Disease Name	**Homocystinuria**
Alternate name(s)	Cystathionine beta-synthase deficiency
Acronym	HCY
Disease Classification	Amino Acid Disorder
Variants	Yes
Variant name	Pyridoxine-responsive type (the majority of cases are unresponsive to pyridoxine)
Symptom onset	Childhood
Symptoms	Ectopia lentis, vascular occlusive disease, seizures, malar flush, osteoporosis, possible decreased pigmentation of hair, skin and iris, skeletal abnormalities including genu valgum, pectus excavatum, pes cavus and marfanoid habitus. Some patients have failure to thrive and short stature. Mental delays is possible.
Natural history without treatment	Mental delays is common but not invariable. Vascular disease, stroke and psychiatric abnormalities.
Natural history with treatment	Decrease of thromboembolic accidents which may decrease incidence of sequelae including mental delays, ectopia lentis, seizures and psychiatric abnormalities. Normal IQ is possible and typical of the pyridoxine-responsive variant.
Treatment	Pyridoxine supplementation, dietary restriction of methionine with supplementation of L-cysteine, betaine supplementation. Consider folate and vitamin B12 supplementation.
Physical phenotype	Ectopia lentis, decreased pigmentation, malar flush, osteoporosis, skeletal abnormalities and marfanoid habitus
Inheritance	Autosomal recessive
General population incidence	1:200,000 – 300,000
Ethnic differences	Yes
Population	Irish, U.S New England
Ethnic incidence	1:50,000
Enzyme location	Lymphocytes, fibroblasts and liver
Enzyme Function	Degradation of homocysteine
Missing Enzyme	Cystathionine beta-synthase
Metabolite changes	Increased methionine in blood, increased homocystine in urine, increased total homocysteine in blood.
Prenatal testing	Enzyme assay in cultured amniocytes (CVS not possible)
OMIM Link	http://www.ncbi.nlm.nih.gov/omim/236200
Genetests Link	www.genetests.org
Support Group	National Coalition for PKU and Allied Disorders http://www.pku-allieddisorders.org/ Children Living with Inherited Metabolic Diseases http://www.climb.org.uk/

Newborn Screening ACT Sheet
[Increased Methionine]
Homocystinuria (CBS Deficiency)

Differential Diagnosis: Classical homocystinuria (cystathionine ß-synthase (CBS) deficiency); hypermethioninemia due to methionine adenosyltransferase I/III (MAT I/III) deficiency; glycine n-methyltransferase (GNMT) deficiency; adenosylhomocysteine hydrolase deficiency; liver disease; hyperalimentation.

Condition Description: Methionine from ingested protein is normally converted to homocysteine. In classical homocystinuria due to CBS deficiency, homocysteine cannot be converted to cystathionine. As a result, the concentration of homocysteine and its precursor, methionine, will become elevated. In MAT I/III deficiency and the other hypermethioninemias, methionine is increased in the absence of or only with a slightly increased level of homocysteine.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact family to inform them of the newborn screening result and ascertain clinical status.
- Consult with pediatric metabolic specialist.
- Evaluate the newborn with attention to liver disease and refer as appropriate.
- Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- Educate family about homocystinuria and its management, as appropriate.
- Report findings to newborn screening program.

Diagnostic Evaluation: Quantitative plasma amino acids will show increased homocystine and methionine in classical homocystinuria but only increased methionine in the other disorders. Plasma homocysteine analysis will show markedly increased homocysteine in classical homocystinuria and normal or only slightly increased homocysteine in the other disorders. Urine homocysteine is markedly increased in classical homocystinuria.

Clinical Considerations: Homocystinuria is usually asymptomatic in the neonate. If untreated, these children eventually develop mental retardation, ectopia lentis, a marfanoid appearance including arachnodactyly, osteoporosis, other skeletal deformities and thromboembolism. MAT I/III deficiency may be benign. Adenosylhomocysteine hydrolase deficiency has been associated with developmental delay and hypotonia, and both this disorder and GNMT deficiency can cause liver abnormalities.

Additional Information:

Gene Reviews
Genetics Home Reference

Referral (local, state, regional and national):

Testing
Clinical Services