THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Pancreatic Agenesis and Congenital Heart Defects: Mutation Analysis of *GATA6*

Clinical Features

Pancreatic Agenesis and Congenital Heart Defects [PACHD, OMIM#600001] is characterized by neonatal diabetes mellitus and congenital heart defects. Intrafamiliar variability has been reported with regard to both severity of diabetes (ranging from neonatally lethal diabetes to adult-onset diabetes associated with agenesis of the pancreas) and the types of congenital cardiac defects in affected individuals (1). The most common congenital cardiac defects include atrial septal defects, ventral septal defects and tetralogy of fallot.

Molecular Genetics

Mutations in the *GATA6* [OMIM#601656] gene have been reported in patients with PACHD. Lango Allen *et al*, 2011 identified mutations in *GATA6* in 56% of subjects with pancreatic agenesis (2). *GATA6* is a member of a GATA family of zinc-finger transcriptional regulators, which bind to the common WGATAR motif in the regulatory regions of many genes.

Inheritance

Most cases appear to be *de novo*, but familial cases are reported. Recurrence risk for affected individuals with a *GATA6* mutation is 50%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *GATA6* 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.

GATA6 sequencing and deletion/duplication analysis

Sample specifications:	3 to10 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. Yorifuji T, Kawakita R, Hosokawa Y et al. Dominantly inherited diabetes mellitus caused by GATA6 haploinsufficiency: variable intrafamilial presentation. J Med Genet 2012: 49: 642-643.
2. Lango Allen H, Flanagan SE, Shaw-Smith C et al. GATA6 haploinsufficiency causes pancreatic agenesis in humans. Nat Genet 2012: 44: 20-22.

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