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ORIGINAL ARTICLE

# Not just a carrier: Clinical presentation and management of patients with heterozygous disease-causing alkaline phosphatase (*ALPL*) variants identified through expanded carrier screening

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## Abstract

Hypophosphatasia (HPP) is an underrecognized, complex bone mineralization disorder with variable manifestations caused by one or two deleterious variants in the alkaline phosphatase (*ALPL*) gene. Expanded carrier screening (ECS), inclusive of *ALPL*, intends to inform reproductive risk but may incidentally reveal an HPP diagnosis with 50% familial risks. We sought to investigate at-risk individuals and develop a multidisciplinary referral and evaluation protocol for ECS-identified *ALPL* heterozygosity. A retrospective database query of ECS results from 8 years to 1 month for heterozygous pathogenic/likely pathogenic *ALPL* variants was completed. We implemented a clinical protocol for diagnostic testing and imaging, counseling, and interdisciplinary care management for identified patients, and outcomes were documented. Heterozygous *ALPL* variants were identified in 12/2248 unrelated patients undergoing ECS (0.53%; heterozygote frequency 1/187). Of 10 individuals successfully contacted, all demonstrated symptomatology and/or alkaline phosphatase values consistent with HPP. ECS may reveal incidental health risks, including recognition of missed HPP diagnoses in *ALPL*

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heterozygotes. In our cohort, all ECS-identified *ALPL* heterozygotes with clinical and/or biochemical data available demonstrated features of HPP. Referral to a genetics professional familiar with HPP is indicated for family history assessment, genetic counseling, cascade testing, and long-term bone health management.

**KEYWORDS**

ALPL, carrier screening, genetic testing, hypophosphatasia, incidental diagnosis

## 1 | INTRODUCTION

Hypophosphatasia (HPP) is a metabolic bone disorder caused by heterozygous, homozygous, or compound heterozygous variants in the tissue nonspecific alkaline phosphatase gene (*ALPL* or *TNSALP*, MIM#171760), encoding deficient alkaline phosphatase (AP). Features of HPP range from mild to severe/lethal and include fetal long bone bowing or fractures, premature primary tooth shedding with or without root (Logan & Kronfeld, 1933), low trauma and/or recurrent fractures in childhood/adulthood, slow fracture healing, poor growth in childhood with or without hypotonia, premature osteopenia/osteoporosis, chronic pain, seizures, and adult-onset secondary tooth instability and fragility (Whyte et al., 2015). These primary features characterize the six overlapping forms of HPP (perinatal/severe, perinatal/benign, infantile, childhood, adult, and odontohypophosphatasia), based on the age of onset and severity (Bianchi, 2015; Mornet & Nunes, 2007). While some genotype–phenotype correlations are recognized, there is significant clinical and intrafamilial variability and limited information relating enzyme activity to disease manifestations (Bianchi, 2015; Mornet et al., 2011). Mild HPP, often due to *ALPL* heterozygous loss of function, dominant negative or compound heterozygous variants with moderate loss of function is far more common than severe HPP associated with homozygous or compound heterozygous variants with near/complete loss of function (Belkhouribchia et al., 2016; Bianchi, 2015; Fauvert et al., 2009; Mornet et al., 2011). Interpreting the effect of one or more *ALPL* variants presents a challenge for the clinician, as many of the >400 documented variants (Johannes Kepler University, n.d.) are private and uncharacterized in the literature, whereas others remain in commercial laboratory databases as proprietary information; a phenomenon that is not unique to ALPL.

The American College of Obstetricians and Gynecologists (ACOG) recommends offering prenatal/preconception carrier screening (CS) so individuals may consider reproductive options pertaining to autosomal recessive (AR) and X-linked (XL) conditions (Committee Opinion No. 690, 2017; Committee Opinion No. 691, 2017). In contrast to smaller panels that screen for select conditions more commonly seen in certain ethnic groups, expanded carrier screening (ECS) includes 10's to 100's of AR disorders and XL conditions. Professional society guidelines have also recommended that all patients be counseled on the possibility that CS may identify an AR condition, or one pathogenic variant that perhaps negatively impacts the patient's personal health in the heterozygous state, such as with manifesting heterozygotes (Edwards et al., 2015; Gregg et al., 2021). An incidental diagnosis from ECS may lead to additional testing options for patients undergoing in vitro fertilization (IVF) or for gamete donors who are often required to complete ECS by fertility centers for prospective parents seeking a screen-negative anonymous donor (Mertes et al., 2018; Zhang et al., 2019). Gbur et al. (2021) illustrated that most patients do not receive ECS pretest counseling, highlighting that little is known regarding patients' understanding of the potential diagnostic aspect of ECS, and what differences may exist based on the consenting provider (e.g., OB/GYN, general practitioner, or genetic counselor). Similar to exome sequencing, an informed consent process detailing each condition is not feasible with current ECS panels consisting of as many as 500+ genes, and focusing on

**What is known about this topic?**

- Expanded carrier screening (ECS) for reproductive risk assessment may provide results that identify the tested person to be at risk for manifestations of conditions on the panel, including various forms of hypophosphatasia (HPP).

**What does this study add to the topic?**

- Investigation of ECS-identified *ALPL* heterozygotes revealed biochemical and clinical HPP symptomatology in all evaluated persons.
- All patients with heterozygous *ALPL* variants on ECS should be referred for evaluation of bone health and long-term management.

high-level themes of possible test results may be preferable for patient comprehension (Ormond et al., 2009, 2007). Patients also should be apprised that incidental diagnoses from ECS may extend beyond their medical care to policies not protected under the Genetic Information Nondiscrimination Act (GINA) (Genetic Information Nondiscrimination Act of 2008, 2008).

The purpose of including *ALPL* on ECS is to identify unaffected heterozygotes ("carriers") of one *ALPL* variant. Aside from the rare perinatal severe form, all other HPP presentations may occur in patients with one or two *ALPL* gene variants (Bianchi, 2015; Moore et al., 1999; Mornet et al., 2021; Salles, 2020). This makes the terms "recessive HPP" and "dominant HPP" now too vague to accurately provide clinical guidance or genetic counseling for reproductive risks over the HPP disease spectrum (Bianchi, 2015; Moore et al., 1999; Mornet, 2018; Mornet et al., 2011; Mornet et al., 2021). Due to the variability, neither adults pursuing ECS nor their ordering clinicians may be aware of clinical symptoms of HPP (i.e., early onset osteoporosis or chronic pain) or relevant medical and family histories suggestive of HPP (e.g., premature primary tooth loss, low/no trauma fractures, low AP) (Logan & Kronfeld, 1933; Moore et al., 1999). There are age-/sex-specific reference ranges for AP, included in routine blood chemistry lab studies (e.g., complete metabolic panel, CMP). By adulthood, all nongravid unaffected persons should have AP > 40 U/L (Bianchi, 2015; Colantonio et al., 2012; Mornet et al., 2011; Mornet & Nunes, 2007). AP is known to be elevated during pregnancy (Whyte et al., 1995) due to normal placental production of ALP; the lower limit for AP in gravid patients with HPP is not yet established. Making the diagnosis of HPP at any age has additional importance today because of both the recent FDA approval of enzyme replacement therapy (ERT) to treat infantile and childhood-onset HPP as well as the contraindication of bisphosphonate treatment for bone fragility in persons with HPP (Belkhouribchia et al., 2016; Mornet, 2018; Sutton et al., 2012). Furthermore, the features of HPP may evolve over the lifespan and longitudinal re-evaluation is crucial for those who have this diagnosis (Bianchi, 2015; Mornet et al., 2011; Mornet et al., 2021; Whyte, Madson, et al., 2016; Whyte, Rockman-Greenberg, et al., 2016).

The identification of heterozygous *ALPL* variants from ECS has larger implications for the health of these patients as well as immediate family members, including a fetus, with up to a 50% recurrence risk. To examine these issues, we identified and recontacted all patients with *ALPL* heterozygous variants identified by ECS in our prenatal clinics. Our multidisciplinary team developed a clinical assessment protocol to ensure a uniform and comprehensive medical genetics evaluation of each patient, tailored to HPP. Based on our collaborative multidisciplinary clinical experience caring for patients and families with HPP, including multiple fetal cases with longitudinal follow-up (Blakemore et al., 2019; Sagaser et al., 2019) and throughout adulthood, we hypothesized patients identified via ECS have a single *ALPL* variant may be affected/symptomatic from HPP with potential health implications beyond "carrier status." Herein, we describe the clinical features and diagnostic implications of patients with *ALPL* heterozygous variants identified through ECS at our institution.

## 2 | MATERIALS AND METHODS

A database of all Johns Hopkins Medicine Gynecology and Obstetrics patients undergoing ECS at one commercial laboratory as ordered by their provider from July 2011 to August 2019 was queried for heterozygous P/LP *ALPL* variant results as part of routine quality assurance of clinical care. VUS unblinding was not requested by the laboratory, as this is not within the standard of care for routine ECS. Patients identified were recontacted by phone and/or letter to inform them of our updated interpretation of their *ALPL* results. Respondents completed a brief questionnaire about their bone and tooth health with the prenatal genetic counselor (Figure S1). All individuals were offered a referral for HPP diagnostic clinical evaluation including a complete history and physical exam, family history collection, radiographic studies, and serum/urine biochemistry (i.e., CMP, serum Vitamin B6, urine phosphoethanolamine [PEA]). Individuals with a heterozygous P/LP *ALPL* variant, AP ≤ 40 U/L, and at least one of the characteristic clinical features of HPP were considered to have a clinical diagnosis of HPP.

## 3 | EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Under a Johns Hopkins IRB-approved protocol (#00066333) with a waiver of consent, data were compiled from these 12 patients for the analysis presented here.

## 4 | RESULTS

A total of 2248 reproductive-aged patients underwent ECS through a single laboratory for reproductive risk assessment; 12 unrelated patients had heterozygous P/LP variants in *ALPL* (9 female, 3 male partners) (Table 1).

All 12 were reported by the laboratory to be consistent with "heterozygous carriers" of HPP; thus,

| Clinic setting | Patients tested through ECS | *ALPL* heterozygotes |
|---|---|---|
| Maternal Fetal Medicine Clinic | 65 | 1 |
| General OB Office | 449 | 1 |
| Reproductive Endocrinology and Infertility Center | 592 | 3 |
| Prenatal Genetic Counseling Clinic | 1142 | 7 |
| Total | 2248 | 12 |
| Heterozygote frequency | 12/2248 (1/187 = 0.53%) | |

**TABLE 1** During the study period, 2248 reproductive-aged patients underwent expanded carrier screening (ECS) for reproductive risk assessment in our institution. Twelve unrelated patients were identified with heterozygous pathogenic/likely pathogenic (P/LP) variants in *ALPL*

there is a heterozygote frequency of 1/187 (0.53%) (12/2248 = 0.5338%) in this study population.

Demographic data, clinical features, and molecular variants of the 12 patients are detailed in Table 2. All patients were referred for clinical evaluation in the Johns Hopkins Greenberg Skeletal Dysplasia Genetics Clinic and their obstetrical providers were notified. Six patients (1–6) presented for evaluation. Patients 7, 10, 11, and 12 completed the phone questionnaire but declined evaluation. Patients 8 and 9 did not respond to recontact.

The *ALPL* variants reported by the ECS laboratory are presented with citations indicating those that have been reported in publicly available databases or publications. AP values were available from previously completed CMPs for 7/12 patients at the time of patient recontact and in 5/6 who presented for skeletal genetics evaluation (nonmutually exclusive) (Figure 1 and Table 2).

Overall, AP levels were available for 10/12. Seven were from nongravid females and two from males, all <40 U/L. A 10th AP level (patient 9) was collected during pregnancy and was within normal limits for adults (>40 U/L); a nongravid AP value was not available for review. The remaining two patients declined clinical evaluation and no prior AP levels were available.

In Table 2, dental and skeletal health information is shown for 10 patients (83.3%) via recontact telephone screening questionnaire and/or clinical evaluation. The checklist used to ascertain features supportive of a diagnosis of HPP is shown in Figure 2.

In this subgroup, 10/10 (100%) reported a positive personal history of dental anomalies including 30% with premature primary tooth shedding with or without the root intact. The remaining 70% reported tooth fragility and tooth instability. Although 6/10 (60%) of our patients did not recall the age at which they first lost their primary teeth, they could readily recall the ages of their own children with many endorsing premature tooth shedding including the root for some of their offspring.

Regarding bone fragility, 6/10 (60%) endorsed having prior fractures. Patient 1 had a normal DXA scan 4 years prior due to the risk for osteopenia from an autoimmune medication. None of the remaining 9/10 patients had a DXA or prior diagnosis of osteopenia or osteoporosis. Musculoskeletal pain was determined to be a clinical feature potentially supportive of an HPP diagnosis if it was severe enough to hinder activities of daily living, sleep, and/or ambulation. Severe musculoskeletal pain was reported in 7 of 10 patients.

All patients were queried for family members with signs or symptoms of HPP. Nine of 10 ECS patients had at least one relative with one of these clinical features. Family members with these features were offered a clinical evaluation for biochemical screening and molecular testing. Three of the four patients who declined an in-person clinical evaluation reported family members with premature tooth loss with the root intact, fragile or loose teeth, and musculoskeletal pain sufficient to alter activities of daily life. Without further medical history from these family members or genetic testing for their potential familial variant, we are unable to conclude whether each is affected by HPP. However, Patients 1–6 were seen for clinical evaluation, and a more detailed family history was acquired along with cascade testing of relatives with presentations highly suggestive of HPP, ultimately resulting in additional family member diagnoses. An example is shown in Figure 3 for Patient 6. Clinical evaluation, laboratory studies, and cascade testing of family members allowed for dental and bone health surveillance recommendations to be provided to Patient 6's affected daughter and mother. Furthermore, all patients seen for clinical evaluation were offered ALPL testing via diagnostic sequencing and deletion/duplication analysis. Their reproductive partners were also offered this diagnostic testing or ALPL VUS unblinding from their previous ECS assay. Additional ALPL partner testing was chosen by the pregnant partner of Patient 6, as they sought to further clarify reproductive risk beyond the known 50% chance for a heterozygous P/LP ALPL variant.

In summary, of the 10 investigated patients with heterozygous *ALPL* variants identified via ECS as "carriers" of HPP, we conclude all 10 are affected by HPP based on their biochemical, molecular, and clinical histories which are further supported by family history in several.

## 5 | DISCUSSION

Our multidisciplinary team identified 12 individuals with heterozygous P/LP variants in *ALPL* via retrospective review of ECS results, and all 10 *ALPL* heterozygotes with available clinical and family history information demonstrated features consistent with HPP due to their *ALPL* P/LP variant, abnormally low AP level, abnormal bone and dental histories, and/or family history of similar features as presented. This cohort of 12 patients with a heterozygous variant in *ALPL* classified by the testing lab as P/LP yielded a heterozygote frequency of 1/187 (0.56%), comparable to the rate reported by the ECS laboratory of 1/190–1/290 based on ethnicity (Myriad, n.d.). Using the recognized biochemical and clinical features of HPP (Figure 2) and maintaining a low threshold for further investigation and clinical evaluation, we were able to identify persons who would benefit from long-term surveillance and management. HPP directly affects the natural mineralization and maintenance of the skeleton and it is difficult to predict each patient's course, necessitating longitudinal follow-up. In distinct contrast to other AR conditions on ECS panels, these data suggest that *ALPL* heterozygotes are not "just carriers" of HPP but instead are at risk for manifestations of the disease. The addition of ERT (asfotase alfa) for HPP since 2015 has altered the natural history of the disease and increased the urgency to identify affected individuals who had HPP features since infancy/childhood to optimize their health (Strensiq, n.d.; Belkhouribchia et al., 2016; Kishnani et al., 2019; Michigami, Ohata, et al., 2020; Michigami, Tachikawa, et al., 2020; Mornet, 2018; Salles, 2020; Whyte, Madson, et al., 2016; Whyte, Rockman-Greenberg, et al., 2016). The wide clinical spectrum of this already variable condition has been further broadened as new patients have come to be recognized, along with cascade testing of their relatives, and longitudinal natural history studies (ClinicalTrials.gov, 2014; Kishnani et al., 2019; Michigami, Ohata, et al., 2020; Michigami, Tachikawa, et al., 2020). While limited by the small sample size, given our experience with the *ALPL* heterozygotes from this cohort, other clinicians may wish to re-examine their ECS results to identify P/LP variants in *ALPL* and offer further clinical evaluation for patients based on implications for bone health management, laboratory reporting, reproductive risk, prenatal diagnosis, and "carrier" terminology.

### 5.1 | Implications for bone health management

Deleterious *ALPL* variants disrupt the process of skeletal mineralization in the matrix vesicles (MV) of human osteoblast and chondrocyte cells, causing the defective bone mineralization features of HPP. Normally, AP converts pyrophosphate (PPi) to inorganic phosphate (Pi) for Pi to be transported into the MV, allowing a cascade of subsequent steps which culminate in the mineralization of collagen fibrils in the extracellular matrix. People with HPP are deficient in AP, causing a lack of Pi necessary for normal mineralization and an excess of the precursor PPi which further inhibits mineralization of the extracellular matrix. Collectively, this defect leads to rickets in children and osteomalacia in adults (Bianchi, 2015; Mornet, 2018; Michigami, 2019; Moulin et al., 2009). ERT for HPP reintroduces functional AP to allow normal mineralization to resume and decrease the toxic load of PPi (Strensiq, n.d.). Since the FDA approval of ERT in 2015, patients of any age with the infantile and childhood forms of HPP had an FDA-indicated treatment option (Whyte, 2017).

Currently, there is no indication for patients with the adult or odonto-forms of HPP to receive ERT. However, it is essential to identify these individuals because bisphosphonates, the most common treatment for osteoporotic bone fragility, are contraindicated in those with HPP (Belkhouribchia et al., 2016; Mornet, 2018; Sutton et al., 2012). Bisphosphonates, a chemically stable analog of pyrophosphate, aggravate the HPP disease process by impeding AP function, suppressing bone turnover, and increasing the risk of fractures (Belkhouribchia et al., 2016; Sutton et al., 2012; Whyte, 2009).

Additional diagnostic delays for seemingly asymptomatic adults may occur when there is a lack of longitudinal follow-up to monitor for evolution of HPP complications and the fact that routine bone health surveillance by DEXA in the US is not recommended until age 65 years (females) or 70 years (males) unless additional risk factors for low bone density are known (Whyte, 2009). The absence of DEXA results for 90% of our subgroup of 10 *ALPL* heterozygotes is not surprising given the ascertainment bias of the study toward younger patients seeking reproductive risk via ECS. Baseline DEXAs were recommended for all 10 patients in our cohort as well as any relatives identified from cascade molecular testing as a baseline measurement of bone density. This, along with additional biochemical tests, ascertainment of family history and longitudinal assessments of evolving signs and symptoms of HPP (Bianchi, 2015; Mornet, 2018; Mornet et al., 2011; Saraff et al., 2016) are part of the recommended management guidelines for patients with known or suspected HPP (Kishnani et al., 2019; Michigami, Ohata, et al., 2020; Michigami, Tachikawa, et al., 2020; Moulin et al., 2009). Current guidelines recommend follow-up by medical geneticists, pediatricians, gynecologists, general practitioners, and/or endocrinologists for patients from birth through late adulthood due to changes in bone

**TABLE 2** HPP symptomatology in persons with heterozygous ALPL variants identified by ECS for reproductive risk assessment following recontact and or clinical skeletal genetics evaluation

| Patient | Sex | Age | Ethnicity[a] | *ALPL* variant; variant type | *ALPL* database (Johannes Kepler University, n.d.); heterozygous phenotype | ClinVar |
|---|---|---|---|---|---|---|
| 1 | F | 35 | Ashkenazi Jewish | c.862+1G>A; splice donor | Absent; – | LP |
| 2 | F | 40 | East Asian | c.979T>C (F327L) (Del Angel et al., 2020; Michigami, Ohata, et al., 2020; Michigami, Tachikawa, et al., 2020); missense | Present; N/A | P/LP |
| 3 | F | 38 | White, non-Hispanic | c.407G>A (R136H) (Del Angel et al., 2020; Fanous & Barb, 2020); missense | Present; adult (Del Angel et al., 2020) | P |
| 4 | F | 34 | White, non-Hispanic | c.881A>C (D294A) (Del Angel et al., 2020); missense | Present; N/A | N/A |
| 5 | F | 33 | Ashkenazi Jewish | c.542C>T (S181L) (Del Angel et al., 2020); missense | Present; infantile (Del Angel et al., 2020) | LP |
| 6 | M | 38 | White, non-Hispanic | c.1250A>G (N417S) (Del Angel et al., 2020); missense | Present; perinat benign (Del Angel et al., 2020), childhood (Del Angel et al., 2020), adult (Del Angel et al., 2020), odonto (Del Angel et al., 2020) | LP |
| 7 | M | 35 | White, non-Hispanic | c.526G>A (A176T) (Del Angel et al., 2020); missense | Present; adult (Del Angel et al., 2020), odonto | P/LP |
| 8 | M | 42 | South Asian | c.211C>T (R71C) (Del Angel et al., 2020); missense | Present; odonto (Del Angel et al., 2020) | LP |
| 9 | F | 32 | White, non-Hispanic | c.571G>A (E191K) (Del Angel et al., 2020); missense | Present; childhood, adult (Del Angel et al., 2020), odonto (Del Angel et al., 2020) | P/LP |
| 10 | F | 39 | African American | c.571G>A (E191K) (Del Angel et al., 2020); missense | Present; childhood, adult (Del Angel et al., 2020), odonto (Del Angel et al., 2020) | P/LP |
| 11 | F | 42 | African American | c.46_49delAACT (N16Pfs*2) (Del Angel et al., 2020); frameshift | Present; N/A | N/A |
| 12 | F | 37 | Hispanic | c.571G>A (E191K, E174K) (Del Angel et al., 2020); missense | Present; childhood, adult (Del Angel et al., 2020), odonto (Del Angel et al., 2020) | P/LP |
| Positive finding/total available data | | | | | | |

Abbreviations: AP, alkaline phosphatase; N/A, not available as variant has only been described in compound heterozygous or homozygous state in *ALPL* gene mutations database; P, pathogenic; LP, likely pathogenic; yo, years old; B, bilateral.

[a]Ethnicities displayed are the only available categories by the testing lab and patients could not self-report additional ethnicities beyond reporting "other."

[b]Fractures reported are atraumatic, low-trauma, or fragility.

[c]Muscular/Musculoskeletal pain severe enough to hinder activities of daily living, ambulation, and/or sleep.

| AP (U/L) | Dental anomalies | Fractures[b] | Family history | Additional features |
|---|---|---|---|---|
| 22 | Primary tooth loss 3 yo, tooth fragility, "soft teeth", multiple caries | None | Children with delayed tooth eruption | Osteopenia |
| 30 | Multiple caries and root canals since childhood | None | Multiple relatives with dental problems | Lower extremity bowing and pain[c]; elevated Vitamin B6 |
| 36; 43 | "Soft teeth," multiple caries and root canals, weak enamel, tooth fragility | None | Child with delayed tooth eruption; relatives with multiple fractures, "weak teeth" and caries | Vitamin D deficiency |
| 17; 24 | "Weak teeth," tooth fragility | B heel stress fracture, elbow, and atraumatic toe fracture | Relatives with fractures, tooth fragility | Vitamin D deficiency |
| 26 | Delayed primary tooth eruption | Low-trauma wrist | Relatives with fractures, dental problems | Musculoskeletal pain[c] |
| 20 | Tooth fragility, multiple chipped teeth | >20 including B ankle, tibia/fibula, B wrist, elbow, multiple fingers | The child lost primary tooth with intact root | Musculoskeletal pain[c], vitamin D deficiency |
| N/A | Primary tooth loss with intact root, "soft teeth and enamel," multiple caries | None | Child with premature primary tooth loss at 4 yo with intact root | Musculoskeletal pain[c] |
| 37 | N/A | N/A | N/A | N/A |
| 102 (gravid) | N/A | N>A | N/A | N/A |
| N/A | Tooth instability | Atraumatic toe | Parent with tooth instability, musculoskeletal pain | Muscular pain[c], Vitamin D deficiency |
| 17 | Primary tooth loss 4 yo, tooth fragility | Jaw | None | Muscular pain[c], low phosphorous levels |
| 20 | Tooth fragility, tooth instability | Wrist, atraumatic finger | Sibling with tooth fragility | Musculoskeletal pain[c] |
| | 10/10 | 6/10 | 9/10 | |

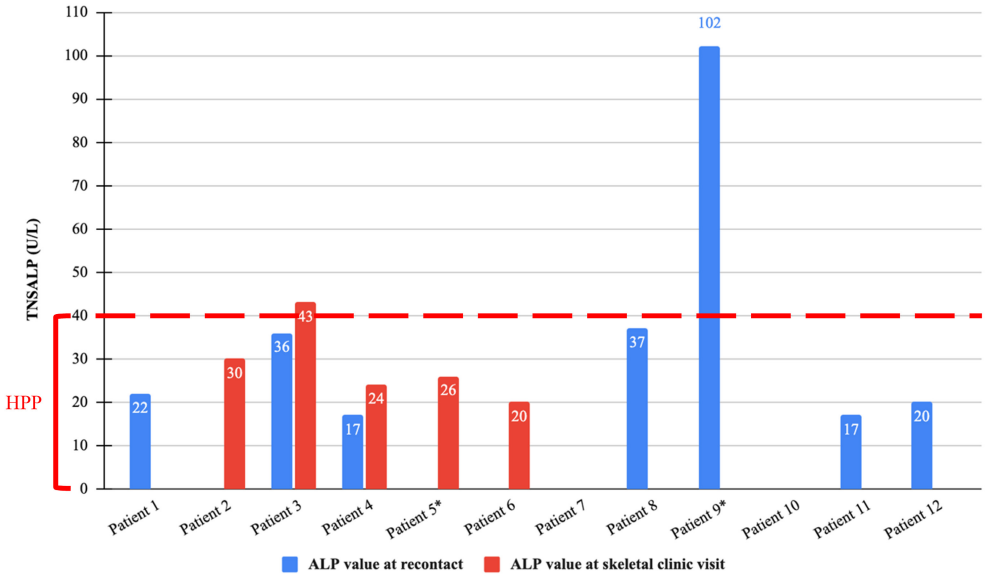


**FIGURE 1** All available tissue nonspecific alkaline phosphatase (TNSALP) levels for patients 1–12. Reference ranges for TNSALP are age and gender based on childhood. In nongravid adults, TNSALP is normal when ≥40 U/L and is suspicious for HPP when <40 U/L (Bianchi, 2015; Colantonio et al., 2012; Mornet et al., 2011; Mornet & Nunes, 2007). *Value obtained during pregnancy; nongravid value not available.

health that can occur throughout the lifespan (Michigami, Ohata, et al., 2020; Michigami, Tachikawa, et al., 2020; Mornet, 2018; Salles, 2020).

## 5.2 | Implications for ECS laboratory reporting and reproductive risk

Clinicians ordering ECS as well as those evaluating/managing those with HPP should be aware of the unique difficulties of *ALPL* testing through ECS due to the intrafamilial clinical variability in HPP and the frequently private nature of *ALPL* variants. These challenges are reflected in the limited number of publications describing clear genotype–phenotype correlations in HPP. This data paucity further hinders the accurate classification of *ALPL* variants by ECS laboratories according to the current ACMG variant interpretation guidelines which rely heavily on the public sharing of genotype–phenotype correlations. Therefore, potentially disease-causing *ALPL* variant may not be reported as P/LP on ECS due to both the broad limitations of phenotype data for many *ALPL* variants as well as the historical lack of data in non-White populations which may skew variant classification towards VUS (and thus, not reported on ECS).

Generally, ECS laboratories only report P/LP variants; reporting of VUSs is not standard and is released only when requested by the ordering clinician. Instances when a clinician may consider requesting VUSs for an individual who completed ECS include (1) when the individual may be suspected to have the condition and a second variant is needed to clarify the diagnosis or (2) when there is a fetal presentation of a condition and one parent is known to have a P/LP variant from ECS and the other parent had screen-negative results for that gene. This first scenario is most applicable for patients presenting with conditions on ECS that require two variants in trans, which is not required for all forms of HPP. In the second scenario, involving fetal features of perinatal/severe HPP (Whyte et al., 2015), providers may be able to utilize ECS results in conjunction with parental clinical, laboratory, and family histories to refine fetal risk for perinatal/severe HPP caused by inheritance of a second *ALPL* variant which, due to the reasons above, is currently excluded from ECS reporting. Of our 12 identified patients, 11/12 had a partner who completed ECS with no reported P/LP variants in *ALPL*. The partner of the 12th patient declined testing during prenatal/preconception work-up but completed *ALPL* gene analysis to assess for VUSs in lieu of unblinding ECS data later during their partner's HPP evaluation due to a current pregnancy to better assess fetal risk; which was negative. While residual risks exist for all screening panels, clinicians should be reminded that high detection rates from ECS depend not only on thorough variant identification but also on accurate variant classification. With HPP, VUSs lacking published data may have health implications and be relevant in fetal risk assessment and should prompt additional studies.

Comprehensive care throughout the lifespan for those with HPP must include accurate reproductive risk assessment for those with heterozygous P/LP ALPL variants and their reproductive partners. As outlined, our primary

| Evaluation Protocol - Clinical Findings Suggestive of Hypophosphatasia in *ALPL* Heterozygote Adults | | |
|---|---|---|
| BIOCHEMICAL RESULT | | |
| *Low Total Alkaline Phosphatase* | ☐ | <40 U/L is abnormally low for any nongravid adult[3-5,21] |
| *Serum Vitamin B6* | ☐ | Abnormally elevated |
| *Urine phosphoethanolamine (PEA)* | ☐ | Abnormally elevated |
| CLINICAL FEATURE | | |
| *Dental Features* | ☐ | Nontraumatic primary tooth shedding <5yo +/- root[1] |
| | ☐ | Loose/lost secondary teeth (any age) |
| | ☐ | Delayed/absent eruption of primary teeth |
| | ☐ | Delayed/absent eruption of secondary teeth |
| | ☐ | Cracking/chipping at any age |
| | ☐ | Excessive or young age caries/root canals |
| *Skeletal Features* | ☐ | In utero or postnatal bowing of long bones |
| | ☐ | Multiple low/no trauma fractures |
| | ☐ | Nonunion stress fractures, and/or pseudofractures |
| | ☐ | Rickets (childhood) |
| | ☐ | Early onset (premenopausal) osteopenia/osteoporosis |
| | ☐ | Males with osteopenia/osteoporosis |
| | ☐ | Chronic musculoskeletal or bone pain (any age) that hinders sleep, ADLs, ambulation |
| *Additional Features* | ☐ | Nephrocalcinosis |
| | ☐ | Seizures (rare; in infantile HPP only) |
| | ☐ | Craniosynostosis/dura ossification |
| | ☐ | Respiratory insufficiency (in infantile only) |
| | ☐ | Short stature/poor growth (pediatric) |
| FAMILY HISTORY | ☐ | Positive family history of any feature(s) above |
| MOLECULAR RESULT | ☐ | Published |
| | ☐ | ClinVar |
| | ☐ | *ALPL* database (Mornet) |
| | ☐ | Indeterminate |

**FIGURE 2** Clinical checklist for HPP diagnosis, utilized in screening questionnaire (Figure S1) and final diagnostic classification.

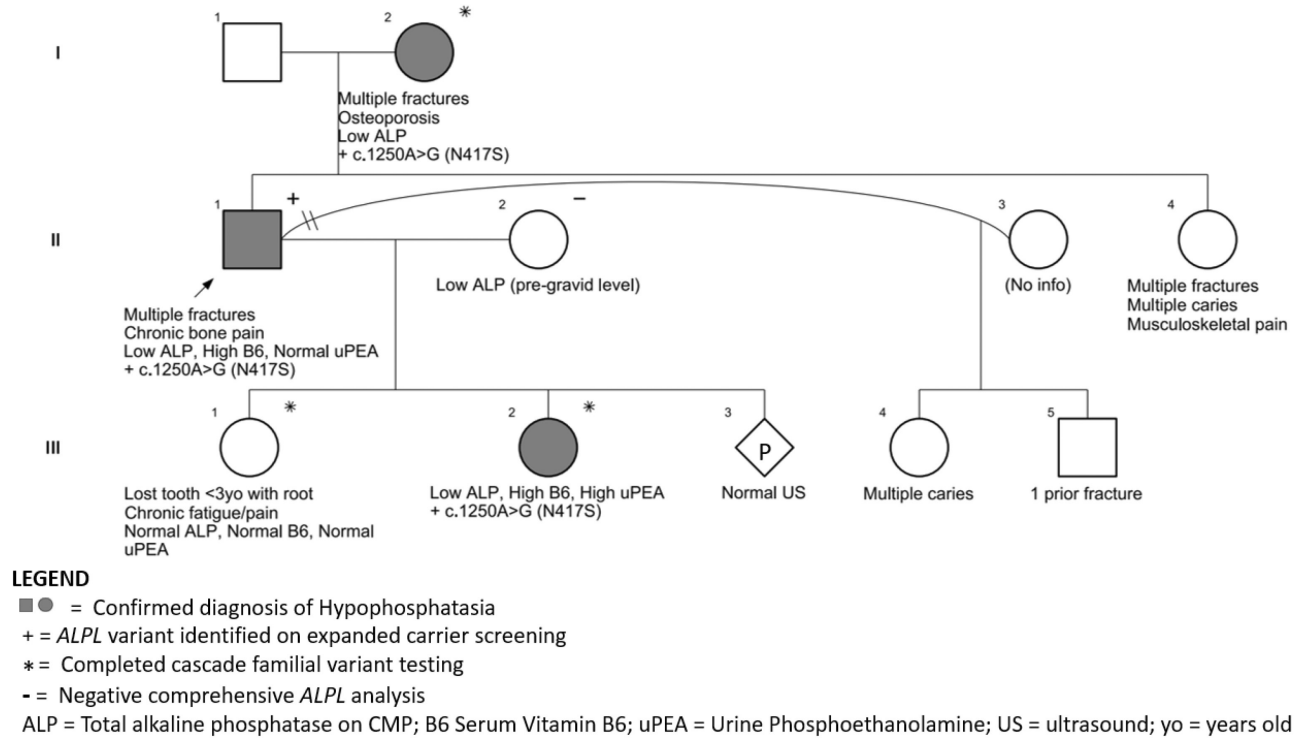


**FIGURE 3** Pedigree for patient 6 (II-1), including clinical features, biochemical lab results, and molecular test results collected during clinical evaluation following recontact for heterozygous *ALPL* variant identified on expanded carrier screening (ECS) and from familial cascade testing (biochemical and molecular) following clinical evaluation.

aim was to evaluate those with documented risk for HPP due to a single detected P/LP variant. ALPL VUSs were not requested from the commercial ECS laboratory for all 2248 ECS patients; while this was outside the scope of our investigation, clinical evaluation in those with only ALPL VUSs may be an important area of future research.

## 5.3 | Implications for prenatal diagnosis

When fetal long bone bowing is observed on prenatal sonograms and patients decline diagnostic amniocentesis with a skeletal dysplasia panel, clinicians can consider additional options to provide patients with more information. Particularly, in the setting of isolated fetal long bone bowing, (1) ordering parental ECS, (2) requesting VUSs for *ALPL* from previously completed parental ECS, and (3) reviewing nongravid TNSALP levels for both parents can provide additional clinical and genotype information to support or rule out HPP as the potential cause of fetal long bone bowing. Given the variability of HPP, fetal long bone bowing can present in a fetus heterozygous for an *ALPL* variant inherited from a parent with no recognized symptoms (Blakemore et al., 2019; Mornet, 2018; Mornet et al., 2021). Ordering providers or the fetal management providers can request VUSs in the *ALPL* gene from the ECS laboratory. Rapid access to prior nongravid TNSALP levels on chart review and fast turnaround of a new CMP for a reproductive partner may provide potentially useful diagnostic information. While fetal long bone bowing may represent diagnoses beyond HPP, other causes have no biochemical screening markers available in the parents and additional prenatal ultrasound findings beyond long bone bowing are expected in more severe dysplasias (Alanay et al., 2007).

## 5.4 | Implications for HPP "carrier status" terminology

The terminology surrounding HPP deserves reconsideration. The previously accepted approach of describing early onset and severe presentations of HPP as AR with unaffected "obligate carrier" parents is not consistent with our current understanding of the forms and genotypes of HPP, nor with the range of clinical presentation for those who are *ALPL* variant heterozygotes (Mornet, 2018; Mornet et al., 2011; Mornet et al., 2021). The inclusion of *ALPL* on ECS panels will identify heterozygotes who may be asymptomatic or mildly affected by HPP (Gregg et al., 2021). This not only challenges the classic AR terms "carrier" vs. "affected," but also has far-reaching implications for a patient's fetus and other family members (ClinicalTrials.gov, 2014). This shift in terminology related to HPP may prompt additional evaluation by ECS laboratories as to

how to identify and report *ALPL* heterozygous variants. Moving toward using the terminology of "one or two *ALPL* variants" in lieu of "AD or AR HPP" can further strengthen pre- and post-ECS discussions with patients.

## 6 | CONCLUSION

*ALPL* heterozygotes identified by ECS present a unique paradigm compared with other ECS-included AR conditions with distinct health risks for heterozygotes—importantly, *ALPL* heterozygotes are not just carriers of HPP (Table 2). The inclusion of the *ALPL* gene raises issues regarding appropriate informed consent for patients pursuing ECS, as many patients undergoing ECS may be unaware of the possibility of diagnostic results for themselves and providers should critically self-reflect on current practices of ECS pretest counseling. The topics outlined above should be considered when updating societal guidelines surrounding health risks that are identifiable through ECS. HPP is unique in that there are additional biochemical values and clinical history features that can help the clinician further interpret unexpected P/LP and/or VUS *ALPL* results. Biochemical, molecular, or family histories alone may raise suspicion for HPP, but it is the combination of these data that is key, and which forms the basis for the clinical evaluation protocol we have developed (Figure 2). Additionally, commercial laboratories should consider highlighting the possibility of incidental diagnosis/health risks for any person with a single P/LP variant in *ALPL* identified through ECS. Genetic counselors, obstetrician gynecologists, reproductive endocrinologists, maternal-fetal medicine specialists, and other healthcare providers ordering and interpreting ECS can feel empowered to provide appropriate counseling, referrals, and follow-up recommendations upon identification of *ALPL* heterozygosity from ECS that was ordered for reproductive risk assessment with the knowledge of the potential diagnostic implications.

### AUTHOR CONTRIBUTIONS

Authors NMB and KGS confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors gave final approval for this version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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### CONFLICT OF INTEREST

CSL, CH, AL, KRF, KAM, ACJ, and KJB declare that they have no conflict of interest. NMB reports having served as a consultant for Illumina outside the scope of the submitted work. NMB is a clinical genetic counselor at Genome Medical Services, which is not affiliated with any commercial laboratory interests. KGS is now employed by Juno Diagnostics, a precommercial biotechnology company. JHF has participated in advisory board meetings and served as a consultant to BioMarin, Ascendis, Therachon, QED, and Alexion on topics related to achondroplasia and other genetic skeletal conditions. These arrangements have been reviewed by the Office of Policy Coordination at her Institution.

### HUMAN STUDIES AND INFORMED CONSENT

This study was approved by and conducted according to the ethical standards of the Johns Hopkins Institutional Review Board. All applicable international, national, and/or institutional guidelines were followed. Informed consent for genetic testing was obtained from all individuals undergoing testing. This study was approved by the Johns Hopkins IRB and was granted an informed consent waiver.

### ANIMAL STUDIES

No nonhuman animal studies were carried out by the authors of this article.

### DATA AVAILABILITY STATEMENT

Composite data are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

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