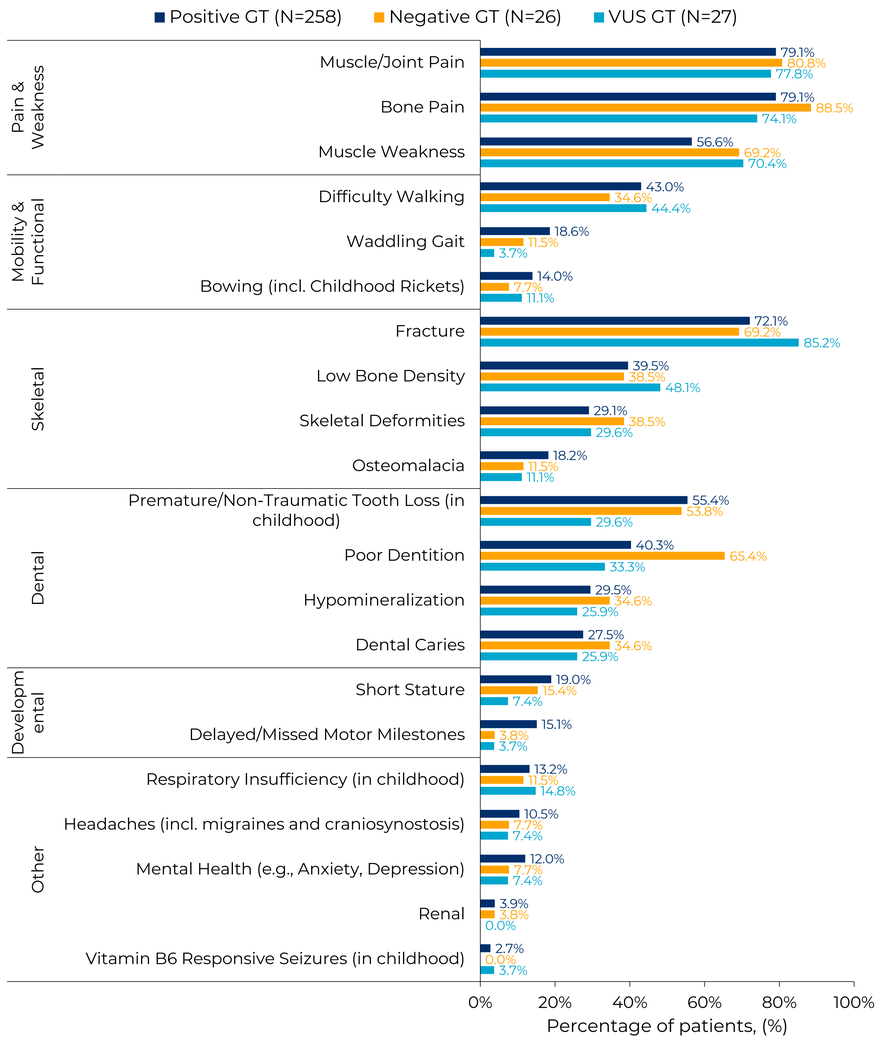
GT, genetic testing results; VUS, variant of uncertain significance.

- Dental manifestations were the only symptoms found to differ significantly between groups (**Figure 3**):
  - Poor dentition affected 40.3%, 65.4%, and 33.3% of patients with positive, negative, and VUS results, respectively (P=0.03).
  - Premature tooth loss was reported by 55.4%, 53.8%, and 29.6% of patients with positive, negative, and VUS results, respectively (P=0.04).

ALP Levels

- Among patients with HPP, 98% had low (≤40 IU/L) or borderline low (≤45 IU/L) ALP levels.
  - The proportion of patients with low ALP levels was similar across the groups: 94.2%, 89.1%, and 93.9% among those with positive, negative, and VUS results, respectively (P=0.12).

Figure 3: Symptoms Reported by Patients with HPP, by Genetic Testing Results (N=311)



GT, genetic testing results; VUS, variant of uncertain significance.

Evolution of VUS Classifications

- Data on specific variants detected were available for 47 (70.1%) of 67 VUS. Most of these VUS were later re-classified as Pathogenic/Likely Pathogenic: 38 (80.9%) according to Franklin and 27 (57.4%) according to Varsome databases (**Table 2**).
- The *ALPL* Gene Variant database uses primarily expert curation based on published literature, rather than automated scoring algorithms.[7] As many of the VUS are rare, they may not be supported by sufficient evidence to be included in the *ALPL* Gene Variant database.
- Discordance among the various references speaks to the complexity of the genetic landscape of HPP and the need for nuance in interpretation of genetic testing results.

A majority of variants originally described as VUS have since been re-classified as pathogenic / likely pathogenic

Table 2: Current Classification of Variants Originally Reported as VUS (N=47)

	ALPL Gene Variant	Varsome	Franklin
Pathogenic / Likely Pathogenic	20 (42.6%)	27 (57.4%)	38 (80.9%)
VUS	9 (19.1%)	19 (40.4%)	9 (19.1%)
Benign / Likely Benign	0 (0%)	1 (2.1%)	0 (0%)
Not reported[a]	18 (38.3%)	0 (0%)	0 (0%)

VUS, variant of uncertain significance.
a: Variants not reported in a given database but included in ≥1 other database.

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