# *CBS* Gene Analysis in Homocystinuria due to Cystathionine ß-Synthase Deficiency

**Clinical Features:**
Homocystinuria due to cystathionine ß-synthase (CBS) deficiency is the most common inborn error of methionine metabolism, characterized by involvement of the eye (ectopia lentis and/or severe myopia), skeletal system (marfanoid habitus, osteoporosis, scoliosis, pectus excavatum, genu valgum), vascular system (premature atherosclerosis and thromboembolism), and central nervous system (developmental delay/intellectual disability, seizures, psychiatric problems). Any or all of these systems may be involved. There is variable expressivity even among patients within the same family. Ectopia lentis may be the only presenting feature in some patients, other individuals can present with a thromboembolic event as an adult. About half of all CBS deficient patients respond to pharmacologic doses of pyridoxine (vitamin $B_6$). Pyridoxine-responsiveness is constant within sibships.[1] It has been estimated that newborn screening for elevated methionine levels detects only about one-third of patients.[2]

**Genetics:**
Homocystinuria due to CBS deficiency is caused by variants in the *CBS* gene that encodes cystathionine ß-synthase, which catalyzes the condensation of homocysteine with serine, forming cystathionine and ultimately cysteine. Deficiency of the CBS enzyme results in elevated levels of total homocysteine and methionine and decreased levels of cystathionine and cysteine. The enzyme activity is very low in chorionic villi, not allowing for prenatal diagnosis in this tissue. Heterozygote enzyme activity overlaps with controls. The *CBS* gene is located on chromosome 21q22.3 and has 17 exons of which exons 3-17 are coding exons (in the literature the coding exons are frequently numbered 1-14 and 16[1]). Estimates of the prevalence of CBS deficiency have ranged from 1 in 20,500 in Denmark to 1 in 800,000 in Japan.[2] Molecular genetic screening of newborns in Norway has estimated an incidence of approximately 1 in 6,400.[3]

**Inheritance Pattern:**
Autosomal Recessive

**Test Methods:**
Variant analysis of the *CBS* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons 3-17, and the corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *CBS* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene.

Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

**Test Sensitivity:**
Variant analysis is expected to identify a sequence variant in greater than 95% of patients with homocystinuria due to deficiency of the CBS enzyme.[2,4,5] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

**Variant Spectrum:**
Variants are dispersed throughout the coding exons of the *CBS* gene with most individuals identified as compound heterozygotes for private variants. The vast majority of the over 130 described variants are missense variants; however, nonsense, splicing, small deletions/insertions and a large deletion have also been reported. Certain variants are common in specific ethnic groups. Most notably, the I278T (c.833 T>C) variant has been identified in nearly 25% of all *CBS* alleles from patients of varied ethnic backgrounds and the G307S (c.919 G>A) variant that is found on approximately 70% of alleles in patients of Celtic origin.[4] Approximately 25% of point variants occur in exon 3. The I278T variant has been associated with $B_6$ responsiveness and a relatively mild clinical phenotype when homozygous; whereas, G307S is associated with a more severe non-B6 responsive phenotype.[4]

**References:**

1. Kraus et al., (1999) Hum Mutat 13:362-375 (PMID: 10338090).
2. Kruger et al., (2003) Hum Mutat 22:434-441 (PMID: 14635102).
3. Refsum et al., (2004) J Pediatr 144 :830-832 (PMID: 15192637).
4. Urreizti et al., (2006) J Hum Genet 51:305-313 (PMID: 16479318).
5. Linnebank et al., (2004) Hum Mutat 24:352-353 (PMID: 15365998).