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Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency

Synonym: Classic Homocystinuria

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Summary

Clinical characteristics

Homocystinuria caused by cystathionine β-synthase (CBS) deficiency is characterized by involvement of the eye (ectopia lentis and/or severe myopia), skeletal system (excessive height, long limbs, scolioisis, and pectus excavatum), vascular system (thromboembolism), and CNS (developmental delay/intellectual disability). All four - or only one - of the systems can be involved; expressivity is variable for all of the clinical signs. It is not unusual for a previously asymptomatic individual to present in adult years with only a thromboembolic event that is often cerebrovascular. Two phenotypic variants are recognized, B_6-responsive homocystinuria and B_6-non-responsive homocystinuria. B_6-responsive homocystinuria is usually milder than the non-responsive variant.

Thromboembolism is the major cause of early death and morbidity. IQ in individuals with untreated homocystinuria ranges widely, from 10 to 138. In B_6-responsive individuals the mean IQ is 79 versus 57 for those who are B_6-non-responsive. Other features that may occur include: seizures, psychiatric problems, extrapyramidal signs (e.g., dystonia), hypopigmentation of the skin and hair, malar flush, livedo reticularis, and pancreatitis.

Diagnosis/testing

The cardinal biochemical features of homocystinuria include markedly increased concentrations of plasma total homocysteine and methionine. The diagnosis can be substantiated by detection of biallelic pathogenic variants in *CBS*, the gene encoding cystathionine β-synthase.

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Management

Treatment of manifestations: Treatment aims to correct the biochemical abnormalities, especially to control the plasma homocysteine concentrations and prevent thrombosis. Complications of homocystinuria should be managed appropriately; e.g., by surgery for ectopia lentis.

Prevention of primary manifestations: Individuals are treated to maintain normal or near-normal plasma total homocysteine concentrations using vitamin B_6 (pyridoxine) therapy (if shown to be B_6 responsive), a methionine-restricted diet, and folate and vitamin B_{12} supplementation. Betaine therapy is usually added to the therapeutic regimen; in adolescents and adults, betaine may be the major form of treatment, but it is preferable to remain on life-long metabolic diet.

Surveillance: Affected individuals should be monitored at regular intervals to detect any clinical complications that may develop, for dietary compliance and for measurement of plasma total homocysteine and amino acids.

Agents/circumstances to avoid: Oral contraceptives in affected females. Surgery if possible. If surgery is required, intravenous fluid with 5% dextrose in 0.5 normal saline at 1.5 times maintenance should be given and continued until oral fluids are taken ad lib, with close monitoring to avoid fluid overload.

Evaluation of relatives at risk: Measurement of total homocysteine and amino acids in at-risk sibs immediately after birth ensures reduction of morbidity and mortality by early diagnosis and treatment. If the *CBS* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of sibs

Pregnancy management: For women with classic homocystinuria: dietary treatment and betaine, and vitamin B_6 for those B_6 responsive, with careful biochemical monitoring throughout pregnancy. Prophylactic anticoagulation with low molecular-weight heparin is recommended during the third trimester and post partum to reduce risk of thromboembolism.

Genetic counseling

Homocystinuria is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for a pregnancy at increased risk are possible if the *CBS* pathogenic variants have been identified in an affected family member.

Diagnosis

Guidelines for the diagnosis and management of classic homocystinuria have been developed in Europe [Morris et al 2017]. These European guidelines recommend total homocysteine (tHcy) accompanied by plasma amino acid analysis as the frontline tests for diagnosis; tHcy above 100 umol/L but occasionally lower (normal: <15 umol/L), when accompanied by high or borderline high methionine, makes the diagnosis very likely. For classic homocystinuria diagnosis, it is imperative that both the total plasma homocysteine concentration and the methionine concentration (as determined by plasma amino acid analysis) be obtained.

Classic homocystinuria is caused by deficiency of cystathionine β-synthase (CBS), a pyridoxine (vitamin B_6)-dependent enzyme. Because homocysteine is at the branch point between transsulfuration and methionine remethylation in the methionine metabolic cycle, a block at CBS limits transsulfuration and results in both increased homocysteine and increased methionine, the latter caused by enhanced remethylation (Figure 1).

Suggestive Findings

Homocystinuria caused by CBS deficiency (classic homocystinuria) **should be suspected** in newborns with an abnormal newborn screen due to increased methionine and individuals with clinical findings that range from

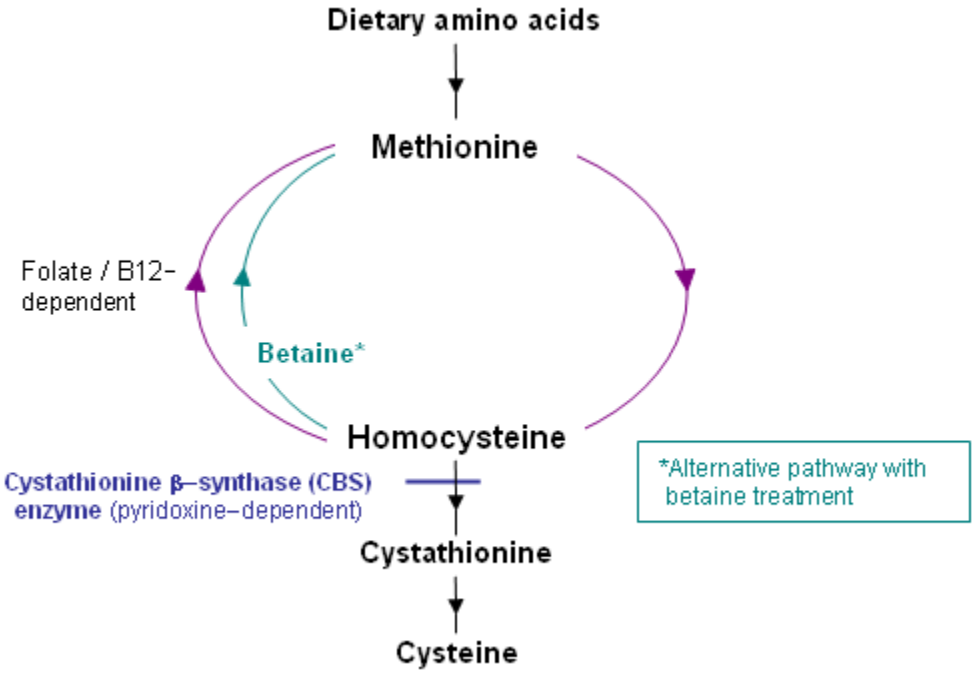

Figure 1. Methionine metabolic pathway

multiple organ disease beginning in infancy or early childhood to thromboembolism only, expressed in early to middle adult years.

Newborn Screening

Classic homocystinuria can be detected in some (not all) affected individuals by screening the newborn blood spot specimen for hypermethioninemia.

The method used to measure methionine on newborn screening is tandem mass spectrometry (MS/MS).

If the initial screening test result exceeds the cut-off level of methionine, follow-up testing is required. This may be:

1. A repeat dried blood specimen submitted to the newborn screening program; or
2. Quantitative plasma amino acid analysis and analysis of plasma total homocysteine as recommended in Newborn Screening ACT Sheets and Confirmatory Algorithms for Methionine by the American College of Medical Genetics (see ACMG ACT Sheet and ACMG Algorithm).

The choice between the dried blood specimen and the plasma analyses is based on the recommendation of the screening program, which usually depends on the degree of the methionine increase in the initial screen.

If (1) above is selected, and if the result confirms hypermethioninemia, plasma total homocysteine analysis and plasma amino acid analysis for methionine concentration should be performed to confirm or exclude the diagnosis of classic homocystinuria (Table 1).

Of note:

- At least one newborn screening program performs second-tier testing for homocysteine on all newborn specimens with elevated methionine in order to reduce the frequency of false positive results [Turgeon et al 2010].

- Newborn screening is for methionine and not for homocysteine. Thus, other causes of elevated total homocysteine, such as disorders of remethylation (e.g., methylenetetrahydrofolate reductase deficiency and the cobalamin defects; see Differential Diagnosis) may not be detected because the methionine level in these disorders is reduced (or normal). Some newborn screening laboratories may flag a low methionine [Tortorelli et al 2010].
- Virtually all infants with classic homocystinuria detected by newborn screening programs have had pyridoxine (vitamin B_6) non-responsive homocystinuria (see Clinical Description). It is likely very rare for infants who are pyridoxine responsive to have increased methionine during the first two to three days of life, when the newborn screening specimen is obtained.
- Measurement of total homocysteine as a primary newborn screening marker is used in Qatar, which has the highest reported incidence of homocystinuria [Gan-Schreier et al 2010].

Clinical Findings

The major clinical findings in classic homocystinuria:

- Ectopia lentis (dislocation of the ocular lens) and/or severe myopia
- Skeletal abnormalities (e.g., excessive height, long narrow limbs [dolichostenomelia], scoliosis, pectus excavatum) that may give the clinical impression of Marfan syndrome, but without joint hypermobility
- Vascular abnormalities characterized by thromboembolism
- Developmental delay/intellectual disability

Establishing the Diagnosis

The diagnosis of classic homocystinuria **is established** in a proband by measurement of plasma total homocysteine (tHcy) and amino acids in plasma (see Plasma Homocysteine and Amino Acids) and/or by identification of biallelic pathogenic variants in *CBS* through molecular genetic testing (see Table 2). Enzyme analysis of cystathionine β-synthase (CBS) activity may be performed if pathogenic variants are not identified.

Plasma Homocysteine and Amino Acids

Plasma homocysteine concentration must be determined in the absence of pyridoxine supplementation (including a multivitamin) for two weeks.

The cardinal biochemical features, including markedly increased concentrations of plasma total homocysteine (tHcy) and methionine, are summarized in Table 1.

Table 1. Cardinal Biochemical Findings that Establish the Diagnosis of Homocystinuria

Analyte	Specimen	Expected Findings		
		Neonate with homocystinuria	Untreated older person with homocystinuria	Control
Total homocysteine [1] (tHcy)	Plasma [2]	50 to >100 µmol/L	>100 µmol/L	<15 µmol/L
Methionine (on amino acid analysis)	Plasma	200-1500 µmol/L (3-23 mg/dL)	>50 µmol/L (>0.7 mg/dL)	10-40 µmol/L (0.2-0.6 mg/dL)

1. Click here (pdf) for terms used to describe sulfur amino acids.
2. Plasma tHcy measurement is an effective method for assuring accurate diagnosis of homocystinuria. Even after a week of storage without deproteinization, virtually all tHcy can still be recovered by a method of preparation that includes a reducing agent such as dithiothreitol [Smith et al 1998].

Molecular Genetic Testing

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Single-gene testing

- Sequence analysis of *CBS* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- Targeted analysis is performed only in the Qatari population, in which a single pathogenic variant (p.Arg336Cys; c.1006C>T) is present in 93% of the affected population [Gan-Schreier et al 2010].

A multigene panel that includes *CBS* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 2. Molecular Genetic Testing Used in Homocystinuria Caused by Cystathionine β-Synthase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
CBS	Sequence analysis [3]	95%-98% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gaustadnes et al [2002], Kruger et al [2003], Cozar et al [2011], Karaca et al [2014]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Nine individuals with deletions or duplications involving 25 or more nucleotides have been reported to date [*CBS* Mutation Database].

CBS Enzyme Activity in Cultured Fibroblasts

Analysis of CBS enzyme activity may be performed when molecular analysis fails to identify two pathogenic variants in *CBS*. CBS enzyme activity can be measured in fibroblasts [Smith et al 2012, Mendes et al 2014] or plasma [Krijt et al 2011, Alcaide et al 2015]. However, activity may be normal in mild cases, especially in those who are B_6-responsive [Mendes et al 2014, Alcaide et al 2015]. Enzyme analysis cannot reliably distinguish B_6-responsive from B_6-non-responsive individuals.

Note: Enzyme activity testing, which has been used in the past to confirm the diagnosis of homocystinuria when molecular testing genetic testing results are not diagnostic, is no longer available in the US.

Testing Following Establishment of the Diagnosis

Pyridoxine (B_6) challenge test. The two phenotypic variants of classic homocystinuria – B_6-responsive and B_6-non-responsive homocystinuria – can have differing natural history and management. Once the diagnosis of homocystinuria caused by deficiency of cystathionine β synthase (CBS) is established, a pyridoxine challenge to measure vitamin B_6-responsiveness is used to determine which phenotype is present.

- **In the neonate.** While continuing a normal diet, plasma is obtained for baseline measurements of total homocysteine and amino acids.

  The affected individual is given 100 mg pyridoxine daily for two consecutive days; concentrations of plasma total homocysteine and amino acids are measured 48 hours after the first dose.

  - A reduction of 30% or more in plasma total homocysteine and/or plasma methionine concentration suggests B_6 responsiveness.
  - If no significant change occurs, 200 mg pyridoxine is given orally for two consecutive days and the plasma total homocysteine and amino acid analysis are repeated after 48 hours on this dose.
  - If still no change has occurred, 300 mg of pyridoxine is given to the neonate. If plasma homocysteine and methionine concentrations are not significantly decreased after the last dose of pyridoxine, it is concluded that the individual is B_6-non-responsive.

- **Beyond the neonatal period.** For a clinically identified individual, continue a normal diet and provide folate supplement of 5 mg (for children and adults); correct B_{12} deficiency if present. Obtain plasma for baseline measurements of total homocysteine and amino acids.

  The affected individual is given 100 mg pyridoxine daily for two consecutive days, and the concentrations of plasma total homocysteine and amino acids are again measured 48 hours after the first dose.

  - A reduction of 30% or more in plasma total homocysteine and/or plasma methionine concentration suggests B_6 responsiveness.
  - If no significant change occurs, 200 mg pyridoxine is given orally for two consecutive days and the plasma total homocysteine and amino acid analysis are repeated after 48 hours on this dose.
  - If still no change has occurred, 500 mg of pyridoxine is given orally to a child or adult. If plasma homocysteine and methionine concentrations are not significantly decreased after the last dose of pyridoxine, it is concluded that the individual is B_6-non-responsive.

Note: (1) Infants should not receive more than 300 mg of pyridoxine. Several infants given daily doses of 500 mg pyridoxine developed respiratory failure and required ventilatory support. The respiratory symptoms resolved on withdrawal of pyridoxine [Shoji et al 1998, Mudd et al 2001]. (2) Peripheral neuropathy has been seen as an adverse effect of pyridoxine doses exceeding 900 mg per day [Morris et al 2017].

Clinical Characteristics

Clinical Description

Homocystinuria is characterized by involvement of the eye, skeletal system, vascular system, and CNS. All four or only one of the systems can be involved. Expressivity is variable for all of the clinical signs. It is not unusual for a previously asymptomatic individual to present in adult years with only a thromboembolic event that is often cerebrovascular [Yap 2003, Skovby et al 2010].

The two phenotypic variants of classic homocystinuria are B_6-responsive and B_6-non-responsive homocystinuria. B_6-responsive homocystinuria is typically (but not always) milder than the non-responsive variant. Vitamin B_6 responsiveness is determined by a pyridoxine challenge test (see Testing Following Establishment of the Diagnosis).

Eyes. Myopia followed by ectopia lentis typically occurs after age one year. In the majority of untreated individuals, ectopia lentis occurs by age eight years. Ectopia lentis usually occurs earlier in affected individuals who are B_6 non-responsive than in those who are B_6 responsive. Rarely, ectopia lentis occurs in infancy [Mulvihill et al 2001].

High myopia may be present in the absence of ectopia lentis.

Skeletal system. Affected individuals are often tall and slender with a marfanoid habitus.

Individuals with homocystinuria are prone to osteoporosis, especially of the vertebrae and long bones; 50% of individuals show signs of osteoporosis by their teens. Osteoporosis may be detected radiographically by lateral view of the lumbar spine or bone density studies. DXA bone density analysis usually shows reduced density in the lumbar spine and hip [Weber et al 2016].

Scoliosis, high-arched palate, arachnodactyly, pes cavus, pectus excavatum or pectus carinatum, and genu valgum are also frequently seen.

Vascular system. Thromboembolism is the major cause of morbidity and early death [Yap 2003]. It can affect any vessel. Cerebrovascular accidents have been described in infants, although problems typically appear in young adults [Yap et al 2001a, Kelly et al 2003].

Among B_6-responsive individuals, a vascular event in adolescence or adulthood is often the presenting feature of homocystinuria [Magner et al 2011, Sarov et al 2014]. Cerebral venous sinus thrombosis has been a presenting sign in childhood [Karaca et al 2014, Saboul et al 2015].

Pregnancy increases the risk for thromboembolism, especially in the postpartum period [Novy et al 2010]; most pregnancies, however, are uncomplicated. See Pregnancy Management.

CNS. Developmental delay is often the first abnormal sign in individuals with homocystinuria. IQ in individuals with homocystinuria ranges from 10 to 138. B_6-responsive individuals are more likely than individuals with B_6-non-responsive homocystinuria to be cognitively intact or only mildly affected; the mean IQ of untreated individuals with B_6 responsiveness is 79 versus 57 for those who are B_6 non-responsive. B_6-non-responsive individuals who were identified on newborn screening, received early treatment, and had good compliance (maintenance of plasma free homocystine <11 µmol/L) had a mean IQ of 105 [Yap et al 2001b].

Seizures occur in 21% of untreated individuals.

Many individuals have psychiatric problems including personality disorder, anxiety, depression, obsessive-compulsive behavior, and psychotic episodes. Psychosis may be a presenting sign in adolescence [Hidalgo Mazzei et al 2014].

Extrapyramidal signs such as dystonia may occur.

Other features include hypopigmentation of the skin and hair, malar flush, livedo reticularis, and pancreatitis.

Genotype-Phenotype Correlations

The presence of a single p.Gly307Ser allele predicts B_6 non-responsiveness, while presence of a p.Ile278Thr allele usually predicts B_6 responsiveness [Gaustadnes et al 2002, Kruger et al 2003, Skovby et al 2010]. Other pathogenic alleles are associated with either B_6 responsiveness or non-responsiveness [Kraus et al 1999].

Nomenclature

"Homocystinuria" was named for excess homocystine in the urine, though now it is primarily detected by increased total homocysteine in plasma. Homocystinuria may be caused by genetically determined deficient

activity of cystathionine β-synthase (CBS), or a variety of genetic problems that ultimately interfere with conversion of homocysteine to methionine (e.g., methylenetetrahydrofolate reductase deficiency and abnormalities of cobalamin transport or metabolism). For details on the latter conditions, see Watkins & Rosenblatt [2014]. (See also Disorders of Intracellular Cobalamin Metabolism.)

Non-genetically determined severe dietary lack of cobalamin (vitamin B_{12} deficiency) may also cause "homocystinuria" [Mudd et al 2000].

To attain maximum specificity when using the term "homocystinuria," the particular defect in question may be added; e.g., "homocystinuria caused by CBS deficiency" [Mudd et al 2000], which has also been called "classic homocystinuria."

Classic homocystinuria as defined in this *GeneReview* is caused by deficiency of cystathionine β-synthase (CBS), a pyridoxine (vitamin B_6)-dependent enzyme.

Prevalence

Prevalence is at present undetermined; both newborn screening and clinical ascertainment underestimate prevalence because of undetected cases [Skovby et al 2010]. Prevalence has been reported as 1:200,000 to 1:335,000.

- **Qatar.** The prevalence, estimated at 1:1800, may be the highest in the world [Gan-Schreier et al 2010].
- **Ireland.** Prevalence is reported to be as high as 1:65,000 [Naughten et al 1998].
- **Germany.** Molecular genetic screening of a normal population estimated the prevalence of classic homocystinuria at 1:17,800 [Linnebank et al 2001].
- **Norway.** Molecular genetic screening of newborns employing a panel of six pathogenic variants estimated the prevalence of classic homocystinuria at 1:6400, based on the heterozygosity rate [Refsum et al 2004].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are associated with pathogenic variants in *CBS*.

Differential Diagnosis

The clinical condition that most closely mimics classic homocystinuria is Marfan syndrome, which shares the features of long thin body habitus, arachnodactyly, and predisposition for ectopia lentis and myopia. Although ectopia lentis can also occur early in sulfite oxidase deficiency, this condition is clinically distinct from homocystinuria. Individuals with sulfite oxidase deficiency and Marfan syndrome have normal concentrations of plasma homocysteine and methionine.

Increased concentrations of homocysteine or methionine also occur in biochemical genetic disorders that generally fall into two groups (see Figure 2 and Table 3) and can be secondary to other disorders or to nutritional aberrations:

- **Defects of methionine, S-adenosylmethionine, or S-adenosylhomocysteine metabolism**, which typically have increased methionine concentration but normal or only slightly increased total homocysteine concentration. Included in this category are several hypermethioninemic disorders such as methionine adenosyltransferase I/III deficiency, glycine N-methyltransferase deficiency and S-adenosylhomocysteine hydrolase deficiency [Mudd 2011, Barić et al 2017].
- **Methionine remethylation** defects, which typically have increased plasma total homocysteine but low methionine concentrations. Because newborn screening is based on the detection of methionine (not homocysteine), disorders of remethylation (e.g., methylenetetrahydrofolate reductase deficiency and the

cobalamin defects) may not be detected since plasma methionine concentration in these disorders is reduced (or normal). These disorders are usually folate or vitamin B_{12} dependent [Huemer et al 2017].
- **Secondary hypermethioninemia** with normal or only mildly increased total homocysteine, which can occur in liver disease associated with tyrosinemia type I [Grompe 2001] or galactosemia and in cases of excessive methionine intake from high-protein diet or methionine-enriched infant formula [Mudd et al 2003]

Table 3. Biochemical Aspects of Disorders Affecting Methionine Metabolism

Type of Defect	Disorder	Total Homocysteine	Methionine
Methionine transmethylation	MAT I/III deficiency	↑ (normal, slight)	↑↑
	GNMT deficiency		
	S-adenosylhomocysteine hydrolase deficiency		
Transsulfuration	Homocystinuria	↑↑	↑↑
Remethylation	MTHFR deficiency	↑↑	↓↓ (rarely normal)
	Cobalamin defects		

GNMT = glycine N-methyltransferase; MAT = methionine adenosyltransferase; MTHFR = methylenetetrahydrofolate reductase

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in all individuals diagnosed with homocystinuria caused by cystathionine β-synthase deficiency, the following are recommended:

- Consultation with a clinical geneticist/medical biochemical geneticist for additional testing and treatment plan
- Pyridoxine (vitamin B_6) challenge prior to initiation of treatment (see Testing Following Establishment of the Diagnosis, **Pyridoxine (B_6) challenge test**)
- Consultation with a genetic counselor for genetic counseling and recurrence risk counseling

Treatment of Manifestations

Treatment should be managed by a biochemical geneticist and metabolic dietician and aimed at prevention of primary manifestations of homocystinuria. For published management guidelines, see Morris et al [2017].

Complications should be managed appropriately (e.g., surgery for ectopia lentis) [Neely & Plager 2001].

Prevention of Primary Manifestations

The principles of treatment are to correct the biochemical abnormalities – especially to control the elevated plasma homocysteine concentrations as much as possible, to prevent or at least reduce the complications of homocystinuria [Yap & Naughten 1998], and to prevent further complications such as thrombosis [Morris et al 2017].

The best results have been reported in those individuals identified by newborn screening and treated shortly after birth in whom the plasma free homocystine concentration is maintained below 11 µmol/L (preferably, ≤5 µmol/L) [Yap et al 2001b]. This corresponds to a plasma total homocysteine concentration below 120 µmol/L or, preferably, below 100 µmol/L [Morris et al 2017]. For B_6-responsive individuals, the goal for plasma total homocysteine is below 50 µmol/L [Morris et al 2017].

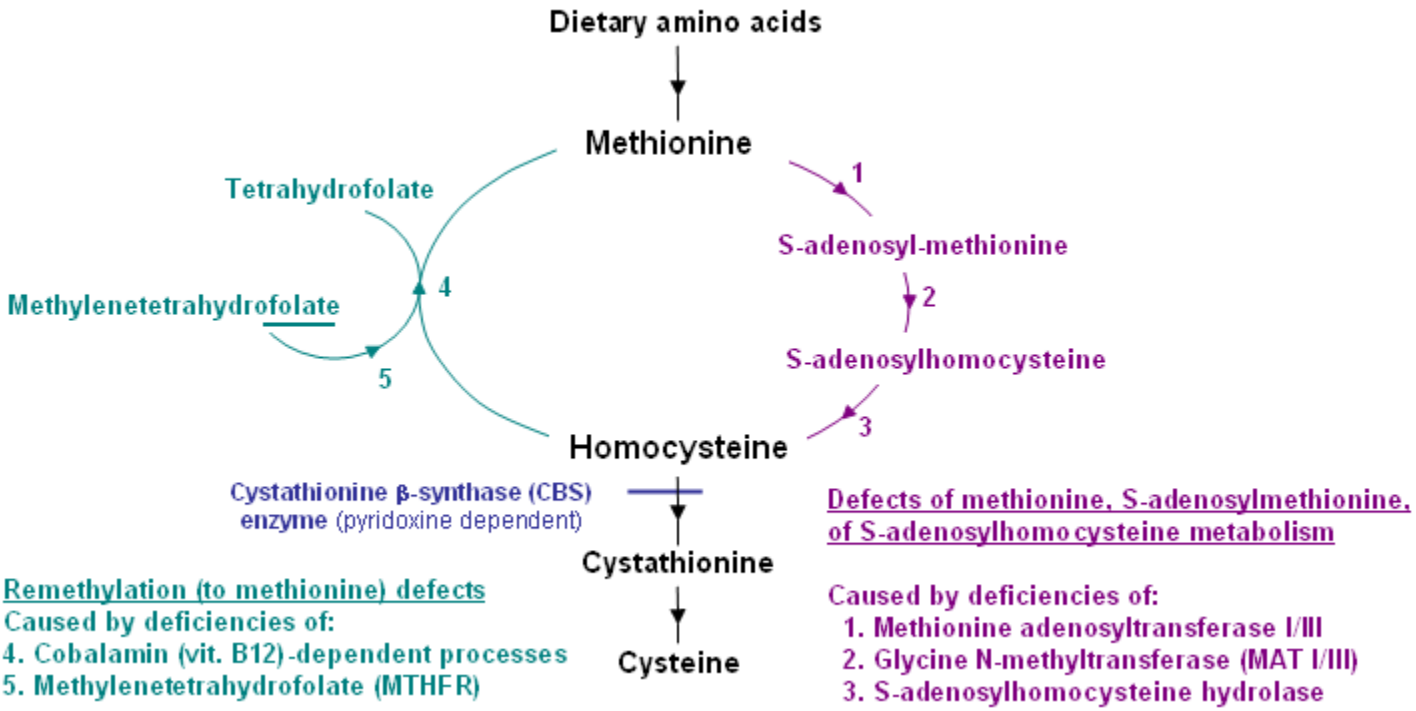

Figure 2. Pathway demonstrating disorders in the biochemical differential diagnosis for homocystinuria

These goals may need revision when very long-term data becomes available.

Measures used to control total plasma homocysteine concentration include vitamin B_6 (pyridoxine) therapy (if shown to be B_6 responsive), methionine-restricted diet, and folate and vitamin B_{12} supplementation. Betaine therapy is usually added to the therapeutic regimen; in adolescents and adults betaine may be the major form of treatment but it is preferable to remain on life-long metabolic diet. In those who have already had a vascular event, betaine therapy alone may prevent recurrent events [Lawson-Yuen & Levy 2010].

Details about each aspect of treatment follow.

Vitamin B_6 (pyridoxine) therapy. In those who are shown to be B_6 responsive, treatment with pyridoxine in a dose of approximately 200 mg/day or the lowest dose that produces the maximum biochemical benefit (i.e., lowest plasma homocysteine and methionine concentrations), as determined by measurement of total homocysteine and amino acid levels, should be given.

Pyridoxine may also be included in treatment despite evidence of B_6 non-responsiveness, typically in doses of 100-200 mg daily (although some adults receive 500-1000 mg daily).

Dietary treatment. B_6-non-responsive neonates or those only very poorly responsive to pyridoxine require a **methionine-restricted diet** with frequent metabolic monitoring. This diet should be continued indefinitely. Dietary treatment should be considered for clinically diagnosed individuals but often is not tolerated if begun in mid-childhood or later.

The majority of B_6-responsive individuals also require a methionine-restricted diet for metabolic control.

The diet for homocystinuria is very complex and the skills of an experienced metabolic dietician must be utilized. Dietary treatment reduces methionine intake by restricting natural protein intake. However, to prevent protein malnutrition, a methionine-free amino acid formula supplying the other amino acids (as well as cysteine, which may be an essential amino acid in CBS deficiency) is provided. Breast feeding may be continued in

combination with the methionine-free amino acid infant formula [MacDonald et al 2006]. The amount of methionine required is calculated by a metabolic dietician and supplied in natural food and special low-protein foods and monitored on the basis of plasma concentrations of total homocysteine as well as methionine.

Folate and vitamin B_{12} supplementation. Folate and vitamin B_{12} optimize the conversion of homocysteine to methionine by methionine synthase, thus helping to decrease the plasma homocysteine concentration. When the red blood cell folate concentration and serum B_{12} concentration are reduced, folic acid is given orally at 5 mg per day; and vitamin B_{12} is given as hydroxycobalamin at 1 mg IM per month.

Betaine treatment. Treatment with betaine provides an alternate remethylation pathway to convert excess homocysteine to methionine (see Figure 1) and may help to prevent complications, particularly thrombosis [Yap et al 2001a, Lawson-Yuen & Levy 2010]. By converting homocysteine to methionine, betaine lowers plasma total homocysteine concentrations but raises the plasma concentration of methionine.

For children the initial betaine dose is 50 mg/kg twice daily, adjusted according to response (increased weekly by 50 mg/kg increments). For adults the initial dose is 3 g twice daily. The dose and frequency are adjusted according to biochemical response. There is unlikely to be any benefit in exceeding a dose of 150-200 mg/kg/day [Morris et al 2017].

Betaine may be added to the treatment regimen in individuals poorly compliant with dietary treatment or may become the major treatment modality in those intolerant of the diet. Individuals who are pyridoxine non-responsive who were unable to attain metabolic control with diet substantially reduced their plasma homocysteine concentrations when betaine was supplemented [Singh et al 2004].

Side effects of betaine are few. (1) Some affected individuals develop a detectable body odor, resulting in reduced compliance. (2) The increase in methionine produced by betaine is usually harmless; however, cerebral edema has occurred when hypermethioninemia is extreme (>1000 µmol/L) [Yaghmai et al 2002, Devlin et al 2004, Tada et al 2004, Braverman et al 2005]. Eliminating betaine resulted in rapid reduction of the hypermethioninemia and resolution of the cerebral edema.

Note: In a murine model for homocystinuria the effect of betaine treatment diminished significantly over time [Maclean et al 2012].

Surveillance

Affected individuals should be monitored at regular intervals to detect any clinical complications that may develop, to assess dietary compliance, and to measure plasma total homocysteine and methionine concentrations. Infants should be monitored monthly for the first six months of life and bimonthly until age one year, then every three months until age three years. Semiannual monitoring through the remainder of childhood and annual monitoring in adolescence and adulthood are indicated. Complications should be promptly addressed with appropriate therapy.

Plasma total homocysteine and methionine concentrations should be monitored in all persons receiving betaine (see Prevention of Primary Manifestations, **Betaine treatment**).

Vitamin B_{12} and folate levels should be monitored.

Regular ophthalmology assessments can identify eye complications such as progressive myopia and ectopia lentis and allow for early treatment and prevention of further complications such as retinal detachment.

DXA scans should be performed every three to five years following adolescence to monitor for osteoporosis [Morris et al 2017].

Agents/Circumstances to Avoid

Oral contraceptives, which may tend to increase coagulability and represent risk for thromboembolism, should be avoided in females with homocystinuria.

Surgery should also be avoided if possible because the increase in plasma homocysteine concentrations during surgery and especially post-surgery elevates the risk for a thromboembolic event. If surgery is required, intravenous fluids containing 5% dextrose in 0.5 N saline at 1.5 times maintenance should be administered before, during, and after surgery until fluids can be taken orally. If fluids at 1.5 times maintenance represent a cardiovascular risk as a result of fluid overload, basic fluid maintenance may be administered with careful clinical observation.

Evaluation of Relatives at Risk

Plasma concentrations of total homocysteine and amino acids should be measured in at-risk sibs as soon as possible after birth so that morbidity and mortality can be reduced by early diagnosis and treatment.

If the *CBS* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of sibs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Because women with homocystinuria may be at greater than average risk for thromboembolism, especially post partum, prophylactic anticoagulation during the third trimester of pregnancy and post partum is recommended. The usual regimen is injection of low molecular-weight heparin during the last two weeks of pregnancy and the first six weeks post partum [Pierre et al 2006]. Aspirin in low doses has also been given throughout pregnancy.

Maternal homocystinuria, unlike maternal phenylketonuria (see Phenylalanine Hydroxylase Deficiency), does not appear to have major teratogenic potential requiring additional counseling or, with respect to the fetus, more stringent management [Levy et al 2002, Vilaseca et al 2004]. Nevertheless, treatment with pyridoxine or methionine-restricted diet or both should be continued during pregnancy [Morris et al 2017]. Betaine may also be continued and appears not to be teratogenic [Yap et al 2001b, Levy et al 2002, Vilaseca et al 2004, Pierre et al 2006].

Therapies Under Investigation

CBS enzyme replacement therapy is currently in development in the preclinical phase [Bublil et al 2016].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Homocystinuria caused by cystathionine β-synthase deficiency (classic homocystinuria) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The unaffected parents of an affected individual are obligate heterozygotes (i.e., carriers of at least one *CBS* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing homocystinuria.
- Because it is possible (though unlikely) that a parent has classic homocystinuria but has remained asymptomatic, it is appropriate to obtain a detailed medical history and perform an examination as well as plasma homocysteine and amino acid analysis in both parents. This becomes even more imperative if the mother is considering future pregnancies, as affected women are at increased risk for thromboembolic events during pregnancy.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing homocystinuria.

Offspring of a proband. Because classic homocystinuria is treatable, affected individuals who have the benefit of effective treatment may be physically and intellectually normal and can reproduce.

- The offspring of an individual with classic homocystinuria have at least one *CBS* pathogenic variant.
- The offspring of a proband whose partner is a carrier have a 50% chance of being affected and a 50% chance of being carriers.
- All offspring of a proband whose partner also has classic homocystinuria will have classic homocystinuria.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CBS* pathogenic variant.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk family members requires prior identification of both *CBS* pathogenic variants in the family.

Biochemical genetic testing. A single biochemical test cannot distinguish heterozygotes for CBS deficiency from controls.

- Heterozygotes for CBS deficiency have normal fasting plasma total homocysteine concentration.
- Plasma total homocysteine concentration response after methionine loading (100 mg methionine/kg [671 µmol/kg]) is abnormal in 73% of heterozygotes with pyridoxine non-responsive homocystinuria and 33% of heterozygotes with pyridoxine-responsive homocystinuria [Guttormsen et al 2001].

  Note: Caution should be exercised in performing a methionine loading test because adverse reactions have been reported [Cottington et al 2002, Krupková-Meixnerová et al 2002].

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *CBS* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

If the *CBS* pathogenic variants are unknown, measurement of CBS enzyme activity assayed in cultured amniocytes is theoretically possible. However, identifying a laboratory to perform this testing may be challenging; currently no such testing is available in the US.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  HCU
- **Homocystinuria: Genetic Fact Sheet for Parents**
  Screening, Technology and Research in Genetics (STAR-G)
  newbornscreening.info/cbs-homocystinemia-cystathionine-beta-synthase-deficiency
- **MedlinePlus**
  Homocystinuria
- **National Organization for Rare Disorders (NORD)**
  Homocystinuria Due to Cystathionine Beta-Synthase Deficiency
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173

metabolicsupportuk.org

- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CBS	21q22.3	Cystathionine beta-synthase	CBS database	CBS	CBS

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency (View All in OMIM)

236200	HOMOCYSTINURIA DUE TO CYSTATHIONINE BETA-SYNTHASE DEFICIENCY
613381	CYSTATHIONINE BETA-SYNTHASE; CBS

Gene structure. *CBS* has 23 exons, is 25-30 kb in length, and, depending on the tissue, is expressed as alternatively spliced mRNA isoforms with size varying from 2.5 to 3.7 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Of the 164 pathogenic variants currently identified, 67% in individuals with CBS deficiency are missense variants, the vast majority of which are private. Among the other pathogenic variants, only five are nonsense variants and the remainder are various deletions, insertions, and splicing variants (see *CBS* Mutation Database for a database of current pathogenic variants) [Urreizti et al 2003, Linnebank et al 2004, Miles & Kraus 2004, Moat et al 2004].

The two most common *CBS* pathogenic variants, p.Ile278Thr and p.Gly307Ser, are found in exon 8.

- p.Ile278Thr is pan ethnic; overall, it accounts for nearly 25% of all pathogenic variants, including 29% of the variant alleles in the UK and 18% in the US [Moat et al 2004]. In some countries (e.g., Denmark) it may account for the majority of pathogenic variants [Skovby et al 2010].
- p.Gly307Ser is the leading cause of homocystinuria in Ireland (71% of pathogenic variants). It has also been detected frequently in US and Australian affected individuals of "Celtic" origin, including families of Irish, Scottish, English, French, and Portuguese ancestry. It accounts for 21% of pathogenic variants in the UK and 8% in the US [Moat et al 2004].
- p.Arg336Cys is present in 93% of affected individuals in the Qatari population [Gan-Schreier et al 2010].

Table 4. *CBS* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.833T>C	p.Ile278Thr	NM_000071.2 NP_000062.1
c.919G>A	p.Gly307Ser	
c.1006C>T	p.Arg336Cys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The primary gene splice form encodes a subunit of 63 kd. The active form of the enzyme is a homotetramer that contains one heme and one pyridoxal 5'-phosphate per each subunit [Kraus et al 1999, Miles & Kraus 2004].

Abnormal gene product. Most pathogenic variants affect the active core of cystathionine β-synthase. Pathogenic variants may also impair the binding of adenosine derivatives (e.g., AMP, ATP, S-adenosylmethionine), thus interfering with cellular energy [Scott et al 2004].

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Chapter Notes

Author Notes

Authors' website: New England Consortium of Metabolic Programs

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