# Homocystinuria

Homocystinuria is a metabolic defect characterized by an accumulation of homocysteine in the serum and increased homocysteine in the urine. Homocysteine is involved in two cycles: the folate cycle which helps produce pyrimidines, and the methionine cycle. When one of the enzymes involved in these metabolic pathways is dysfunctional, elevated levels of homocysteine will be seen. This homocysteine is atherogenic and damages blood vessels, and also causes various neurological and connective tissue abnormalities. There are four causes of homocystinuria, all of which are inherited in an autosomal recessive fashion. They include methionine synthase deficiency, cystathionine synthase deficiency, decreased affinity of cystathionine synthase for pyridoxal phosphate, and methylenetetrahydrofolate (MTHFR) deficiency. Individuals are typically tall and thin with a Marfanoid body habitus, and suffer from kyphosis and lens subluxation. Intellectual disability, osteoporosis, and thrombotic or clotting events are also common. An especially important cause of morbidity and mortality is vascular disease including atherosclerosis. Patients exhibit extensive atheroma formation at a young age. Almost one fourth of patients die before the age of 30 as a result of thrombotic complications. In patients without these enzyme deficiencies, dietary deficiencies of B vitamins can elevate homocysteine levels, though these patients are primarily at risk only for atherosclerotic disease.




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## Pathophysiology

### Autosomal Recessive

Recessive-chocolate

All four causes of homocystinuria are inherited in an autosomal recessive fashion.

### 4 Forms

(4) Fork

There are four forms of homocystinuria. These four forms include cystathionine synthase deficiency, decreased affinity of cystathionine synthase for pyridoxal phosphate, methionine synthase deficiency, and methylenetetrahydrofolate reductase (MTHFR) deficiency.

### Cystathionine Synthase Deficiency

Broken Sisters-with-thimbles Broken

Cystathionine synthase is an enzyme that catalyzes the reaction of homocysteine to cystathionine. This enzyme uses the cofactor pyridoxal phosphate. A deficiency in this enzyme can cause an accumulation of homocysteine in the blood and urine.

### Decreased Affinity of Cystathionine Synthase For Vitamin B6

Down-arrow Sisters-with-thimbles fighting with Viking (B) Bee (6) Sax

Homocystinuria can be caused by a decreased affinity of cystathionine synthase for Vitamin B6 (in the form of pyridoxal phosphate), which is an essential cofactor in the reaction. Due to the decreased affinity, cystathionine synthase is unable to catalyze the reaction, leading to a buildup of homocysteine in the blood and urine.

### Methionine Synthase Deficiency

Broken Methyl-thimble

Methionine synthase, which is also called homocysteine methyltransferase, is responsible for the regeneration of methionine from homocysteine. A deficiency of methionine synthase can cause a buildup of homocysteine in the blood and urine.

### Methylenetetrahydrofolate Reductase (MTHFR) Deficiency

MoTHer-FatheR Broken

MTHFR is an enzyme in the folate cycle that catalyzes the conversion of 5,10-methylenetetrahydrofolate (THF) to 5-methyl THF, which is then used for pyrimidine synthesis. The folate cycle depends on homocysteine metabolism to function. MTHFR deficiency, therefore, leads to a build-up of homocysteine, or homocystinuria.

## Signs and Symptoms

### Marfanoid Body Habitus

Marfan-the-martian Body

Marfanoid habitus describes a constellation of physical findings, including tall stature, long limbs, spider-like fingers, and hyperlaxity of joints. Associated conditions include Marfan syndrome, MEN2B, homocystinuria, and spontaneous pneumothorax.

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**Kyphosis**

Curvy-K-spine

Kyphosis is a condition of extreme curvature of the upper back. This pathologic curving of the spine can be seen in homocystinuria.

**Lens Subluxation (Inferior)**

Camera-lens Sub

Eye anomalies are common in homocystinuria, especially lens subluxation. Lens subluxation in homocystinuria is characterized by an inferiorly displaced or malpositioned lens in the eyes. Contrast this with Marfan's syndrome, where there is superior lens subluxation.

**Intellectual Disability**

Tar Covered Book

Intellectual Disability is characterized by significantly impaired cognitive functioning and deficits in two or more adaptive behaviors. It is common in individuals with homocystinuria.

**Atherosclerosis**

Clogged Artery-guy

An especially important cause of morbidity and mortality is vascular disease, including atherosclerosis. Patients exhibit extensive atheroma formation at a young age. Almost one-fourth of patients die before the age of 30 as a result of thrombotic complications.

## Consideration

**Dietary Deficiencies Can Elevate Homocysteine Levels**

Broken Nutritional-plate Up-arrow Homer

While homocystinuria generally describes patients with a genetic disorder leading to elevated homocysteine levels, otherwise healthy patients could also have elevated levels in certain circumstances. For example, people with low dietary intake of folate, vitamin B6, or B12 can have increased levels of homocysteine. Though these patients don't have the genetic enzyme deficiencies described in classical homocystinuria, they may still be at elevated risk for atherosclerosis.

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