THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Mowat-Wilson syndrome testing: Mutation analysis of *ZEB2*

Clinical Features:

Mowat-Wilson syndrome (MWS) [OMIM # 235730] is characterized by distinctive facial features, which in young children include hypertelorism, medially flared and broad eyebrows, prominent or pointed chin, uplifted earlobes and an opened mouth expression. In older children the eyebrows become heavier, the chin and nasal tip become more prominent and the face elongates (1, 2). Individuals with MWS also present with moderate-to-severe mental retardation, seizures and microcephaly. Congenital anomalies are also common, including Hirschsprung disease, genitourinary anomalies, congenital heart defects, agenesis of the corpus callosum and eye anomalies (1, 2).

Molecular Genetics:

Mutations of the Zinc Finger E Box-Binding Homeobox 2 gene *(ZEB2)* [OMIM #605802] have been identified in patients with MWS. The *ZEB2* gene maps to 2q22 and has 9 coding exons. Sequencing of *ZEB2* detects mutations in approximately 80% of individuals with a clinical diagnosis of MWS (3). An additional 17% of ZEB2 mutations are large or intermediate-sized deletions that would not be detected by sequencing (4).

ZEB2 encodes the transcriptional corepressor, Smad Interacting Protein 1 (SIP1), which is detected in nearly all human tissues (heart, brain, placenta, lung liver, skeletal muscle) and is likely to have a crucial role in embryonic development (3).

Inheritance:

The frequency of MWS remains unknown. *ZEB2* mutations are inherited in an autosomal dominant pattern and most cases are *de novo*. Germline mosaicism has been reported; recurrence risk for unaffected parents of an isolated case is approximately 2% (2).

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *ZEB2* gene 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. 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.

ZEB2 sequencing and deletion/duplication analysis

Sample specifications:	3 to 10cc 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. Adam M, Bean L, Miller V. Mowat-Wilson Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2007.
2. Garavelli L, Mainardi PC. Mowat-Wilson syndrome. Orphanet J Rare Dis 2007: 2: 42.
3. Mowat DR, Wilson MJ, Goossens M. Mowat-Wilson syndrome. J Med Genet 2003: 40: 305-310.
4. Dastot-Le Moal F, Wilson M, Mowat D et al. ZFHX1B mutations in patients with Mowat-Wilson syndrome. Hum Mutat 2007: 28: 313-321.