PHEX Gene Testing in X-linked Hypophosphatemia

Disorder also known as: Hypophosphatemic rickets; Vitamin D-resistant rickets

Clinical Features:
X-linked hypophasphatemia is the most common form of inherited rickets. Affected individuals have hypophosphatemia due to decreased renal tubular serum inorganic phosphorous reabsorbtion. It is resistant to treatment with Vitamin D. The disorder includes short stature, bowing of the lower limbs, poor dental development and extraskeletal ossification. Occasionally, spinal cord compression is present. As an X-linked dominant trait, this disorder affects both males and females. The disease is equally severe in young boys and girls, although adult males may be more severely affected than adult females. A less common form of dominant hypophosphatemia that is phenotypically similar to the X-linked form is due to gain-of-function variant in the autosomal FGF23 gene.

Genetics:
X-linked dominant

Test Methods:
Using genomic DNA obtained from the submitted biological material, the 22 coding exons and splice junctions of the PHEX gene are screened by bi-directional sequence analysis. In females, where sequencing fails to identify a pathogenic variant, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. If a sequence change or deletion is identified, it is confirmed by a second analysis, using sequence, heteroduplex or restriction fragment analysis, quantitative PCR or another appropriate method.

Test Sensitivity:
In one study of 68 X-linked hypophasphatemic rickets probands, 31 variants in the PHEX gene were identified (46%). Of the variants identified, approximately 77% were observed in familial cases and 23% in sporadic cases. Multiple partial gene deletions have been reported in PHEX, which would not be detectable in carrier females by gene sequencing. Therefore, we perform in females deletion/duplication analysis (ExonArrayDx) concurrently with sequencing to evaluate for a whole or partial gene deletion in PHEX.

Variants in PHEX are scattered throughout the gene and most are consistent with loss of protein function. The types of variants include missense, nonsense, deletion, insertion, frameshift and splice site. Most variants are novel, and *de novo* variant in PHEX is not

uncommon. Multiple gross deletions, insertions and rearrangement of the PHEX gene have been reported.

References:

1. Francis, F et al., Genomic Organization of the Human PEX Gene Mutated in X-Linked Dominant Hypophosphatemic Rickets Genome Research 7 573-585 (1997).
2. Dixon, PH et al., Mutational Analysis of PHEX Gene in X-linked Hypophosphatemia J Clin Endocrin & Metab 83(10):3615-3623 (1998)
3. Sabbagh, Y et al., PHEXdb, a Locus-Specific Database for Mutations Causing X-linked Hypophasphatemia Hum Mut 16:1-6 (2000);
4. Jan, SM et al., Perspective: Molecular Pathogenesis of Hypophasphatemic Rickets J of Clin Endocrin & Metab 87(6):2467-2473 (2002).