



## **Homocystinuria Information for Health Professionals**

Homocystinuria is an amino acid disorder. Most individuals are lacking, or have low function, of the enzyme cystathionine beta-synthase, leading to a buildup of methionine and homocysteine in the body.

### ✓ **Clinical Symptoms**

Most newborns do not have symptoms. If the condition is left untreated, symptoms are usually recognizable between the ages of 1 and 3 and include growth delays, psychiatric disturbances, delayed developmental milestones, and learning disabilities or intellectual disabilities. If untreated, homocystinuria can cause lens dislocation and glaucoma, osteoporosis, scoliosis, heart disease or stroke due to thrombi, or pancreatitis.

### ✓ **Incidence**

Homocystinuria occurs in less than 1 in 100,000 births. The incidence is higher in Caucasians from the New England region of the United States and in individuals of Irish ancestry.

### ✓ **Genetics of homocystinuria**

Mutations in the CBS, MTR (methionine synthase), MTRR (methionine synthase reductase), and MTHFR genes cause homocystinuria.

Most cases are caused by mutations in the CBS gene, which prevents or reduces the production of cystathionine beta-synthase. This results in a build-up of homocysteine and methionine in the blood and urine.

Mutations in other genes rarely cause homocystinuria. Mutations of the MTR, MTRR, or MTHFR gene prevent or reduce the conversion of homocysteine back into methionine. MTHFR deficiency is NOT detectable by current newborn screening since it is associated with decreased plasma methionine level.

### ✓ **How do people inherit homocystinuria?**

Homocystinuria is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition. Carrier individuals are more likely to be vitamin B12 and folic acid deficient than other individuals. Carrier parents have a 25% recurrence risk in each pregnancy to have an affected offspring.

### ✓ **Treatment**

Immediate diagnosis and treatment of homocystinuria is critical to normal growth and development. Treatment is very effective if started early. Recommended treatment is a low methionine diet. Individuals may also benefit from vitamin B6, betaine, vitamin B12, folic acid, or supplements. Even when treated, some people will develop lens dislocation.

## Screening Methodology

Primary newborn screening for homocystinuria utilizes tandem mass spectrometry. Individuals who screen positive for homocystinuria will have elevated levels of methionine. MTHFR deficiency causes low methionine level, therefore, it is not detected by current newborn screening. False positive and false negative results are possible with this screen.

### ✓ What to do After Receiving Presumptive Positive Homocystinuria Screening Results

- 1) The clinician should immediately check on the clinical status of the baby with attention to liver disease.
- 2) Consultation with a metabolic specialist is essential.
- 3) The specialist may request plasma amino acid analysis and plasma homocysteine on the baby.
- 4) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 5) Report Clinical Findings to Newborn Screening Program at 785-291-3363.
- 6) Same birth siblings (twins, triplets) of infants diagnosed with homocystinuria should be re-screened; additional testing of these siblings also may be indicated.

### ✓ Confirmation of Diagnosis

The diagnosis of homocystinuria is confirmed through quantitative plasma amino acid analysis to measure the levels of methionine and homocystine, as well as total plasma homocysteine. Urine testing may also be done.

### ✓ Communication of Results to Parents

**If a baby has a presumptive positive homocystinuria newborn screening result, additional testing needs to be performed to confirm a diagnosis.** In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with homocystinuria, the following points should be conveyed to parents:

- ***Parents should understand that treatment for homocystinuria will be life-long.***
- ***Parents should understand that treatment is not curative and that not all medical complications can necessarily be prevented. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended. Infants and children may need periodic evaluation with ophthalmology and orthopedics.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation, contact:

Bryce Heese, MD  
Biochemical Genetics  
Children's Mercy Hospital- Kansas City, MO

Clinic phone: 816-234-3771  
Hospital Operator: 816-234-3000  
Office Fax: 816-302-9963