THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Hypophosphatemic Rickets

Clinical Features:

Phosphate is a mineral that is vital to bone growth and maintenance. Low levels of phosphate in the blood (hypophosphatemia) can lead to abnormalities in bone metabolism. Rickets is an abnormality of bone mineralization in children, with symptoms including slow growth, short stature, and bone abnormalities including bowing of the legs and genu valgum (knock knees) (1). Rickets may be environmental or hereditary. Environmental forms of rickets may be due to vitamin D deficiency or abnormal absorption of vitamin D, such as in patients with celiac disease or kidney problems (2). Hereditary forms of hypophosphatemic rickets may be due to abnormalities of vitamin D metabolism or recognition, or due to a decrease in tubular reabsorption of phosphorus in the kidneys (3). Additionally, hypophosphatasia, a condition caused by deficient activity of tissue-nonspecific isozyme of alkaline phosphatase (TNSALP), may have rickets as a characteristic in the neonatal, infantile and childhood forms of the disorder (4, 5). Hereditary forms of hypophosphatemic rickets may be inherited in an X-linked, autosomal dominant, or autosomal recessive manner. Treatment for hereditary hypophosphatemic rickets may be impacted by identification of an underlying genetic etiology. For example, hereditary vitamin D resistant rickets may respond to pharmacologic doses of vitamin D. Hypophosphatemic rickets not due to vitamin D resistance may be corrected by phosphate replacement (3, 6). Hypophosphatasia can be treated with TNSALP enzyme replacement therapy (4).

Our Hypophosphatemic Rickets Sequencing and Deletion/Duplication Panels include analysis of the 10 genes listed below.

Rickets Panel Genes			
ALPL	CYP27B1	FGF23	VDR
CLCN5	DMP1	PHEX	
CYP2R1	ENPP1	SLC34A3	

Gene	Condition	Inheritance
ALPL	Hypophosphatasia [OMIM#s 146300, 241510, 241500]	Autosomal dominant or autosomal recessive
CLCN5	Hypophosphatemic rickets [OMIM# 300554]	X-linked
CYP2R1	Rickets due to defect in vitamin D 25-hydroxylation [OMIM# 600081]	Autosomal recessive
CYP27B1	Vitamin D deficient rickets type I [OMIM# 264700]	Autosomal recessive
DMP1	Hypophosphatemic rickets [OMIM# 241520]	Autosomal recessive
ENPP1	Hypophosphatemic rickets [OMIM# 613312]	Autosomal recessive
FGF23	Hypophosphatemic rickets [OMIM# 193100]	Autosomal dominant
PHEX	Hypophosphatemic rickets [OMIM# 307800]	X-linked
SLC34A3	Hypophosphatemic rickets with hypercalciuria [OMIM# 241530]	Autosomal recessive
VDR	Vitamin D deficient rickets type II [OMIM# 277440]	Autosomal recessive

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Sequencing may not detect low level mosaicism.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Hypophosphatemic Rickets Panel (10 genes sequencing)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2500
CPT codes:	81406
	81407
Turn-around time:	4 weeks

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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2. Elder CJ, Bishop NJ. Rickets. Lancet 2014: 383: 1665-1676.
3. Holick M. Vitamin D Disorders. In: Weiss R, Refetoff S, eds. Genetic Diagnosis of Endocrine Disorders: Elsevier, 2016: 191-199.
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5. Mornet E, Nunes M. Hypophosphatasia. In: Pagon R, Adam M, Ardinger H et al., eds. GeneReviews [Internet]. Seattle, WA: University of Washington, 2007 [last update 2016].
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