



## GCH1 gene

GTP cyclohydrolase 1

### Normal Function

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

### Health Conditions Related to Genetic Changes

#### 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.

#### 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.

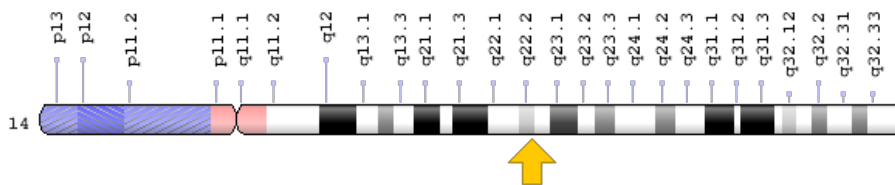
Additionally, a reduction in GTP cyclohydrolase 1 activity disrupts the production of certain neurotransmitters in the brain. Because neurotransmitters are necessary for normal brain function, changes in the levels of these chemicals contribute to intellectual disability in people with GTPCH1 deficiency.

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.

### Chromosomal Location

Cytogenetic Location: 14q22.2, which is the long (q) arm of chromosome 14 at position 22.2

Molecular Location: base pairs 54,842,005 to 54,902,826 on chromosome 14 (Homo sapiens Updated Annotation Release 109.20200522, GRCh38.p13) (NCBI)



Credit: Genome Decoration Page/NCBI

### Other Names for This Gene

- DYT5
- DYT5a
- GCH
- GCH1\_HUMAN

- GTP cyclohydrolase 1 (dopa-responsive dystonia)
- GTPCH1

## **Additional Information & Resources**

### Educational Resources

- Neuroscience (second edition, 2001): The Biogenic Amines  
<https://www.ncbi.nlm.nih.gov/books/NBK11035/>

### Clinical Information from GeneReviews

- GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia  
<https://www.ncbi.nlm.nih.gov/books/NBK1508>

### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28GCH1%5BTIAB%5D%29+OR+%28GTP+cyclohydrolase+1%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5BIa%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

### Catalog of Genes and Diseases from OMIM

- GTP CYCLOHYDROLASE I  
<http://omim.org/entry/600225>

### Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology  
[http://atlasgeneticsoncology.org/Genes/GC\\_GCH1.html](http://atlasgeneticsoncology.org/Genes/GC_GCH1.html)
- ClinVar  
<https://www.ncbi.nlm.nih.gov/clinvar?term=GCH1%5Bgene%5D>
- HGNC Gene Symbol Report  
[https://www.genenames.org/data/gene-symbol-report/#!/hgnc\\_id/HGNC:4193](https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:4193)
- Monarch Initiative  
<https://monarchinitiative.org/gene/NCBIGene:2643>
- NCBI Gene  
<https://www.ncbi.nlm.nih.gov/gene/2643>
- UniProt  
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