

0087 - MOLECULAR DIAGNOSES OF X-LINKED HYPOPHOSPHATEMIA FROM A MULTI-COUNTRY SPONSORED GENETIC TESTING PROGRAM IN LATIN AMERICA

Mode: Research paper

Thematic Unit: Rare Diseases

Thematic Unit 2: Phosphocalcic Metabolism

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Background/Objectives: X-linked hypophosphatemia (XLH) is a rare dominant disorder caused by disease-associated variants in the PHEX gene and affects males and females of all ages. Patients with XLH have chronic hypophosphatemia and lifelong musculoskeletal symptoms. Although more than 1000 unique disease-causing PHEX variants have been identified, data on the genetic landscape of PHEX variants in Latin America (LATAM) are limited, and patients from this region are underrepresented in global variant databases. This study aimed to expand knowledge of XLH molecular diagnoses and PHEX variant characterization through a multi-country sponsored genetic testing program in LATAM.

Methods: Individuals with suspected genetic hypophosphatemia from 12 LATAM countries were referred for genetic testing. Saliva samples were analyzed using an 18-gene next-generation sequencing panel. Variant classifications were interpreted by the testing laboratory (Mendelics) per ACMG/AMP guidelines. Clinical and biochemical data were collected for individuals with positive or potential positive PHEX findings. To protect patient privacy, data were reported in aggregate for variants found in at least 5 individuals.

Results: 1631 individuals were tested between November 2017 and December 2023; most were female (65%) and from Brazil (59%). Overall, 50% (817/1631) received a positive molecular diagnosis for XLH (pathogenic [P] or likely pathogenic [LP] PHEX variant) and 4% (67/1631) received a potential positive diagnosis (variant of uncertain significance [VUS]). Only 119 (13%) individuals with a P/LP/VUS variant had phenotypes reported on the test requisition form; the most common phenotypes were lower limb deformities (110, 92%), short stature (107, 90%), and bone/joint pain or stiffness (49, 41%). A total of 875 recurrent variants representing 472 unique PHEX variants were identified (74% P, 16% LP, 10% VUS). Of the 472 unique variants, 78% (366) were not present in a global locus-specific database of PHEX variants and 60% (279) were not present in ClinVar. Only 21 variants occurred in ≥5 individuals, and no genotype-phenotype correlations were observed.

Conclusion: This program substantially expanded the molecular diagnostic landscape of XLH in LATAM and identified many novel variants. These findings underscore the importance



of region-specific genetic data for accurate XLH diagnosis and management and advance understanding of PHEX variants in patients with XLH.

