



Electronic Resources Reviews

Navigating the National Center for Biotechnology Information's Databases on the Medicinal Chemistry of Homocystinuria

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Introduction

The National Center for Biotechnology Information's (NCBI) databases are authoritative, current information sources intended for researchers, faculty, graduate students, information professionals, and the public for finding the genetic, protein, and structural molecular biological data ([NCBI Resource Coordinators 2016](#)). NCBI Gene, Nucleotide, Protein, and Structure databases are considered the four core linked, annotated genetic and protein sequence information sources curated by NCBI scientists based on the scientists' raw data deposited into GenBank, which became publicly available in 1982 ([Choudhuri 2014](#)). MedGen is an authoritative information portal for inherited human diseases and was launched in 2012 by NCBI ([Louden 2020](#)). MedGen uses standardized terminology from "NLM's Unified Medical Language system (UMLS®), the NIH Genetic Testing Registry (GTR®), and ClinVar" ([Halavi et al. 2018](#)). OMIM (Online Mendelian Inheritance in Man) is a curated database for finding the genotype and phenotype of inherited human diseases, which was created in 1985 through collaboration between the National Library of Medicine and the William H. Welch Medical Library of Johns Hopkins University and developed by NCBI in 1995 ([About OMIM 2021](#)). PubChem, launched in 2004 by NCBI, is a linked data repository of standardized chemical compounds and substances with provenance of chemical structures ([Hähnke et al. 2018](#)). The Bioassay section of PubChem has been a legacy tool since November 1, 2018 ([About PubChem 2021](#)). In this article, the reader will understand how to find an allele associated with the phenotype of an inherited human disease, the biomolecular pathway causing the physical manifestation of this disease, and finally, the treatment in the management of the condition.

NCBI Database Search Strategy of the Biochemical Pathway and Medicinal Chemistry of Homocystinuria

Classic homocystinuria
MedGen UID: 199606 • Concept ID: C0751202 • Disease or Syndrome

Synonyms: CBS deficiency; Cystathionine beta-synthase deficiency; Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency; Homocystinuria due to CBS deficiency; Homocystinuria due to cystathionine beta-synthase deficiency; HOMOCYSTINURIA WITH OR WITHOUT RESPONSE TO PYRIDOXINE

SNOMED CT: Deficiency of serine sulphydrase (24308003); Deficiency of methylcysteine synthase (24308003); Deficiency of beta-thionase (24308003); Cystathionine beta-synthase deficiency (24308003); CBS deficiency (24308003)

Modes of inheritance: Autosomal recessive inheritance (HPO, OMIM)

Gene (location): CBS (21q22.3)

Monarch Initiative: MONDO:0009352
OMIM®: 236200
Orphanet: ORPHA394

Definition
Classical homocystinuria due to cystathionine beta-synthase (Cbs) deficiency is characterized by the multiple involvement of the eye, skeleton, central nervous system, and vascular system. [from ORDO]

Figure 1. Entry for Homocystinuria in the NCBI MedGen database.

Start by searching for Homocystinura in the NCBI MedGen database, and follow the link to the OMIM database by clicking on 236200 <https://www.ncbi.nlm.nih.gov/medgen/199606> (Figure 1).

#236200
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HOMOCYSTINURIA DUE TO CYSTATHIONINE BETA-SYNTASE DEFICIENCY

Alternative titles/symbols
HOMOCYSTINURIA WITH OR WITHOUT RESPONSE TO PYRIDOXINE
CYSTATHIONINE BETA-SYNTASE DEFICIENCY
CBS DEFICIENCY

Other entities represented in this entry:
HYPERHOMOCYSTEINEMIA, THROMBOTIC, CBS-RELATED, INCLUDED

Phenotype-Genotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
21q22.3	Homocystinuria, B6-responsive and nonresponsive types	236200	AR	3	CBS	613381
21q22.3	Thrombosis, hyperhomocysteinemic	236200	AR	3	CBS	613381

External Links
Protein
Clinical Resources
Clinical Trials
EuroGentest
Gene Reviews
Genetic Alliance
GTR
Newborn Screening
GARD
Orphanet
POSSUM
Variation
Animal Models
Cell Lines

Figure 2. OMIM phenotype of Homocystinuria.

From OMIM #236200 Homocystinuria <https://omim.org/entry/236200> (Figure 2), follow the link to the Gene/Locus MIM #613381.

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* 613381
CYSTATHIONINE BETA-SYNTHASE; CBS

HGNC Approved Gene Symbol: *CBS*

Cytogenetic location: *21q22.3* Genomic coordinates (GRCh38): *21:43,053,189-43,076,872 (from NCBI)*

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
21q22.3	Homocystinuria, B6-responsive and nonresponsive types	236200	AR	3
	Thrombosis, hyperhomocysteinemic	236200	AR	3

PheneGene Graphics

TEXT

Description

The CBS gene encodes cystathionine beta-synthase (EC 4.2.1.22), which catalyzes the first irreversible step of transsulfuration. The enzyme conjugates homocysteine and serine to form cystathionine, which is subsequently converted into cysteine and alpha-ketobutyrate. Homocysteine can also undergo remethylation to form methionine. The CBS enzyme is a homotetramer of 63-kD subunits and requires pyridoxal phosphate and heme for activity. It can also be stimulated by the addition of S-adenosylmethionine (AdoMet) (Kraus et al., 1993; Shan et al., 2001).

External Links

- Genome
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- Protein
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- Variation
 - 1000 Genome
 - ClinVar
 - gnomAD
 - GWAS Catalog
 - GWAS Central
 - HCMD
 - HCVS
 - NHLBI EVS
 - PharmGKB
- Animal Models
- Cellular Pathways

Figure 3. Cystathionine Beta-Synthase (CBS) gene.

The Cystathionine Beta-Synthase (CBS) gene <https://omim.org/entry/613381> (Figure 3) encodes for a key enzyme in metabolism, and its deficiency causes Homocystinuria.

From OMIM database (<https://omim.org/entry/613381>) follow the link to see Allelic Variants. This takes you to: <https://omim.org/entry/613381#allelicVariants>

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External Links

- Genome
- DNA
- Protein
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 - BioGPS
 - Ensembl
 - GeneCards
 - Gene Ontology
 - KEGG
 - MARRVEL
 - Monarch
 - NCBI Gene**
 - UCSC
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Figure 4. OMIM #613381 Cystathionine Beta-Synthase gene.

From the OMIM entry for the Cystathionine Beta-Synthase gene <https://omim.org/entry/613381> (Figure 4), follow the link to the NCBI Gene database to get the canonical protein.

NCBI Resources How To Sign in to NCBI

Gene Gene Search Advanced Help

Full Report Send to: Hide sidebar >>

Links from Protein
Showing Current items.

CBS cystathionine beta-synthase [*Homo sapiens* (human)]
Gene ID: 875, updated on 5-Apr-2021

[Download Datasets](#)

Summary **Genomic context** **Genomic regions, transcripts, and products** **Expression** **Bibliography** **Phenotypes** **Variation** **Pathways from PubChem** **Interactions** **General gene information** **General protein information**

Preferred Names
cystathionine beta-synthase

Names
Cystathionine beta-synthase-like protein
beta-thionase
methylcysteine synthase
serine sulphydrase

NP_000062.1
EC 4.2.1.22
NP_001171479.1

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Genome Browsers
Genome Data Viewer
Variation Viewer (GRCh37.p13)
Variation Viewer (GRCh38)
1000 Genomes Browser (GRCh37.p13)
Ensembl
UCSC

Related information
Order cDNA clone
3D structures
BioAssay by Target (List)

Figure 5. Entry for human cystathionine beta-synthase gene in the NCBI Gene database.

From the NCBI Gene record of the human cystathionine beta-synthase gene <https://www.ncbi.nlm.nih.gov/gene/875> (Figure 5), look up the canonical protein (NP_000062.1) associated with Homocystinuria in the NCBI Protein database https://www.ncbi.nlm.nih.gov/protein/NP_000062.1.

NCBI Resources How To Sign in to NCBI

Protein Protein Search Advanced Help

GenPept Send to: Change region shown Customize view

cystathionine beta-synthase-like protein isoform 1 [Homo sapiens]
NCBI Reference Sequence: NP_000062.1
[Identical Proteins](#) [FASTA](#) [Graphics](#)

Go to:

LOCUS	NP_000062	551 aa	linear	PRI 04-APR-2021
DEFINITION	cystathionine beta-synthase isoform 1 [Homo sapiens].			
ACCESSION	NP_000062			
VERSION	NP_000062.1			
DBSOURCE	REFSEQ; accession NM_000071.3			
KEYWORDS	RefSeq; NMR Select.			
SOURCE	Homo sapiens (human)			
ORGANISM	Homo sapiens			
REFERENCE	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorhini; Catarrhini; Hominoidea; Homo.			
AUTHORS	Harris C, Atlas N, Taylor AK, Mazza A, Schaefer MH, Russ J, Riechers SP, Jain S, Coughlin M, Fontaine JF, Freibaum BD, Brusendorf L, Zenkner M, Porras P, Stroedicke M, Schnoegl S, Arnsburg K, Boeddrich A, Figazzini L, Heutink P, Taylor JP, Kirstein J, Andrade-Navarro AM, Sharan S and Wanker EE.			
TITLE	Interactome Mapping Provides a Network of Neurodegenerative Disease Proteins and Uncovers Widespread Protein Aggregation in Affected			
JOURNAL	Brain			
PUBMED	22814553			
REFERENCE	Cell Rep 32 (7), 108050 (2020)			

Protein 3D Structure
Human Cystathionine Beta-synthase (db) Pp49l Delta409-551 PDB: 5MMS Source: Homo sapiens Method: X-Ray
Diffraction Resolution: 2.8 Å
[See all 6 structures.](#)

Figure 6. Entry for the canonical protein associated with Homocystinuria in the NCBI Protein database.

You can link to 8 protein 3-D structures of cystathionine beta-synthase-like protein isoform 1 from NCBI Protein database by following the link to “See all 8 structures...”
https://www.ncbi.nlm.nih.gov/protein/NP_000062.1 (Figure 6).

NCBI Resources How To

Structure Structure Advanced

Summary 20 per page Sort by Default order Send to

Links from Protein
Items: 8

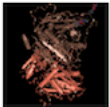
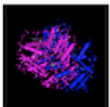

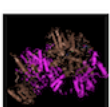

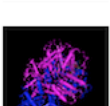
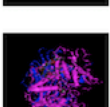
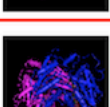
- ☐  [Human Cystathionine Beta-synthase \(cbs\) P.p49l Delta409-551 Variant\[Lyase, EC: 4.2.1.22\]](#)
Taxonomy: Homo sapiens
Proteins: 2 Chemicals: 6 modified: 2017-08-18
MMDB ID: 150447 PDB ID: 5MMS
[View in iCn3D](#) [Similar Structures](#) [PubMed](#) [Proteins](#) [Conserved Domains](#) [PubChem Compound](#)
- ☐  [Crystal Structure Of Human Cystathionine Beta-synthase \(delta516-525\) At 2.0 Angstrom Resolution\[Lyase, EC: 4.2.1.22\]](#)
Taxonomy: Homo sapiens
Proteins: 2 Chemicals: 19 modified: 2015-01-15
MMDB ID: 117969 PDB ID: 4COO
[View in iCn3D](#) [Similar Structures](#) [PubMed](#) [Proteins](#) [Conserved Domains](#) [PubChem Compound](#)
- ☐  [Crystal Structure Of Delta516-525 Human Cystathionine Beta-synthase\[Lyase, EC: 4.2.1.22\]](#)
Taxonomy: Homo sapiens
Proteins: 2 Chemicals: 4 modified: 2013-10-21
MMDB ID: 113600 PDB ID: 4L3V
[View in iCn3D](#) [Similar Structures](#) [PubMed](#) [Proteins](#) [Conserved Domains](#) [PubChem Compound](#)
- ☐  [Crystal Structure Of Delta516-525 Human Cystathionine Beta-synthase D444n Mutant Containing C-terminal 6xhis Tag\[Lyase, EC: 4.2.1.22\]](#)
Taxonomy: Homo sapiens
Proteins: 2 Chemicals: 4 modified: 2013-10-21
MMDB ID: 113599 PDB ID: 4L28
[View in iCn3D](#) [Similar Structures](#) [PubMed](#) [Proteins](#) [Conserved Domains](#) [PubChem Compound](#)
- ☐  [Crystal Structure Of Delta1-39 And Delta516-525 Human Cystathionine Beta-synthase D444n Mutant Containing C-terminal 6xhis Tag\[Lyase, EC: 4.2.1.22\]](#)
Taxonomy: Homo sapiens
Proteins: 2 Chemicals: 4 modified: 2013-10-21
MMDB ID: 113598 PDB ID: 4L27
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- ☐  [Crystal Structure Of Delta516-525 Human Cystathionine Beta-synthase Containing C-terminal 6xhis-tag\[Lyase, EC: 4.2.1.22\]](#)
Taxonomy: Homo sapiens
Proteins: 2 Chemicals: 4 modified: 2013-10-21
MMDB ID: 113597 PDB ID: 4LOD
[View in iCn3D](#) [Similar Structures](#) [PubMed](#) [Proteins](#) [Conserved Domains](#) [PubChem Compound](#)
- ☐  [Cystathionine-Beta Synthase: Reduced Vicinal Thiols\[Lyase, EC: 4.2.1.22\]](#)
Taxonomy: Homo sapiens
Proteins: 2 Chemicals: 5 modified: 2012-10-19
MMDB ID: 20506 PDB ID: 1M54
[View in iCn3D](#) [Similar Structures](#) [PubMed](#) [Proteins](#) [Conserved Domains](#) [PubChem Compound](#)
- ☐  [Structure Of Human Cystathionine Beta-Synthase: A Unique Pyridoxal 5'- Phosphate Dependent Hemeprotein\[Lyase, EC: 4.2.1.22\]](#)
Taxonomy: Homo sapiens
Proteins: 2 Chemicals: 4 modified: 2012-11-01
MMDB ID: 16774 PDB ID: 1JBQ
[View in iCn3D](#) [Similar Structures](#) [PubMed](#) [Proteins](#) [Conserved Domains](#) [PubChem Compound](#)

Figure 7. 3-D structures of cystathionine beta-synthase-like protein isoform 1 in the NCBI Structure database.

In NCBI Structure database, protein structure #8
https://www.ncbi.nlm.nih.gov/structure?Db=structure&DbFrom=protein&Cmd=Link&LinkName=protein_structure&LinkReadableName=Structure&IdsFromResult=4557415 (Figure 7) seems to be the wild type protein structure of human Cystathionine Beta-Synthase.

1JBQ: Structure Of Human Cystathionine Beta-Synthase: A Unique Pyridoxal 5'-Phosphate Dependent Hemeprotein

Citation: ?

Structure of human cystathionine beta-synthase: a unique pyridoxal 5'-phosphate-dependent heme protein

Meier M, Janosik M, Kery V, Kraus JP, Burkhard P

EMBO J (2001) 20 p.3910-6

» All references (2)

Abstract

Cystathionine beta-synthase (CBS) is a unique heme- containing enzyme that catalyzes a pyridoxal 5'-phosphate (PLP)-dependent condensation of serine and homocysteine to give cystathionine. Deficiency of CBS leads to homocystinuria, an inherited disease of sulfur metabolism characterized by increased levels of the toxic metabolite homocysteine. Here we present the X-ray crystal...

[read more](#)

PDB ID: 1JBQ [Download](#) ?

MMDB ID: 16774 ?

PDB Deposition Date: 2001/6/6 ?

Updated in MMDB: 2012/11 ?

Experimental Method: x-ray diffraction ?

Resolution: 2.6 Å ?

Source Organism: Homo sapiens ?

Similar Structures: [VAST+](#) ?

[Download sequence data](#) ?


Default Biological Unit

All Biological Units (3)

Asymmetric Unit ?

Biological Unit for 1JBQ: dimeric; determined by author and by software (PISA) ?

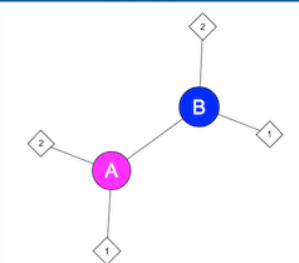
Molecular Graphic ?



3D view

full-featured 3D viewer

Interactions ?



Drag symbols to move
Double click symbols to explore molecules

[Download Structure Data](#) ?

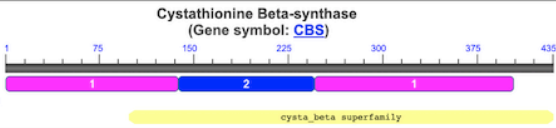
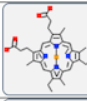

[Download](#)

Format: [ASN.1 \(Cn3D\)](#)

Data Set: [Single 3D structure](#)

[Download Cn3D](#)

Molecular Components in 1JBQ ?

Label	Count	Molecule
Proteins (2 molecules)		
A B	2	<p>Cystathionine Beta-synthase (Gene symbol: CBS)</p>  <p>2 Proteins</p> <p>3D Domains</p> <p>Domain Families</p> <p>Super Families</p> <p>cysta_beta superfamily</p>
Chemicals and Non-standard biopolymers (4 molecules)		
1	2	<p>Protoporphyrin IX Containing Fe</p> 
2	2	<p>Pyridoxal-5'-Phosphate</p> 

* Click molecule labels to explore molecular sequence information.

Citing MMDB

Madaj T, Lanczycki CJ, Zhang D, Thiessen PA, Geer RC, Marchler-Bauer A, Bryant SH. " MMDB and VAST+: tracking structural similarities between macromolecular complexes. *Nucleic Acids Res.* 2014 Jan; 42(Database issue):D297-303

Figure 8. Entry for 3-D structure of the wild type, canonical protein PDB ID: 1JBQ Human Cystathionine Beta-Synthase in the NCBI Structure database.

The NCBI Structure entry for PDB ID: 1JBQ Human Cystathionine Beta-Synthase <https://www.ncbi.nlm.nih.gov/Structure/pdb/1JBQ> (Figure 8) has links to PubChem entries for the co-factor pyridoxal 5' phosphate <https://pubchem.ncbi.nlm.nih.gov/substance/152137797> and the heme <https://pubchem.ncbi.nlm.nih.gov/substance/823350>, both of which are required for

Cystathionine Beta-Synthase enzyme activity. On the 3-D conformer part, under ‘Interactive Chemical Structure Model’ of the PubChem record, click the Space-filling radio button to get a rendering of the molecule.

PubChem CID: 834

Structure:

Molecular Formula: $C_7H_{12}NO_2S$

Synonyms: cystathionine, DL-Cystathionine, 535-34-2, D,L-Cystathionine, S-(2-amino-2-carboxyethyl)homocysteine

Molecular Weight: 222.26 g/mol

Dates: Modify: 2021-04-03, Create: 2004-09-16

Cystathionine is a modified amino acid generated by enzymic means from homocysteine and serine. It has a role as a metabolite. It is a member of cystathionines and an organic sulfide.

Sulfur-containing amino acid formed as an intermediate in the conversion of METHIONINE to CYSTEINE.

ChEBI, MeSH

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Figure 9. Entry for Cystathionine compound in the NCBI PubChem database.

You can also search for all the relevant substrates and products and follow the link to Biomolecular Interactions and Pathways of Cystathionine (Figure 9) in the NCBI PubChem database <https://pubchem.ncbi.nlm.nih.gov/compound/834>.

PubChem Cystathionine (Compound)

5 Related Records

5.1 Related Compounds with Annotation

466 items [View More Rows & Details](#)

Download

Structure	Compound CID	Name	Molecular Formula	Molecular Weight, g/mol
	458	S-Methylmethionine	$C_6H_{13}NO_2S^+$	164.25
	876	DL-Methionine	$C_5H_{11}NO_2S$	149.21
	1080	Rhinathiol	$C_7H_9NO_4S$	179.2
	6137	Methionine	$C_5H_{11}NO_2S$	149.21
	6205	DL-Ethionine	$C_6H_{13}NO_2S$	163.24

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PubChem

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Figure 10. Related Compounds for Cystathionine in the NCBI PubChem database.

In PubChem Section 5.1 Related Compounds with Annotations for Cystathionine <https://pubchem.ncbi.nlm.nih.gov/compound/834#section=Related-Compounds-with->

[Annotation&fullscreen=true](#) (Figure 10), click on “View More Rows & Details,” then sort by Create Date and follow the link to L-Cystathionine to find the biomolecular pathway that causes Homocystinuria.

PUBCHEM > CYSTATHIONINE > RELATED COMPOUNDS WITH ANNOTATION
CID 834

Cystathionine

Related Compounds with Annotation

466 items









#	Structure	Compound CID	Name	IUPAC Name ⓘ	Synonyms	Molecular Formula	Molecular Weight, g/mol	InChIKey ⓘ
1		876	DL-Methionine	2-amino-4-methylsulfanybutanoic acid	DL-METHIONINE 59-51-8 Methionine Racemethionine Acimetion ...	$C_5H_{11}NO_2S$	149.21	FFEARJCKVFRZRR-UHFFFAQDSA-N
2		6137	Methionine	(2S)-2-amino-4-methylsulfanybutanoic acid	L-Methionine 63-68-3 Methionine H-Met-OH (S)-2-Amino-4-(Methylthio)butanoic Acid ...	$C_5H_{11}NO_2S$	149.21	FFEARJCKVFRZRR-BYFFZUCKSA-N
3		67678	L-Cystine	(2R)-2-amino-3-(((2R)-2-amino-2-carboxyethyl)disulfany)propanoic acid	L-Cystine Cystine 56-89-3 L-Cystin L-Dicysteine ...	$C_6H_{12}N_2O_4S_2$	240.3	LEVWYRKDKASIDU-IMJSDKUSA-N
4		84815	D-Methionine	(2R)-2-amino-4-methylsulfanybutanoic acid	D-Methionine 348-67-4 H-D-Met-OH (R)-Methionine Methionine ...	$C_5H_{11}NO_2S$	149.21	FFEARJCKVFRZRR-SCSAIBSYSA-N
5		98504	Lanthionine	(2R)-2-amino-3-(((2R)-2-amino-2-carboxyethyl)sulfany)propanoic acid	Lanthionine L-Lanthionine 922-65-4 UNII-J078O46X3K 3,3'-Thiois-L-Alanine ...	$C_6H_{12}N_2O_4S$	208.24	DWPCPJAHDETAG-IMJSDKUSA-N
6		145692	S-Methyl-L-methionine	[(3S)-3-amino-3-carboxypropyl]-dimethylsulfanium	S-Methyl-L-Methionine 6788-35-6 CHEBI:17728 [(3S)-3-Amino-3-Carboxypropyl]-Dimethylsulfanium [(3S)-3-Amino-3-Carboxypropyl][Dimethyl]Sulfonium Iodide ...	$C_6H_{14}NO_2S^+$	164.25	YDBYJHTYSHBAU-YFKPBYVSA-O
7		193653	Carbocysteine	(2R)-2-amino-3-(carboxymethylsulfany)propanoic acid	Carbocysteine S-Carboxymethyl-L-Cystine 638-23-3 Carbocysteine Carbocystein ...	$C_5H_9NO_4S$	179.2	GBFLZXEEOZUWRN-VQWYTHEASA-N
8		439258	L-Cystathionine	(2S)-2-amino-4-(((2R)-2-amino-2-carboxyethyl)sulfany)butanoic acid	L-Cystathionine 56-88-2 Cystathionine L-(+)-Cystathionine Cystathionine, L- ...	$C_7H_{14}N_2O_4S$	222.26	ILRYLPWNYFXEMH-WYFFBIACZSA-N

Figure 11. Related compounds of Cystathionine in the NCBI PubChem database.

In NCBI PubChem database, sort the list of related compounds of Cystathionine by “Create Date” and follow the link to L-Cystathionine (Figure 11).

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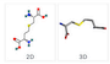
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COMPOUND SUMMARY

L-Cystathionine

PubChem CID: 439258

Structure:  Find Similar Structures

Chemical Safety:  Infant Laboratory Chemical Safety Summary (LCSS) Datasheet

Molecular Formula: $C_4H_9N_2O_2S$

Synonyms: L-cystathionine, 56-88-2, cystathionine, L-(+)-Cystathionine, Cystathionine, L-
More...

Molecular Weight: 222.26 g/mol

Dates: Modify: 2021-04-03 Create: 2004-09-16

L-cystathionine is a modified amino acid generated by enzymic means from L-homocysteine and L-serine. It has a role as a human metabolite, a *Saccharomyces cerevisiae* metabolite, an *Escherichia coli* metabolite and a mouse metabolite. It is a tautomer of a L-cystathionine di-zwitterion.

ChEBI

Sulfur-containing amino acid formed as an intermediate in the conversion of METHIONINE to CYSTEINE.

MeSH

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CONTENTS

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- 8 Safety and Hazards
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- 10 Literature
- 11 Patents
- 12 Biomolecular Interactions and Pathways
- 13 Classification
- 14 Information Sources

Figure 12. Compound Summary of L-Cystathionine in the NCBI PubChem database.

From the Compound Summary of L-Cystathionine from NCBI PubChem database <https://pubchem.ncbi.nlm.nih.gov/compound/439258> (Figure 12), expand the section on “Biomolecular Interactions and Pathways,” then click “Pathways.”

12 Biomolecular Interactions and Pathways

12.1 Chemical-Gene Interactions

12.1.1 CTD Chemical-Gene Interactions

5 items View More Details Download

PubChem Gene	Interaction	Evidence PMID
CBS	[CBS protein results in increased metabolism of Homocysteine] which results in increased chemical synthesis of Cystathionine	23665415
CXCL8	Cystathionine inhibits the reaction [Formaldehyde results in increased expression of CXCL8 protein]	27664576
INS	[1-Methyl-3-isobutylxanthine co-treated with butylbenzyl phthalate co-treated with INS protein] results in increased abundance of Cystathionine analog	26820058
KYAT1	KYAT1 protein results in increased amination of Cystathionine	22093698
MMP1	Cystathionine inhibits the reaction [Formaldehyde results in increased expression of MMP1 protein]	27664576

Comparative Toxicogenomics Database (CTD)

12.2 Pathways

Page 3 of 18 items View More Rows & Details Download

Pathway	Source	External ID
Methionine metabolism leading to Sulphur Amino Acids and related disorders	WikiPathways	WP4282
One carbon donor	WikiPathways	WP3125
One carbon metabolism and related pathways	WikiPathways	WP3940
Selenium Micronutrient Network	WikiPathways	WP15
Sulfate assimilation and copper detoxification	WikiPathways	WP4173

PubChem

Figure 13. Biomolecular Pathways of L-Cystathionine in the NCBI PubChem database.

In PubChem Section 12.2 Pathways of L-Cystathionine <https://pubchem.ncbi.nlm.nih.gov/compound/439258#section=Pathways> (Figure 13), follow the link to WikiPathways database for “Methionine metabolism leading to Sulphur Amino Acids and related disorders.”

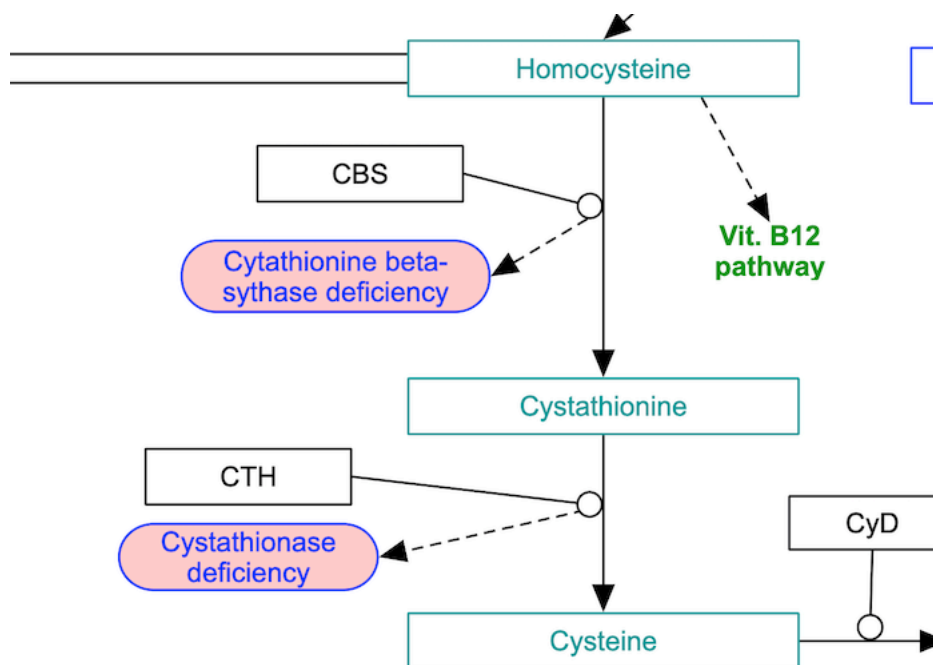


Figure 14. Section of Methionine metabolism leading to sulfur amino acids and related disorders (Homo sapiens) in the WikiPathways database.

In WikiPathways database, the reaction we are looking for is homocysteine to cystathionine in methionine metabolism leading to sulfur amino acids and related disorders (Homo sapiens) <https://www.wikipathways.org/index.php/Pathway:WP4292> (Figure 14), where deficiency of the Cystathionine Beta-Synthase enzyme causes Homocystinuria.

The screenshot shows the NCBI MedGen database entry for 'Classic homocystinuria'. The search bar at the top contains 'homocystinuria due to CBS deficiency'. The entry includes the following information:

- Classic homocystinuria**: MedGen UID: 199606 • Concept ID: C0751202 • Disease or Syndrome
- Synonyms**: CBS deficiency; Cystathionine beta-synthase deficiency; Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency; Homocystinuria due to CBS deficiency; Homocystinuria due to cystathionine beta-synthase deficiency; HOMOCYSTINURIA WITH OR WITHOUT RESPONSE TO PYRIDOXINE
- SNOMED CT**: Deficiency of serine sulfinylase (24308003); Deficiency of methionine synthase (24308003); Deficiency of beta-thionase (24308003); Cystathionine beta-synthase deficiency (24308003); CBS deficiency (24308003)
- Modes of inheritance**: Autosomal recessive inheritance (HPO, OMIM)
- Gene (location)**: CBS (21q22.3)
- Monarch Initiative**: MONDO:0009352
- OMIM**: 236200
- Orphanet**: ORPHA394
- Definition**: Classical homocystinuria due to cystathionine beta-synthase (CBS) deficiency is characterized by the multiple involvement of the eye, skeleton, central nervous system, and vascular system. [from ORDO]
- Additional descriptions**: From GeneReviews: 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, scoliosis, 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.
- Table of contents**: Definition, Additional descriptions, Clinical features, Professional guidelines, Recent clinical studies, Genetic Testing Registry, Clinical resources, Molecular resources, Consumer resources, Reviews (GeneReviews, PubMed Clinical Queries, Reviews in PubMed).

Figure 15. Entry for Classic homocystinuria in the NCBI MedGen database.

Go to the GeneReviews chapter that is linked from the entry for Classic homocystinuria in the NCBI MedGen database. <https://www.ncbi.nlm.nih.gov/medgen/199606> (Figure 15).

Review

Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency

Stephanie J Sacharow¹, Jonathan D Picker², Harvey L Levy¹

Margaret P Adam, Holly H Ardinger, Roberta A Pagon, Stephanie E Wallace, Lora JH Bean, Karen Stephens, Anne Amemiya, editors.

In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2020. 2004 Jan 15 [updated 2017 May 18].

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Excerpt

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, scoliosis, 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, B₆-responsive homocystinuria and B₆-non-responsive homocystinuria. B₆-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 B₆-responsive individuals the mean IQ is 79 versus 57 for those who are B₆-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.

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 B₆ (pyridoxine) therapy (if shown to be B₆ responsive), a methionine-restricted diet, and folate and vitamin B₁₂ 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.

Figure 16. GeneReviews chapter on “Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency” in the PubMed database.

The GeneReviews chapter covers management of the treatment for “Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency” <https://pubmed.ncbi.nlm.nih.gov/20301697/> (Figure 16).

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 $\mu\text{mol/L}$ (preferably, $\leq 5 \mu\text{mol/L}$) [Yap et al 2001b]. This corresponds to a plasma total homocysteine concentration below 120 $\mu\text{mol/L}$ or, preferably, below 100 $\mu\text{mol/L}$ [Morris et al 2017]. For B₆-responsive individuals, the goal for plasma total homocysteine is below 50 $\mu\text{mol/L}$ [Morris et al 2017].

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

Measures used to control total plasma homocysteine concentration include vitamin B₆ (pyridoxine) therapy (if shown to be B₆ responsive), methionine-restricted diet, and folate and vitamin B₁₂ 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 B₆ (pyridoxine) therapy. In those who are shown to be B₆ 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 B₆ non-responsiveness, typically in doses of 100-200 mg daily (although some adults receive 500-1000 mg daily).

Dietary treatment. B₆-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 B₆-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 B₁₂ supplementation. Folate and vitamin B₁₂ 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 B₁₂ concentration are reduced, folic acid is given orally at 5 mg per day; and vitamin B₁₂ 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.

Figure 17. Prevention of Primary Manifestations of Homocystinuria from GeneReviews chapter, “Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency.”

According to the GeneReviews chapter, “Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency,” the homocystinuria condition responds to vitamins B₆ (pyridoxine), B-12 (Cyanocobalamin) and folate and/or a methionine restricted diet and betaine <https://www.ncbi.nlm.nih.gov/books/NBK1524/#homocystinuria.Management> (Figure 17).

Though not drugs in the traditional sense these are all entities that have PubChem records. Search with the terms below in PubChem Compound at <https://pubchem.ncbi.nlm.nih.gov/>.

Pyridoxine <https://pubchem.ncbi.nlm.nih.gov/compound/1054>

Cyanocobalamin does not have a 3-D structure since it is a complex but it has a 2-D rendering <https://pubchem.ncbi.nlm.nih.gov/compound/5311498s>

Folic Acid <https://pubchem.ncbi.nlm.nih.gov/compound/135398658>

L-methionine <https://pubchem.ncbi.nlm.nih.gov/compound/6137>

Betaine <https://pubchem.ncbi.nlm.nih.gov/compound/247>

Multiple articles have been written about searching NCBI databases ([NCBI Resource Coordinators 2016](#)) including GenBank ([Benson et al. 2013](#)), Gene ([Brown et al. 2015](#)), MedGen ([Louden 2020](#)), OMIM ([Amberger et al. 2015](#); [Amberger & Hamosh 2017](#)), and PubChem ([Kim et al. 2021](#); [Kim et al. 2016](#)) for further reading. For additional guidance on NCBI databases, please refer to the National Center for Biotechnology Information's (NCBI) YouTube channel <https://www.youtube.com/ncbinlm>.

Acknowledgement

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