

## Homocystinuria: CBS Gene Sequencing

**Test Code:** EY

**Turnaround time:** 4 weeks

**CPT Codes:** 81406 x1

### Condition Description

Homocystinuria is an autosomal recessive disorder resulting from a deficiency of the enzyme cystathionine beta-synthase (CBS). Laboratory findings include markedly increased concentrations of plasma homocystine, total homocysteine, and methionine; increased concentration of urine homocystine; and reduced cystathionine beta-synthase (CBS) enzyme activity.

The disease presents with findings that can range from multiple organ disease beginning in infancy or early childhood to only thromboembolism expressed in early to middle adult years. The major findings in classic homocystinuria include developmental delay and mental retardation, ectopia lentis and/or severe myopia, skeletal abnormalities, vascular abnormalities such as thromboembolism, and clinical similarities to Marfan syndrome. Expressivity is variable for all of the clinical signs. Two phenotypic variants are recognized, B6-responsive homocystinuria and B6-non-responsive homocystinuria. B6-responsive homocystinuria is typically, but not always, milder than the non-responsive variant. The mean IQ of affected individuals with B6-responsiveness is 79 versus 57 for those who are B6 non responsive. Thromboembolism is the major cause of early death and morbidity. Other features that may occur include seizures, psychiatric problems, extrapyramidal signs such as dystonia, hypopigmentation, pancreatitis, malar flush, and livedo reticularis.

Homocystinuria is caused by mutations in the *CBS* gene (21q22.3). Sequencing of the *CBS* gene is recommended after a biochemical diagnosis of homocystinuria, and provides a complementary method to confirm the presence of mutations in a proband, identify carriers among the proband's relatives, and provide prenatal diagnosis in families with known mutations.

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (EZ).

References:

- [GeneReviews Clinical Summary](#)

### Genes

[CBS](#)

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of homocystinuria
- Carrier testing in adults with a family history of homocystinuria

### Methodology

PCR amplification of 23 exons contained in the *CBS* gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then 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. Large deletions are not detected by this analysis.

### Detection

**Clinical Sensitivity:** It is estimated that sequencing will detect >95% of mutations in the *CBS* gene. 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**

**Type: Saliva**

**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ 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: 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.

**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.

**Special Instructions**

Submit copies of diagnostic biochemical test results 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**

- Plasma Amino Acid Analysis (AA) and Urine Amino Acid Analysis (UA) are used in the diagnosis of a patient with homocystinuria.
- Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- A 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.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor before collecting a fetal sample.