



PHID Testing: Mutation Analysis of *SLC29A3*

Clinical Features

PHID [pigmented hypertrichotic dermatosis with insulin-dependent diabetes mellitus, OMIM#602782] is a rare disorder characterized by childhood onset of pigmented hypertrichotic skin lesions and insulin-dependent diabetes mellitus, which is typically autoantibody negative (1). Circulating insulin is typically not detectable and cannot be induced in response to glucose administration, consistent with a defect of insulin production or secretion, rather than insulin resistance (1). PHID is allelic with H syndrome, which is associated with hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart anomalies, hearing loss, hypogonadism, low height and hyperglycemia (1).

Molecular Genetics

Cliffe *et al* (2009) identified homozygous mutations in the *SLC29A3* gene [OMIM#602782] in five families affected by PHID. *SLC29A3* encodes an equilibrative nucleoside transporter 3 protein, and studies of the *Drosophila* ortholog of this protein have provided evidence that it interacts with the insulin signaling pathway (1). To date, missense, nonsense, splice site and frameshift mutations have been described in the *SLC29A3* gene (1).

Inheritance

PHID is inherited in an autosomal recessive inheritance pattern. Therefore, parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *SLC29A3* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. The constructed genomic DNA library is sequenced 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 novel and/or potentially 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 20bp. 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.

SLC29A3 sequencing and deletion/duplication analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81404, 81405
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.

References:

1. Cliffe ST, Kramer JM, Hussain K et al. *SLC29A3* gene is mutated in pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome and interacts with the insulin signaling pathway. *Hum Mol Genet* 2009; 18: 2257-2265.

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