

GCH1 Gene

Subjects: Genetics & Heredity

Contributor: Vivi Li

GTP cyclohydrolase 1: The GCH1 gene provides instructions for making an enzyme called GTP cyclohydrolase 1.

Keywords: genes

1. Normal Function

This enzyme is involved in the first of three steps in the production of a molecule called tetrahydrobiopterin (BH4). Other enzymes help carry out the second and third steps in this process.

Tetrahydrobiopterin plays a critical role in processing several protein building blocks (amino acids) in the body. For example, it works with the enzyme phenylalanine hydroxylase to convert an amino acid called phenylalanine into another amino acid, tyrosine. Tetrahydrobiopterin is also involved in reactions that produce chemicals called neurotransmitters, which transmit signals between nerve cells in the brain. Specifically, tetrahydrobiopterin is involved in the production of two neurotransmitters called dopamine and serotonin. Among their many functions, dopamine transmits signals within the brain to produce smooth physical movements, and serotonin regulates mood, emotion, sleep, and appetite. Because it helps enzymes carry out chemical reactions, tetrahydrobiopterin is known as a cofactor.

2. Health Conditions Related to Genetic Changes

2.1 Dopa-Responsive Dystonia

More than 140 mutations in the *GCH1* gene have been found to cause dopa-responsive dystonia. This condition is characterized by a pattern of involuntary muscle contractions (dystonia), tremors, and other uncontrolled movements and usually responds to treatment with a medication called L-Dopa. Dopa-responsive dystonia results when one copy of the *GCH1* gene is mutated in each cell. Most *GCH1* gene mutations that cause this condition change single amino acids in the GTP cyclohydrolase 1 enzyme. Researchers believe that the abnormal enzyme may interfere with the activity of the normal version of GTP cyclohydrolase 1 that is produced from the copy of the gene with no mutation. As a result, the amount of working enzyme in affected individuals is reduced by 80 percent or more. A reduction in functional GTP cyclohydrolase 1 enzyme causes less dopamine and serotonin to be produced, leading to the movement problems and other characteristic features of dopa-responsive dystonia.

2.2 Tetrahydrobiopterin Deficiency

At least seven mutations in the *GCH1* gene have been found to cause tetrahydrobiopterin deficiency. When this condition is caused by *GCH1* gene mutations, it is known as GTP cyclohydrolase 1 (GTPCH1) deficiency. GTPCH1 deficiency accounts for about 4 percent of all cases of tetrahydrobiopterin deficiency.

GTPCH1 deficiency results when two copies of the *GCH1* gene are mutated in each cell. Most of the mutations responsible for this condition change single amino acids in GTP cyclohydrolase 1. These mutations greatly reduce or eliminate the activity of this enzyme. Without enough GTP cyclohydrolase 1, little or no tetrahydrobiopterin is produced. As a result, this cofactor is not available to participate in chemical reactions such as the conversion of phenylalanine to tyrosine. If phenylalanine is not converted to tyrosine, it can build up to toxic levels in the blood and other tissues. Nerve cells in the brain are particularly sensitive to phenylalanine levels, which is why excessive amounts of this substance can cause brain damage.

Additionally, a reduction in GTP cyclohydrolase 1 activity disrupts the production of certain neurotransmitters in the brain. Because neurotransmitters are necessary for normal brain function, changes in the levels of these chemicals contribute to intellectual disability in people with GTPCH1 deficiency.

Tetrahydrobiopterin deficiency is more severe than dopa-responsive dystonia likely because both copies of the *GCH1* gene are mutated, which leads to a more severe enzyme shortage than in dopa-responsive dystonia, in which only one copy of the gene has a mutation.

3. Other Names for This Gene

- DYT5
- DYT5a
- GCH
- GCH1_HUMAN
- GTP cyclohydrolase 1 (dopa-responsive dystonia)
- GTPCH1

References

1. Blau N, Bonafé L, Thöny B. Tetrahydrobiopterin deficiencies without hyperphenylalaninemia: diagnosis and genetics of dopa-responsive dystonia and sepiapterin reductase deficiency. *Mol Genet Metab*. 2001 Sep-Oct;74(1-2):172-85. Review.
2. Clot F, Grabli D, Cazeneuve C, Roze E, Castelnau P, Chabrol B, Landrieu P, Nguyen K, Ponsot G, Abada M, Doummar D, Damier P, Gil R, Thobois S, Ward AJ, Hutchinson M, Toutain A, Picard F, Camuzat A, Fedirko E, Sân C, Bouteiller D, LeGuern E, Durr A, Vidailhet M, Brice A; French Dystonia Network. Exhaustive analysis of BH4 and dopamine biosynthesis genes in patients with Dopa-responsive dystonia. *Brain*. 2009 Jul;132(Pt 7):1753-63. doi: 10.1093/brain/awp084.
3. Garavaglia B, Invernizzi F, Carbone ML, Viscardi V, Saracino F, Ghezzi D, Zeviani M, Zorzi G, Nardocci N. GTP-cyclohydrolase I gene mutations in patients with autosomal dominant and recessive GTP-CH1 deficiency: identification and functional characterization of four novel mutations. *J Inher Metab Dis*. 2004;27(4):455-63.
4. Longo N. Disorders of biopterin metabolism. *J Inher Metab Dis*. 2009 Jun;32(3):333-42. doi: 10.1007/s10545-009-1067-2. Erratum in: *J Inher Metab Dis*. 2009 Jun;32(3):457.
5. Müller U, Steinberger D, Topka H. Mutations of GCH1 in Dopa-responsive dystonia. *J Neural Transm (Vienna)*. 2002 Mar;109(3):321-8. Review.
6. Ohta E, Funayama M, Ichinose H, Toyoshima I, Urano F, Matsuo M, Tomoko N, Yukihiro K, Yoshino S, Yokoyama H, Shimazu H, Maeda K, Hasegawa K, Obata F. Novel mutations in the guanosine triphosphate cyclohydrolase 1 gene associated with DYT5 dystonia. *Arch Neurol*. 2006 Nov;63(11):1605-10.
7. Segawa M. Autosomal dominant GTP cyclohydrolase I (AD GCH 1) deficiency (Segawa disease, dystonia 5; DYT 5). *Chang Gung Med J*. 2009 Jan-Feb;32(1):1-11. Review.
8. Shintaku H. Disorders of tetrahydrobiopterin metabolism and their treatment. *Curr Drug Metab*. 2002 Apr;3(2):123-31. Review.
9. Thöny B, Auerbach G, Blau N. Tetrahydrobiopterin biosynthesis, regeneration and functions. *Biochem J*. 2000 Apr 1;347 Pt 1:1-16. Review.
10. Trender-Gerhard I, Sweeney MG, Schwingenschuh P, Mir P, Edwards MJ, Gerhard A, Polke JM, Hanna MG, Davis MB, Wood NW, Bhatia KP. Autosomal-dominant GTPCH1-deficient DRD: clinical characteristics and long-term outcome of 34 patients. *J Neurol Neurosurg Psychiatry*. 2009 Aug;80(8):839-45. doi:10.1136/jnnp.2008.155861.