## Condition Description

X-linked Opitz G/BBB syndrome is a congenital midline malformation syndrome characterized by facial anomalies, laryngo-tracheo-esophageal defects, and genitourinary abnormalities. Facial anomalies seen in X-linked Opitz G/BBB syndrome include ocular hypertelorism, prominent forehead, widow’s peak, broad nasal bridge, and anteverted nares. Genitourinary abnormalities include hypospadias, cryptorchidism, and hypoplastic/bifid scrotum. The condition is genetically heterogeneous, as there is an autosomal dominant form as well.

Hypertelorism and hypospadias are the most frequent manifestations of X-linked Opitz G/BBB syndrome, being present in almost all individuals. Developmental delay and mental retardation are observed in about 50% of affected males. Cleft lip and/or palate are present in approximately 50% of affected individuals. Other malformations present in fewer than 50% of individuals include congenital heart defects, imperforate or ectopic anus, and midline brain defects (Dandy-Walker malformation and agenesis or hypoplasia of the corpus callosum and/or cerebellar vermis). Monozygotic twinning is unusually frequent in families of individuals with X-linked Opitz G/BBB syndrome, and may be a manifestation of the defect; unusually severe cases with early lethality occur as twins. Wide clinical variability occurs even among members of the same family. Female carriers usually manifest only ocular hypertelorism. The prevalence of X-linked Opitz G/BBB syndrome ranges from one in 50,000 to one in 100,000 males.

The diagnosis of X-linked Opitz G/BBB syndrome is established most often by clinical findings. MID1 (Xp22) is the only gene currently known to be associated with X-linked Opitz G/BBB syndrome. Sequence analysis of the MID1 gene detects mutations in 15%-45% of males with clinically diagnosed Opitz G/BBB syndrome. Deletions and duplications in and of the MID1 gene have also been reported. The cohorts tested for MID1 mutations often include simplex cases (i.e., individuals with no family history of Opitz G/BBB syndrome), who therefore cannot be determined to have either the X-linked form or the autosomal dominant form. The detection rate is higher in individuals with clear X-linked inheritance. De novo mutations have been reported.

For patients with suspected X-linked Opitz G/BBB syndrome, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

Click here for the GeneTests summary on this condition.

## Genes

### MID1

## Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of X-linked Opitz G/BBB syndrome
- Carrier testing in adult females with a family history of X-linked Opitz G/BBB syndrome

## Methodology

PCR amplification of 9 exons contained in the MID1 gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

## Detection

Clinical Sensitivity: Sequence analysis of the MID1 gene detects mutations in 15%-45% of males with clinically diagnosed Opitz G/BBB syndrome.
Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. 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**

- Deletion/duplication analysis of the *MID1* gene by CGH array is available for those individuals in whom sequence analysis is negative (ZD).
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.