THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

CISD2 and *WFS1* Analysis for Wolfram Syndrome

Clinical Features

Wolfram syndrome [OMIM#222300 and 604928] is a rare neurodegenerative disorder characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (1). It is also known by the acronym of the key features of the disorder: DIDMOAD (1). Wolfram syndrome has been associated with mutations in both the *WFS1* and *CISD2* genes (1, 2). Additional clinical findings may include renal abnormalities, ataxia, dementia, mental retardation and psychiatric illness (1). The minimal criteria for diagnosing Wolfram syndrome are juvenile onset diabetes mellitus and optic atrophy. Affected individuals described to date with *CISD2* mutations do not have diabetes insipidus (2). Upper gastrointestinal ulceration and bleeding may occur in *CISD2*-related Wolfram syndrome (2). Some heterozygous mutations in *WFS1* can be associated with phenotypic outcomes, including low-frequency non-syndromic deafness, or a Wolfram syndrome-like phenotype, with hearing impairment with diabetes mellitus and/or optic atrophy (1).

Molecular Genetics

WFS1 encodes a glycoprotein called wolframin, which predominantly localizes to the endoplasmic reticulum (3). Mutations associated with Wolfram syndrome typically lead to a loss of protein function, whereas non-activating mutations have been identified in heterozygous carriers with autosomal dominant low frequency sensorineural hearing loss (3). *CISD2* encodes an intermembrane protein in the endoplasmic reticulum. Although the CISD2 protein does not appear to directly interact with wolframin, they both appear to be involved in calcium homeostasis (2).

Inheritance

Wolfram syndrome is inherited in autosomal recessive manner. 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 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. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Wolfram Syndrome Sequencing Panel (sequencing of *WFS1* and *CISD2*)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81406
Turn-around time:	4 weeks

Wolfram Syndrome Deletion/Duplication Panel (deletion/duplication analysis of *WFS1* and *CISD2*)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1545
CPT codes:	81405
Turn-around time:	4 - 6 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. Rendtorff ND, Lodahl M, Boulahbel H et al. Identification of p.A684V missense mutation in the WFS1 gene as a frequent cause of autosomal dominant optic atrophy and hearing impairment. Am J Med Genet A 2011: 155A: 1298-1313.
2. Amr S, Heisey C, Zhang M et al. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. Am J Hum Genet 2007: 81: 673-683.
3. Cryns K, Sivakumaran TA, Van den Ouweland JM et al. Mutational spectrum of the WFS1 gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease. Hum Mutat 2003: 22: 275-287.

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