THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Pancreatic and Cerebellar Agenesis: Mutation Analysis of *PTF1A*

Clinical Features

Pancreatic and Cerebellar Agenesis [OMIM#609069] is characterized by neonatal diabetes mellitus and cerebellar hypoplasia/agenesis. Characteristic dysmorphism can include triangular facies, small chin, beaked nose and low set, dysplastic ears (1). Generalized joint stiffness and bilateral talipes equinovarus have also been noted (2).

Molecular Genetics

Mutations in the *PTF1A* [OMIM#607194] gene have been reported in patients with Pancreatic and Cerebellar Agenesis (3). *PTF1A* encodes a basic helix-loop-helix protein that is a sequence-specific DNA binding subunit of the trimeric pancreas transcription factor.

Inheritance

PTF1A mutations follow an autosomal recessive inheritance pattern and are a rare cause of permanent neonatal diabetes mellitus. 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 *PTF1A* gene is performed. Targets of interests are captured and amplified using Agilent SureSelect target enrichment 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.

PTF1A sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81403, 81404
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. Hoveyda N, Shield JP, Garrett C et al. Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: report of a new recessive syndrome. J Med Genet 1999: 36: 700-704.
2. Al-Shammari M, Al-Husain M, Al-Kharfy T et al. A novel PTF1A mutation in a patient with severe pancreatic and cerebellar involvement. Clin Genet 2011: 80: 196-198.
3. Sellick GS, Barker KT, Stolte-Dijkstra I et al. Mutations in PTF1A cause pancreatic and cerebellar agenesis. Nat Genet 2004: 36: 1301-1305.

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