



ALMS1 Analysis for Alstrom Syndrome

Clinical Features

Alstrom syndrome [OMIM#203800] is characterized by progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, dilated or restrictive cardiomyopathy and child obesity. Type 2 diabetes mellitus is observed in nearly all patients before the second decade. Renal failure, pulmonary, hepatic, and urologic dysfunction are also often observed. Intelligence is typically normal. Wide clinical variability is observed amongst affected individuals, even within the same family (1).

Molecular Genetics

Homozygous or compound heterozygous mutations in the *ALMS1* [OMIM#606844] gene cause Alström syndrome (2). *ALMS1* is widely expressed in tissues that are affected in patients with Alstrom syndrome, including the central nervous, sensorineural, endocrine, cardiopulmonary, reproductive, and urogenital systems, and the location of *ALMS1* to centrosomes suggests roles in intracellular trafficking and ciliary function (3). The majority of mutations identified to date are nonsense and frameshift that are predicted to cause premature protein truncation (3).

Inheritance

Alstrom syndrome follows an autosomal recessive inheritance pattern. Therefore, parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%. Penetrance appears to be 100%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *ALMS1* 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 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 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.

ALMS1 mutation analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81405 81406
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. Marshall J, Paisey R, Carey C et al. Alstrom Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2003.
2. Collin GB, Marshall JD, Ikeda A et al. Mutations in *ALMS1* cause obesity, type 2 diabetes and neurosensory degeneration in Alström syndrome. *Nat Genet* 2002; 31: 74-78.
3. Marshall JD, Hinman EG, Collin GB et al. Spectrum of *ALMS1* variants and evaluation of genotype-phenotype correlations in Alström syndrome. *Hum Mutat* 2007; 28: 1114-1123.

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