EGL Genetics | Eurofins Clinical Diagnostics
2460 Mountain Industrial Boulevard | Tucker, Georgia 30084
Phone: 470-378-2200 or 855-831-7447 | Fax: 470-378-2250
eglgenetics.com

Mowat-Wilson Syndrome: *ZEB2* Gene Sequencing

Test Code: DV
Turnaround time: 6 weeks
CPT Codes: 81405 x1

Condition Description

Mowat-Wilson syndrome (MWS) is a clinically recognizable syndrome characterized by intellectual disability, dysmorphic features, and multiple congenital anomalies. All patients are reported with moderate to severe intellectual disability. Distinct facial features evolve with age. In young children the facial features are characterized by:

- prominent chin
- deep-set eyes
- broad nasal bridge
- open mouth with a full lower lip
- hypertelorism
- broad eyebrows
- posteriorly rotated ears with uplifted earlobes and a central depression

In older children, the chin becomes more prominent, the face elongates and the nasal tip becomes more prominent extending below the ala nasi. Individuals often have a smiling expression. Nearly all individuals have microcephaly and seizures. Many individuals have hypotonia with delayed motor milestones. Speech may be absent or delayed. Hirschprung disease is present in ~60% of patients. Other reported congenital anomalies include heart defects (~45%), genitourinary anomalies, and agenesis of the corpus callosum [1, 2].

De novo deletion or mutation of the *ZEB2* gene located at 2q22 is associated with MWS. In a series of 47 patients with MWS and an identified mutation in *ZEB2*, 39 (83%) had a mutation identifiable by gene sequencing and 8 (17%) had a chromosome deletion or rearrangement detectable by deletion/duplication array analysis [3]. A small number of patients with a clinical diagnosis of MWS but no identified mutation in *ZEB2* have been reported [2]. *ZEB2* encodes the transcriptional corepressor, Smad Interacting Protein 1 (*SIP1*). It is suggested that haploinsufficiency of this gene leads to a gene dosage effect early in development. All reported cases are sporadic, and recurrence risk in families is thought to be low, however, parental mosaicism and germline mosaicism have been reported [4]. For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available.

References:
1. Mowat, D.R., G.D. Croaker, D.T. Cass, B.A. Kerr, J. Chaitow, L.C. Ades, N.L. Chia, and M.J. Wilson, Hirschsprung disease, microcephaly, mental retardation, and characteristic facial features: delineation of a new syndrome and identification of a locus at chromosome 2q22-q23. J Med Genet, 1998. 35(8): p. 617-23.
2. Mowat, D., M. Wilson, and M. Goossens, Mowat-Wilson syndrome. J Med Genet, 2003. 40: p. 305-310.
3. Cerruti Mainardi, P., G. Pastore, C. Zweier, and A. Rauch, Mowat-Wilson syndrome and mutation in the zinc finger homeo box 1B gene: a well defined clinical entity. J Med Genet, 2004. 41(2): p.e16.
4. McGaughran, J., S. Sinnott, F. Dastot-Le Moal, M. Wilson, D. Mowat, B. Sutton, and M. Goossens, Recurrence of Mowat-Wilson syndrome in siblings with the same proven mutation. Am J Med Genet A, 2005. 137(3): p. 302-304.

Genes

ZEB2, ZFHX1B

Indications

This test is indicated for:

- Patients with clinical features indicative of MWS.

Methodology

The 9 coding exons and immediate flanking regions of the *ZEB2* gene are amplified by PCR and sequenced in both forward and reverse directions. The patient's gene sequences are then compared to a normal reference sequence. Sequence variants are classified as previously described mutations, novel mutations, or variants of unknown significance. This analysis may detect novel variants of unclear effect, which require further studies.

Detection

This sequencing assay will detect over 95% of sequence variants in the coding region and splice junctions. Mutations in the promoter region, some mutations in the introns or other regulatory elements, large deletions, and insertion mutations will not be detected by this assay. It is possible that some patients with a typical presentation may not carry a mutation detected by this analysis.

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Reference Range

Gene sequencing is a qualitative assay.

Specimen Requirements

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Submit only 1 of the following specimen types

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old: 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Special Instructions

Please submit copies of diagnostic biochemical test results along with the sample. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Chromosomal microarray analysis is indicated for patients with intellectual disability or congenital anomalies.
- Deletion/Duplication Assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Known Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Prenatal testing is available to individuals with a previous child with Mowat-Wilson syndrome when the mutation in the child has been identified. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.