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Genetic characterization of a large cohort of individuals with a clinical suspicion of hypophosphatasia in the United States

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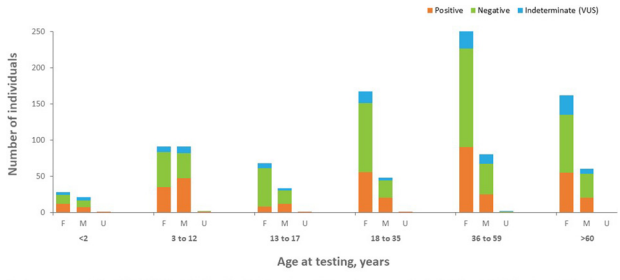
Hypophosphatasia (HPP) is a rare inherited genetic condition caused by pathogenic variants in *ALPL*, which encodes tissue non-specific alkaline phosphatase, resulting in decreased alkaline phosphatase (ALP) activity. ALP deficiency leads to impaired skeletal mineralization resulting in life-threatening manifestations such as respiratory failure in severely affected infants. Children and adults may experience fractures, arthralgia, fatigue, impaired mobility, reduced quality of life, and other signs and symptoms. Severe cases are generally associated with biallelic variants. Over 400 *ALPL* variants associated with HPP have been described.

An Alexion-sponsored genetic testing program was offered to US healthcare providers (HCPs) as a complimentary service to detect *ALPL* variants. HCPs were required to confirm their patients had onset of HPP-related symptoms before age 18 and low ALP levels, other signs or symptoms of HPP, and that genetic testing was medically indicated. The decision to submit a sample for genetic testing was based on the HCPs medical judgment. HCPs sent saliva or blood samples for *ALPL* sequencing to PreventionGenetics; variant detection was by Sanger sequencing. Deletion/duplication analysis was performed using gene-centric array comparative genomic hybridization.

1113 individuals underwent genetic testing between January 15, 2018 and May 13, 2020. Overall, 775 were adults (70%) and 338 were children (30%); 763 (69%) of those tested were female. Of these, 393 individuals (35%) had a positive result [pathogenic [P] or likely pathogenic [LP] variant(s)]. There were 108 individuals (10%) with variant(s) of uncertain significance (VUS). In total, there were 522 individuals (47%) with monoallelic and 31 with biallelic ALPL variants including P, LP, and VUS variants. The five most frequently reported P/LP variants were c.1133A>T (n = 61), c.571G>A (n = 47), c.1250A>G (n = 43), c.881A>C (n = 34), and c.346G>A (n = 12). These actionable variants represented 50% of those with a positive result. The five most frequently reported VUS were c.1034C>T (n = 4), c.1156G>T (n = 4), c.1253G>A (n = 4), c.1010A>G (n = 3), and c.1310C>T (n = 3). Thirty-seven novel variants were identified, of which 26 were missense.

The population distribution by test outcome, cohort and sex is shown in Figure 1. While there were 3 times as many females to males in the adult cohort, there was near equal gender distribution in the youngest cohorts. The proportion of individuals with a positive test was similar for children (37%) and adults (35%). Although not systematically reported, the most common clinical signs/symptoms were early tooth loss and skeletal fracture, and some individuals had a family history of HPP.



Gender was not recorded for 8 (1%) of individuals. Positive = P or LP; indeterminate = VUS; negative = no genetic variant(s). F, female; LP, likely pathogenic; M, male; P, pathogenic; U, sex unknown; VUS, variant of uncertain significance.

Figure 1

Taken together, these results reveal several important findings:

Over 50% of submitted genetic tests did not identify a P/LP variant despite patients having low ALP activity and clinical signs/symptoms consistent with HPP. This reflects the challenge of diagnosing HPP given the non-specific signs and symptoms, particularly in adult patients

The detected *ALPL* variants showed a long-tailed distribution, with five recurrent variants accounting for half of positive patients, and a substantial number of novel variants identified. These novel variants will be an important addition to variant databases. The number of VUS identified was modest yet noteworthy. Functional studies would help determine pathogenicity of these VUS

Over 90% of detected positive cases had a single *ALPL* variant, which may reflect the fact that individuals with biallelic disease are often most severely affected and present with overt findings earlier in life which typically leads to a thorough evaluation resulting in a timely diagnosis

Limitations of these data include the potential for selection bias, the lack of a confirmatory diagnosis, and limited clinical data. However, the data are consistent with the published literature on common variants in the US and the differing sex ratios of infants versus adults with HPP.

These data will aid HPP diagnostics by contributing important information to *ALPL* variant databases and by furthering understanding of the spectrum of *ALPL* variants in individuals suspected of having HPP.

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Novel BCL11A variant Arg3Cys in a patient with intellectual disability and persistence of fetal Hb

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BCL11A is a transcription factor that is highly expressed in brain and lymphocytes, and regulates the switch from fetal to adult hemoglobin after birth. A neurodevelopmental disorder caused by variants in *BCL11A* was first described in 2016 by Dias et al., who identified 9 individuals with similar phenotypes, 6 of whom had loss-of-function variants and 3 of whom had missense variants in *BCL11A* (PMID 27453576). Additional patients have since been reported (PMID 28891213, 28589569, 32903878, 28960836, 30577886, 28333917). Characteristic features of this syndrome include intellectual disability, developmental delay, speech delay, neonatal hypotonia, joint laxity, strabismus, and mild dysmorphic features. Autism, epilepsy, microcephaly, and scoliosis are reported in a subset of patients. The characteristic laboratory finding is persistence of fetal hemoglobin. Persistence of fetal hemoglobin is not known to cause symptoms, and no hematologic problems have been reported in patients with pathogenic *BCL11A* variants so far (PMID 31556984). This disorder is described in OMIM as Dias-Logan syndrome, as well as Intellectual Developmental Disorder with Persistence of Fetal Hemoglobin (#617101). Here, we report a novel *BCL11A* variant in a 20-year old patient with intellectual disability and autism, which contributes to our current understanding of this rare disorder.

Pregnancy history and birth weight of the patient were normal. As a baby, he had feeding difficulties and severe hypotonia. Speech and motor milestones were delayed, and he walked at age 4. He was diagnosed with autism spectrum disorder (ASD) at age 7, and is presently mostly noncommunicative, with speech limited to yes/no. In addition to his neurologic phenotype, he has scoliosis, tachycardia, fatty liver (diagnosed by abdominal ultrasound), and feet/lower extremity pain, but x-ray and MRI of his legs has been unremarkable. At a physical exam at age 19, height was 5′4″, weight was 210 pounds, and head circumference was not available. He was described as overall