

Correlating Disease Genes and Phenotypes

An NCBI Mini-Course

This mini-course focuses on the correlation of a disease gene to the phenotype. It demonstrates how NCBI resources such as the literature, expression and structure information can provide potential functional information for disease genes.

Mutations in the HFE gene are associated with the hemochromatosis disease. A laboratory working on the hemochromatosis disease wants to elucidate the biochemical and structural basis for the function of the mutant protein.

Outline:

In this exercise, we have the following goals:

1. Determine what is known about the HFE gene and protein (using Entrez Gene).
2. Determine identified SNPs and their locations in the HFE gene (using dbSNP).
3. Learn more about hemochromatosis and its genetic testing (using OMIM and Gene Tests)
4. Elucidate the biochemical and structural basis for the function of the wild type and mutant proteins, if possible.

During the first hour, an overview will be given using one disease gene, followed by an hour of hands-on session to practice using another disease gene. The following handout contains the screenshots of the overview.

URL: <http://www.ncbi.nlm.nih.gov/Class/minicourses/pheno.html>

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Problem 1

Mutations in the HFE gene are associated with the hemochromatosis disease. A laboratory working on the hemochromatosis disease wants to elucidate the biochemical and structural basis for the function of the mutant protein.

Outline:

In this exercise, we have the following goals:

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2. Determining identified SNPs and their locations in the HFE gene (using dbSNP).
3. Learning more about the hemochromatosis disease and its genetic testing (using OMIM and Gene Tests)
4. Elucidating the biochemical and structural basis for the function of the wild type and the mutant protein, if possible (using CDD).

Step 1. Determining what is known about the HFE gene and protein (using Entrez Gene):

Search for 'HFE' in [Entrez Gene](#). One entry is for the human HFE gene. Retrieve the entry by clicking on the HFE link.

What is the location and orientation of the HFE gene on the human genome? List the genes adjacent to it. How many alternatively spliced products have been annotated for the HFE gene when the RefSeq mRNA entries were reviewed? What are the differences in the spliced products? List some of the HFE gene aliases. What are the phenotypes associated with the mutations in the HFE gene? What is the name and function of the protein encoded by the HFE gene? What is the conserved domain in the protein? To which cellular component(s) is the protein localized? Obtain the locations of exons and introns for each transcript by choosing "Gene Table" from the Display pull down menu.

Step 2. Determining identified SNPs and their locations in the HFE gene:

From the Links menu on the top right hand side of the page, click on the "SNP: GeneView" to access a list of the known SNPs (reported in dbSNP). By default, the SNPs in the coding region of a gene are reported. Additional SNPs such as in the upstream region or the introns can be viewed by clicking on the "in gene region" button. Currently, how many non-synonymous SNPs are placed on the longest hemochromatosis transcript variant, NM_000410? How many of these have links to OMIM? We will concentrate on the cys282tyr mutant in the following analysis.

Step 3. Learning more about the hemochromatosis disease and its genetic testing:

Click on the OMIM link next to the one of the SNPs in the SNP report. What are the clinical features of hemochromatosis? List the 5 types of iron-overload disorders labeled hemochromatosis. Which of these is associated with mutations in the HFE gene? How many allelic variants of the HFE gene have been reported? What is the phenotype associated with the Cys282Tyr mutant?

Click on the Gene Tests link at top of the page. Identify some of the laboratories performing the clinical testing for hemochromatosis. Now refer to the Reviews section. Mutation analysis is available for which of the HFE alleles? List one explanation for the hemochromatosis phenotype caused by the Cys282Tyr mutant.

Step 4. Elucidating the biochemical and structural basis for the function of the wild type and mutant proteins, if possible:

Go back to the Entrez Gene report. Click on the protein accession number NP_000401 associated with the longest splice variant NM_000410. Select the Blink link. Click on the 3D structures button. The output contains a list of similar proteins with known 3D structures. The first entry, 1A6Z chain C, provides the structure of the part of human hemochromatosis protein. Click on the blue dot next to the accession number to get the sequence alignment of the query protein with 1A6Z chain C. Click on the "View 3D Structure" button. This downloads its 3D structure and its sequence alignment with the query protein. Zoom in the area of the disulphide bridge (colored in tan) by pressing "z" on the keyboard. Select the cysteine residues forming the disulphide bridge by double clicking on them. Mouse over the corresponding cysteine residues on the query line in the alignment and view the amino acid number at the bottom left of the window. One of them is the cysteine at position 282. It is the same cysteine which is mutated to tyrosine causing the hemochromatosis phenotype.

You can now easily explain why the C282Y mutant has an altered function.

Summary:

This mini-course describes how to obtain information about the HFE gene, known SNPs in it, and elucidate the biochemical and structural basis for the function of the wild type and Cys282Tyr mutant protein.

- Summary:
1. The HFE gene is located on chromosome 6 and has at least 11 alternatively spliced products.
 2. Currently, there are 8 non-synonymous SNPs annotated on the protein NP_000401.
 3. The Cys282Tyr mutant is associated with the hemochromatosis disease and the site of mutation is used in hemochromatosis genetic testing.

4. The HFE protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin whereas the Cys282Tyr mutant fails to regulate this interaction leading to iron overload. The conserved cysteine 282 in the immunoglobulin constant region domain of the HFE protein is involved in formation of a disulphide bridge. Its mutation to tyrosine will alter the folding of the protein.


National Center for Biotechnology Information
 National Library of Medicine National Institutes of Health

PubMed All Databases BLAST OMIM Books TaxBrowser Structure

Search for **Go**

SITE MAP
 Alphabetical List
 Resource Guide

What does NCBI do? **Hot Spots**

Established in 1988 as a national resource for molecular biology information. NCBI creates

Assembly Archive



Entrez, The Life Sciences Search Engine

HOME SEARCH SITE MAP PubMed All Databases Human Genome GenBank Map Viewer BLAST

Search across databases **GO** **CLEAR** Help

Welcome to the Entrez cross-database search page

 PubMed: biomedical literature citations and abstracts	 Books: online books
 PubMed Central: free, full text journal articles	 OMIM: online Mendelian Inheritance in Man
 Site Search: NCBI web and FTP sites	 OMIA: online Mendelian Inheritance in Animals

 Nucleotide: sequence database (includes GenBank)	 UniGene: gene-oriented clusters of transcript sequences
 Protein: sequence database	 CDD: conserved protein domain database
 Genome: whole genome sequences	 3D Domains: domains from Entrez Structure
 Structure: three-dimensional macromolecular structures	 UniSTS: markers and mapping data
 Taxonomy: organisms in GenBank	 PopSet: population study data sets
 SNP: single nucleotide polymorphism	 GEO Profiles: expression and molecular abundance profiles
 Gene: gene-centered information	 GEO DataSets: experimental sets of GEO data
 HomoloGene: eukaryotic homology groups	 Cancer Chromosomes: cytogenetic databases
 PubChem Compound: unique small molecule chemical structures	 PubChem BioAssay: bioactivity screens of chemical substances
 PubChem Substance: deposited chemical substance records	 GENSAT: gene expression atlas of mouse central nervous system
 Genome Project: genome project information	 Probe: sequence-specific reagents
 dbGaP: genotype and phenotype	 Protein Clusters: a collection of related protein sequences

 Journals: detailed information about the journals indexed in PubMed and other Entrez databases	 MeSH: detailed information about NLM's controlled vocabulary
 NLM Catalog: catalog of books, journals, and audiovisuals in the NLM collections	

Enter terms and click 'GO' to run the search against ALL the databases, OR
 Click Database Name or icon to go directly to the Search Page for that database, OR
 Click Question Mark for a short explanation of that database.


Entrez Gene

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

Search for **Go** **Clear**

Entrez Gene
 Home
 About
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 Help
 Gene Handbook
 Statistics
 Downloads (FTP)
 Mailing Lists
 Gene
 RefSeq
 Feedback

Entrez Gene is a searchable database of genes, from **Reference** genomes, and defined by sequence and/or located in the NCBI Map Viewer

News Query by accession with version number. [News archives...](#)

Sample Searches

Find genes by...	Search text
free text	<code>human muscular dystrophy</code>
partial name and multiple species	<code>transporter[title] AND ("Drosophila melanogaster"[organ] OR "Mus musculus"[organ])</code>
chromosome and symbol	<code>(11[chr] OR 2[chr]) AND adh*[sym]</code>
associated sequence accession number	<code>M11213[accn]</code>
gene name (symbol)	<code>BRCA1[sym]</code>
publication (PubMed ID)	<code>11331580[PMID]</code>
Gene Ontology (GO) terms or identifiers	<code>"cell adhesion"[GO]</code> <code>1720[GO]</code>
chromosome and species	<code>Y1CHR1 AND human[ORGN]</code>
Sequence Commission (SC) numbers	<code>1.0.1.1651</code>

NCBI Entrez Gene

Search: Gene for hfe Go Clear Save Search

Display: Summary Show: 20 Send to: All: 34 Current Only: 34 Genes Genomes: 30 SNP GeneView: 25

Items 1 - 20 of 34

1: **HFE**

Official Symbol: HFE and **Name:** hemochromatosis [*Homo sapiens*]
Other Aliases: HFE1, HH, HLA-H, MGC103790, dJ221C16.10.1
Other Designations: MHC class I-like protein HFE, hemochromatosis protein; hereditary hemochromatosis protein HLA-H
Chromosome: 6; **Location:** 6p21.3
MIM: 235200
GeneID: 3077

NCBI Entrez Gene

Search: Gene for hfe Go Clear

Display: Full Report Show: 5 Send to: All: 1 Current Only: 1 Genes Genomes: 1 SNP GeneView: 1

1: **HFE hemochromatosis** [*Homo sapiens*]
 GeneID: 3077 updated 06-May-2007

Summary

Official Symbol	HFE	provided by HGNC
Official Full Name	hemochromatosis	provided by HGNC
Primary source	HGNC:4886	
See related	HPRD:01993; MIM:235200	
Gene type	protein coding	
RefSeq status	Reviewed	
Organism	<i>Homo sapiens</i>	
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	
Also known as	HH; HFE1; HLA-H; MGC103790; dJ221C16.10.1	

Summary The protein encoded by this gene is a membrane protein that is similar to MHC class I-type proteins and associates with beta2-microglobulin (beta2M). It is thought that this protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin. The iron storage disorder, hereditary haemochromatosis, is a recessive genetic disorder that results from defects in this gene. At least eleven alternatively spliced variants have been described for this gene. Additional variants have been found but their full-length nature has not been determined.

Genomic regions, transcripts, and products

Genomic regions, transcripts, and products

Go to [reference sequence details](#)

NC_000006.10

Genomic context

chromosome: 6; Location: 6p21.3

See HFE in MapViewer

Entrez Gene Info

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Related Articles in PubMed

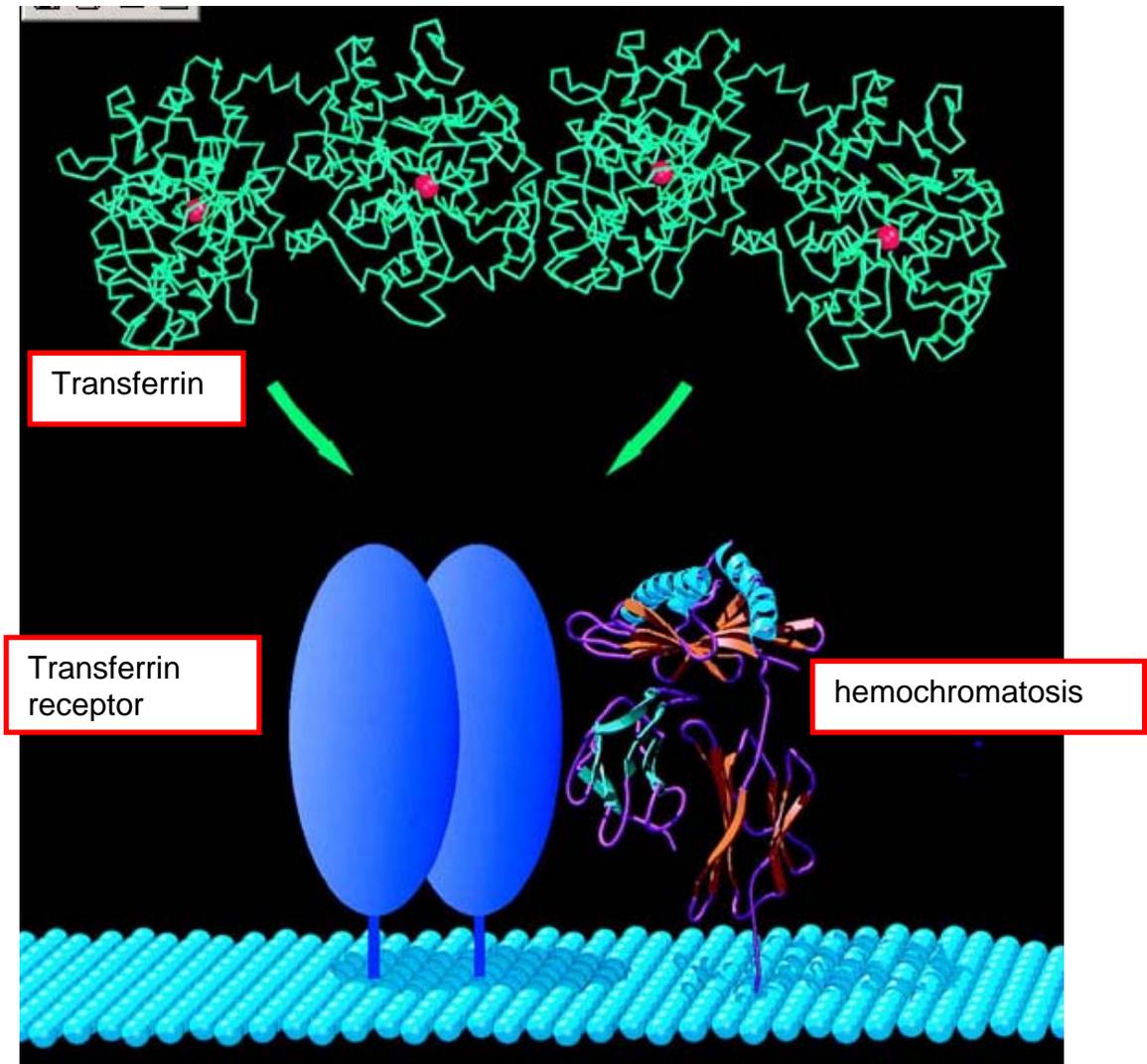
[PubMed](#) links

GeneRIFs: Gene References Into Function

[What's a GeneRIF?](#)

- prevalent mutation is a point mutation(histidine to aspartic acid)in iron overload has been controversial.
- 118. Mutations in HFE protein results in hemochromatosis
 - 119. results suggest that wild-type HFE negatively modulates the endocytic uptake of transferrin
 - 120. genotype and allele frequencies between neonates and referred patients for HFE molecular analysis
 - 121. mutational analysis of the transferrin receptor reveals overlapping HFE and transferrin binding sites
 - 122. REVIEW: C282Y mutant gene product failed to associate with 2-microglobulin and significantly reduced cell surface expression of the HFE-2m complex, thereby affecting the interaction with TfR and its interaction with transferrin.
 - 123. 871 healthy unrelated subjects in Poland were collected to assess the relevant frequencies. Each subject was genotyped for the C282Y and H63D mutations using a PCR-based protocol

Submit: [New GeneRIF](#) [Correction](#)



Bacon et al. Gastroenterology, 116:193-207, Figure 4

The hemochromatosis protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin.

HIV-1 protein interactions ↑ ?

Protein Interaction

1. [Nef](#) Myristoylation of HIV-1 Nef at position 2 and the PxxP proline-rich motif of Nef at positions 62-65 are required for Nef-induced downregulation of HFE; amino acid residue Y282 in HFE is involved in the downregulation by Nef [PubMed](#)
2. HIV-1 Nef downregulates the macrophage-expressed MHC 1b protein HFE by rerouting HFE to a perinuclear structure that overlaps the trans-Golgi network, causing a 90% reduction of surface HFE [PubMed](#)

[Go to the HIV-1, Human Protein Interaction Database](#)

Interactions ↑ ?

Description	Product	Interactant	Other Gene	Complex	Source	Pubs
	NP_000401.1	Beta 2 microglobulin	B2M		HPRD	PubMed
	NP_000401.1	Transferrin receptor 2	TFR2		HPRD	PubMed
	NP_000401.1	NP_003225.1	TFRC		HPRD	PubMed
in vitro	BioGRID:109325	BioGRID:107044	B2M		BioGRID	PubMed
in vivo	BioGRID:109325	BioGRID:112894	TFR2		BioGRID	PubMed
in vitro; in vivo	BioGRID:109325	BioGRID:112895	TFRC		BioGRID	PubMed

General gene information ↑

Markers

RH46796(e-PCR)
Links: [UniSTS:18176](#)
Alternate name: stSG24898

WI-17546(e-PCR)
Links: [UniSTS:30510](#)
Alternate names: EST261382; RH61086

RH46637(e-PCR)
Links: [UniSTS:36001](#)
Alternate name: stSG24673

A004R25(e-PCR)
Links: [UniSTS:41641](#)
Alternate name: RH25814

STS-U60319(e-PCR)
Links: [UniSTS:47384](#)
Alternate names: RH75899; sts-U60319

D6S2377(e-PCR)
Links: [UniSTS:57170](#)
Alternate names: GDB:5584195; sy899g1-19

Phenotypes

Hemochromatosis
[MIM: 235200](#)

Porphyria variegata
[MIM: 176200](#)

Homology

Mouse
[Map Viewer](#)

GeneOntology Provided by [GOA](#)

Function	Evidence
iron ion binding	IEA

Process	Evidence
antigen processing and presentation	IEA
antigen processing and presentation of peptide antigen via MHC class I	IEA
immune response	IEA
ion transport	IEA
iron ion homeostasis	TAS PubMed
iron ion transport	TAS PubMed
protein complex assembly	TAS PubMed
receptor-mediated endocytosis	TAS PubMed

Component	Evidence
MHC class I protein complex	IEA
cytoplasm	TAS PubMed
integral to plasma membrane	TAS PubMed
membrane	IEA
plasma membrane	TAS PubMed

General protein information ↑ ?

Names
hemochromatosis protein
MHC class I-like protein HFE
hereditary hemochromatosis protein HLA-H

NCBI Reference Sequences (RefSeq) ↑ ?

Genomic

1. NG_001335.1 Reference	
Range	71162..80773
Download	GenBank , FASTA

mRNA and Protein(s)

1. NM_000410.3–NP_000401.1 hemochromatosis protein isoform 1 precursor					
Description	Transcript Variant: This variant (1) encodes the longest isoform.				
Source sequence(s)	AF115265 , AJ249337 , U91328				
Consensus CDS	CCDS4578.1				
Conserved Domains (2)	summary				
	<table border="0"> <tr> <td style="vertical-align: top;"> <p>cd00098 Location:223–298 Blast Score:169</p> </td> <td style="vertical-align: top;"> <p>IGc; Immunoglobulin domain constant region subfamily; members of the IGc subfamily are components of immunoglobulins, T-cell receptors, CD1 cell surface glycoproteins, secretory glycoproteins A/C, and Major Histocompatibility Complex (MHC) class I/II molecules</p> </td> </tr> <tr> <td style="vertical-align: top;"> <p>pfam01129 Location:27–202 Blast Score:314</p> </td> <td style="vertical-align: top;"> <p>MHC_1; Class I Histocompatibility antigen, domains alpha 1 and 2</p> </td> </tr> </table>	<p>cd00098 Location:223–298 Blast Score:169</p>	<p>IGc; Immunoglobulin domain constant region subfamily; members of the IGc subfamily are components of immunoglobulins, T-cell receptors, CD1 cell surface glycoproteins, secretory glycoproteins A/C, and Major Histocompatibility Complex (MHC) class I/II molecules</p>	<p>pfam01129 Location:27–202 Blast Score:314</p>	<p>MHC_1; Class I Histocompatibility antigen, domains alpha 1 and 2</p>
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<p>pfam01129 Location:27–202 Blast Score:314</p>	<p>MHC_1; Class I Histocompatibility antigen, domains alpha 1 and 2</p>				

Related Sequences ↑ ?

Nucleotide	Protein
Genomic AF184234.1	AAF01222.1
Genomic AF204869.1	None
Genomic AF331065.1	AAK16502.1
Genomic AF525359.1	AAM82608.1
Genomic AF525499.1	AAM91950.1
Genomic CH471087.1	EAW55516.1
	EAW55517.1
	EAW55518.1
	EAW55519.1
	EAW55520.1
	EAW55521.1
	EAW55522.1
	EAW55523.1
	EAW55524.1
	EAW55525.1
	EAW55526.1
	EAW55527.1
Genomic CS187189.1	CAJ42862.1
Genomic U89014.1	AAD00449.1

NCBI Entrez Gene

Search Gene for [Go] [Clear]

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OMIA

OMIM

Full text in PMC

Probe

Protein

mRNA	bp	exons	Protein	aa	exons
NM_139005.2	1417	5	NP_620574.1	277	5
NM_139002.2	878	4	NP_620571.1	162	4
NM_000410.3	2222	6	NP_000401.1	349	6
NM_139004.2	1946	5	NP_620573.1	257	5
NM_139003.2	1904	5	NP_620572.1	243	5
NM_139009.2	2153	6	NP_620578.1	326	6
NM_139007.2	1958	5	NP_620576.1	261	5
NM_139008.2	1916	5	NP_620577.1	247	5
NM_139010.2	1682	4	NP_620579.1	169	4
NM_139011.2	1406	3	NP_620580.1	77	3
NM_139006.2	1180	6	NP_620575.1	335	6

Exon information:

[NM_139005.2](#) length: 1417 bp, number of exons: 5

[NP_620574.1](#) length: 277 aa, number of exons: 5

EXON	length	Coding EXON	length	INTRON	length
62 - 297	236 bp	222 - 297	76 bp	298 - 3621	3324 bp
3622 - 3885	264 bp	3622 - 3885	264 bp	3886 - 4094	209 bp
4095 - 4370	276 bp	4095 - 4370	276 bp	4371 - 5465	1095 bp
5466 - 5667	202 bp	5466 - 5667	202 bp	5668 - 9171	3504 bp
9172 - 9610	439 bp	9172 - 9184	13 bp		

[NM_139002.2](#) length: 878 bp, number of exons: 4

[NP_620571.1](#) length: 162 aa, number of exons: 4

EXON	length	Coding EXON	length	INTRON	length
62 - 297	236 bp	222 - 297	76 bp	298 - 3621	3324 bp
3622 - 3885	264 bp	3622 - 3885	264 bp	3886 - 4094	209 bp

Review

CCDS

Evidence Viewer

GDB

GeneTests for MIM: 235200

HGMD

HGNC

HPRD

KEGG

MGC

ModelMaker

UniGene

LinkOut

Entrez Gene Info

Feedback

Subscriptions

All: 1 | Current Only: 1 | Genes Genomes: 1 | SNP GeneView: 1

1: HFE hemochromatosis [Homo sapiens] updated 06-May-2007 Entrez Gene Home

GeneID: 3077

Summary

Official Symbol HFE provided by HGNC

Official Full Name hemochromatosis provided by HGNC

Primary source HGNC:4886

See related HPRD:01993; MIM:235200

Gene type protein coding

RefSeq status Reviewed

Organism *Homo sapiens*

Lineage Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as HH; HFE1; HLA-H; MGC103790; dJ221C16.10.1

Summary The protein encoded by this gene is a membrane protein that is similar to MHC class I-type proteins and associates with beta2-microglobulin (beta2M). It is thought that this protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin. The iron storage disorder, hereditary haemochromatosis, is a recessive genetic disorder that results from defects in this gene. At least eleven alternatively spliced variants have been described for this gene. Additional variants have been found but their full-length nature has not been determined.

Genomic regions, transcripts, and products

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- SNP
- SNP: Genotype
- SNP: GeneView
- Taxonomy
- UniSTS
- AceView
- CCDS
- Evidence Viewer
- GDB
- GeneTests for MIM: 235200
- HGMD
- HGNC

NCBI **Single Nucleotide Polymorphism**

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

Search for SNP on NCBI Reference Assembly

Search Entrez SNP for [] Go

SNP linked to Gene HFE(geneID:3077) Via Contig Annotation

Send rs# on all gene models to Batch Query Download all rs# to file. GENE GENOTYPE REPORT

Gene Model (mRNA alignment) information from genome sequence

Total gene model (contig mRNA transcript):				22		
mrna	transcript	protein	mrna orientation	Contig	Contig Label	List SNP
NM_000410	plus strand	NP_000401	forward	NT_007592	reference	<- currently shown
NM_000410	plus strand	NP_000401	forward	NW_922984	Celera	View snp on GeneModel
NM_139002	plus strand	NP_620571	forward	NT_007592	reference	View snp on GeneModel
NM_139002	plus strand	NP_620571	forward	NW_922984	Celera	View snp on GeneModel
NM_139003	plus strand	NP_620572	forward	NT_007592	reference	View snp on GeneModel
NM_139003	plus strand	NP_620572	forward	NW_922984	Celera	View snp on GeneModel
NM_139004	plus strand	NP_620573	forward	NT_007592	reference	View snp on GeneModel
NM_139004	plus strand	NP_620573	forward	NW_922984	Celera	View snp on GeneModel
NM_139005	plus strand	NP_620574	forward	NT_007592	reference	View snp on GeneModel
NM_139005	plus strand	NP_620574	forward	NW_922984	Celera	View snp on GeneModel
NM_139006	plus strand	NP_620575	forward	NT_007592	reference	View snp on GeneModel
NM_139006	plus strand	NP_620575	forward	NW_922984	Celera	View snp on GeneModel

GENERAL

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gene model (contig mRNA transcript):	Contig Label	Contig	mrna	protein	mrna orientation	transcript	snp count
	reference	NT_007592	NM_000410	NP_000401	forward	plus strand	9, coding

Region	Contig position	mRNA pos	dbSNP rs# cluster id	Heterozygosity	Validation	3D	OMIM	Function	dbSNP allele	Protein residue	Codon pos	Amino acid pos
exon_1	16945920	161						start codon				1
exon_2	16949347	264	rs2242956	N.D.		Yes		nonsynonymous	C	Thr [T]	2	35
				N.D.		Yes		contig reference	T	Met [M]	2	35
	16949430	347	rs1799945	0.127		Yes		nonsynonymous	G	Asp [D]	1	63
				0.127		Yes		contig reference	C	His [H]	1	63
	16949436	353	rs1800730	N.D.		Yes		nonsynonymous	T	Cys [C]	1	65
				N.D.		Yes		contig reference	A	Ser [S]	1	65
	16949520	437	rs28934597	N.D.		Yes		nonsynonymous	C	Arg [R]	1	93
				N.D.		Yes	Yes	contig reference	G	Gly [G]	1	93
	16949557	474	rs28934596	N.D.		Yes		nonsynonymous	C	Thr [T]	2	105
				N.D.		Yes	Yes	contig reference	T	Ile [I]	2	105
exon_3	16949833	541	rs28934595	N.D.		Yes		nonsynonymous	C	His [H]	3	127
				N.D.		Yes	Yes	contig reference	A	Gln [Q]	3	127
exon_4	16951197	810	rs4986950	N.D.		Yes		nonsynonymous	T	Ile [I]	2	217
				N.D.		Yes		contig reference	C	Thr [T]	2	217
	16951392	1005	rs1800562	0.024		Yes		nonsynonymous	A	Tyr [Y]	2	282
				0.024		Yes	Yes	contig reference	G	Cys [C]	2	282
exon_6	16952684	1186	rs55201683	0.053				synonymous	T	Tyr [Y]	3	342
				0.053				contig reference	C	Tyr [Y]	3	342

Search for in Highlight: NCBI PubMed Gene Nucleotide My NCBI Clear Uninstall Links

MIM +235200
.0001 HEMOCHROMATOSIS [HFE, CYS282TYR] dbSNP

PORPHYRIA VARIEGATA, INCLUDED
 HEMOCHROMATOSIS, JUVENILE, DIGENIC, INCLUDED
 ALZHEIMER DISEASE, SUSCEPTIBILITY TO, INCLUDED

In patients with hemochromatosis, [Feder et al. \(1996\)](#) identified an 845G-A transition in the HFE gene (which they referred to as HLA-H or cDNA 24'), resulting in a cys282-to-tyr (C282Y) substitution. This missense mutation occurs in a highly conserved residue involved in the intramolecular disulfide bridging of MHC class I proteins, and could therefore disrupt the structure and function of this protein. Using an allele-specific oligonucleotide-ligation assay on their group of 178 patients, they detected the C282Y mutation in 85% of all HFE chromosomes. In contrast, only 10 of the 310 control chromosomes (3.2%) carried the mutation, a carrier frequency of 10/155 = 6.4%. One hundred forty-eight of 178 HH patients were homozygous for this mutation, 9 were heterozygous, and 21 carried only the normal allele. These numbers were extremely discrepant from Hardy-Weinberg equilibrium. The findings corroborated heterogeneity among the hemochromatosis patients, with 83% of cases related to C282Y homozygosity.

[Jazwinska et al. \(1996\)](#) provided convincing evidence that the C282Y mutation in homozygous form in the HFE gene is the cause of hemochromatosis. In studies in Australia, patients properly characterized at the genotypic and phenotypic level all showed homozygosity for the C282Y amino acid substitution. Irrespective of haplotype, all HH heterozygotes were cys/tyr heterozygotes, and all homozygous normal controls were cys/cys homozygotes. The presence of a single mutation in all patients contrasted with the data of [Feder et al. \(1996\)](#), who reported a lower frequency of the mutation. [Jazwinska et al. \(1996\)](#) suggested that different clinical criteria for the diagnosis of HH may account for the difference, or that HH may not be as homogeneous as previously believed. They noted that a key question is why there is a variation in severity of iron loading in HH that is haplotype-related when the mutation is identical in all haplotypes tested. [Jazwinska et al. \(1996\)](#) hypothesized that the HFE locus is the primary HH locus, but that there are likely to be other 6p-linked modifying genes that would explain both the HLA-linked haplotype variation in expression of the disorder and the large region of linkage disequilibrium present in all populations and spanning at least 4.5 Mb distal of D6S265.

[Jouanolle et al. \(1996\)](#) commented on the significance of the C282Y mutation on the basis of a group of 65 unrelated affected individuals who had been under study in France for more than 10 years and identified by stringent criteria. Homozygosity for the C282Y mutation was found in 59 of 65 patients (90.8%); 3 of the patients were compound heterozygotes for the C282Y mutation and the H63D mutation ([235200.0002](#)); 1 was homozygous for the H63D mutation, and 2 were heterozygous for H63D. These results corresponded to an allelic frequency of 93.1% for the C282Y and 5.4% for the H63D mutations, respectively. Of note, the C282Y mutation was never observed in the family-based controls, while it was present in 5.8% of the general Breton population. In contrast, the H63D allelic frequency was nearly the same in both control groups (15% and 16.5% in the family-based and general population controls, respectively). The C282Y mutation was never observed, even in heterozygous form, in the family-based controls in whom all signs of iron overload had been excluded, whereas the general population displayed 5.8% of heterozygotes. This corresponds to a theoretical frequency of about 1 per 1,000 for the disease, which is slightly lower than generally estimated. While the experience of [Jouanolle et al. \(1996\)](#) appeared to indicate a close relationship of C282Y to hemochromatosis, the implication of the H63D variant was not clear.

[Beutler et al. \(1996\)](#) reported mutation analysis of 147 patients with hereditary hemochromatosis and 193 controls; 121 (82.3%) HH patients were homozygous for the C282Y mutation, while 10 (6.8%) were heterozygous. All of the C282Y homozygous patients were also homozygous for the wildtype nucleotide 187C (see H63D; [235200.0002](#)), and all C282Y heterozygotes had at least 1 copy of 187C. Thus, the 2 nucleotides, 845 and 187, were in complete linkage disequilibrium: nucleotide 187 was a

Entrez Gene
 Nomenclature

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Clinical Synopsis
 Gene map

Done

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OMIM
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Display Allelic Variants Show 20 Send to

All: 1 OMIM dbSNP: 1 OMIM UniSTS: 1

+235200
HEMOCHROMATOSIS; HFE

GeneTests, Links

ALLELIC VARIANTS
 (selected examples)

- 0001 HEMOCHROMATOSIS [HFE, CYS282TYR] dbSNP PORPHYRIA VARIEGATA, INCLUDED
 HEMOCHROMATOSIS, JUVENILE, DIGENIC, INCLUDED
 ALZHEIMER DISEASE, SUSCEPTIBILITY TO, INCLUDED
- 0002 HEMOCHROMATOSIS [HFE, HIS63ASP] dbSNP
- 0003 HEMOCHROMATOSIS [HFE, SER65CYS] dbSNP
- 0004 HFE INTRONIC POLYMORPHISM [HFE, 5569G-A]
- 0005 HFE POLYMORPHISM [HFE, VAL53MET] dbSNP
- 0006 HFE POLYMORPHISM [HFE, VAL59MET] dbSNP
- 0007 PORPHYRIA VARIEGATA [HFE, GLN127HIS] dbSNP
- 0008 HEMOCHROMATOSIS [HFE, ARG330MET]
- 0009 HEMOCHROMATOSIS [HFE, ILE105THR] dbSNP
- 0010 HEMOCHROMATOSIS [HFE, GLY93ARG] dbSNP
- 0011 HEMOCHROMATOSIS [HFE, GLN283PRO]

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Search Result for OMIM# 235200

HFE- Associated Hereditary Hemochromatosis [Testing](#) [Research](#) [Reviews](#) [Resources](#)

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HFE-Associated Hereditary Hemochromatosis

Select all clinical laboratories

Laboratories offering clinical testing:	Analysis of the entire coding region: Sequence analysis	Sequence analysis of select exons	Analysis of the entire coding region: Mutation scanning	Targeted mutation analysis	Prenatal diagnosis	Clinical confirmation of mutations identified in a research lab	Carrier testing
ARUP Laboratories Molecular Genetics Laboratory Salt Lake City, UT				•			•
Elaine Lyon, PhD; Rong Mao, MD; Edward R Ashwood, MD; Marzia Pasquali, PhD; Pinar Bayrak-Toydemir, MD, PhD				•			•
Acibadem Healthcare Group Acibadem Genetic Diagnostic Center Istanbul, Turkey				•			•
Ender Altioik, MD, PhD				•			
Alberta Children's Hospital Molecular Diagnostic Laboratory Calgary, Alberta, Canada				•			
Peter Bridge, PhD, FCCMG, FACMG; Jillian Parboosingh, PhD, FCCMG				•			
Baylor College of Medicine Medical Genetics Laboratories Houston, TX				•			
Christine M Eng, MD, FACMG; William E O'Brien, PhD; Lee-Jun Wong, PhD; Sau W. Cheung, PhD				•			
Biolab spol. s.r.o. Molecular Biology Laboratory Klatovy, Czech Republic				•			
Frantisek Musil, MUDr				•			
BloodCenter of Wisconsin Molecular Diagnostics Laboratory Milwaukee, WI				•			
Daniel B Bellissimo, PhD							
Boston University School of Medicine Center for Human Genetics							

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Search Result for OMIM# 235200

HFE- Associated Hereditary Hemochromatosis [Testing](#) [Research](#) [Reviews](#) [Resources](#)

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HFE-Associated Hereditary Hemochromatosis

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Robin L Bennett, MS
Arno G Motulsky, MD

About the Authors

Initial Posting: 3 April 2000 **Last Update:** 4 December 2006

Summary

Disease characteristics. *HFE*-associated hereditary hemochromatosis (*HFE*-HHC) is characterized by inappropriately high absorption of iron by the gastrointestinal mucosa, resulting in excessive storage of iron particularly in the liver, skin, pancreas, heart, joints, and testes. Abdominal pain, weakness, lethargy, and weight loss are early symptoms. Without therapy, males may develop symptoms between age 40 and 60 years and females after menopause. Hepatic fibrosis or cirrhosis may occur in untreated individuals after age 40 years. Other findings in untreated individuals may include progressive increase in skin pigmentation, diabetes mellitus, congestive heart failure and/or arrhythmias, arthritis, and hypogonadism.

This description applies to individuals with clinical expression of *HFE*-HHC. A large, but yet as undefined, fraction of **homozygotes** for *HFE*-HHC do not develop clinical symptoms (i.e., **penetrance** is low).

Diagnosis/testina. The diagnosis of *HFE*-HHC in individuals with clinical symptoms consistent with *HFE*-HHC and/or biochemical

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OMIM Entries for HFE-Associated Hereditary Hemochromatosis

235200	HEMOCHROMATOSIS; HFE
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Genomic Databases for HFE-Associated Hereditary Hemochromatosis

Gene Symbol	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
<i>HFE</i>	235200	HFE	<i>HFE</i>	119309	<i>HFE</i>

For a description of the genomic databases listed, click [here](#).

Normal allelic variants: The *HFE* gene is about 13 kb in size and contains seven exons [Feder et al 1996 , Albig 1998]; *HFE* gives rise to at least eleven alternative transcripts encoding four to seven exons.

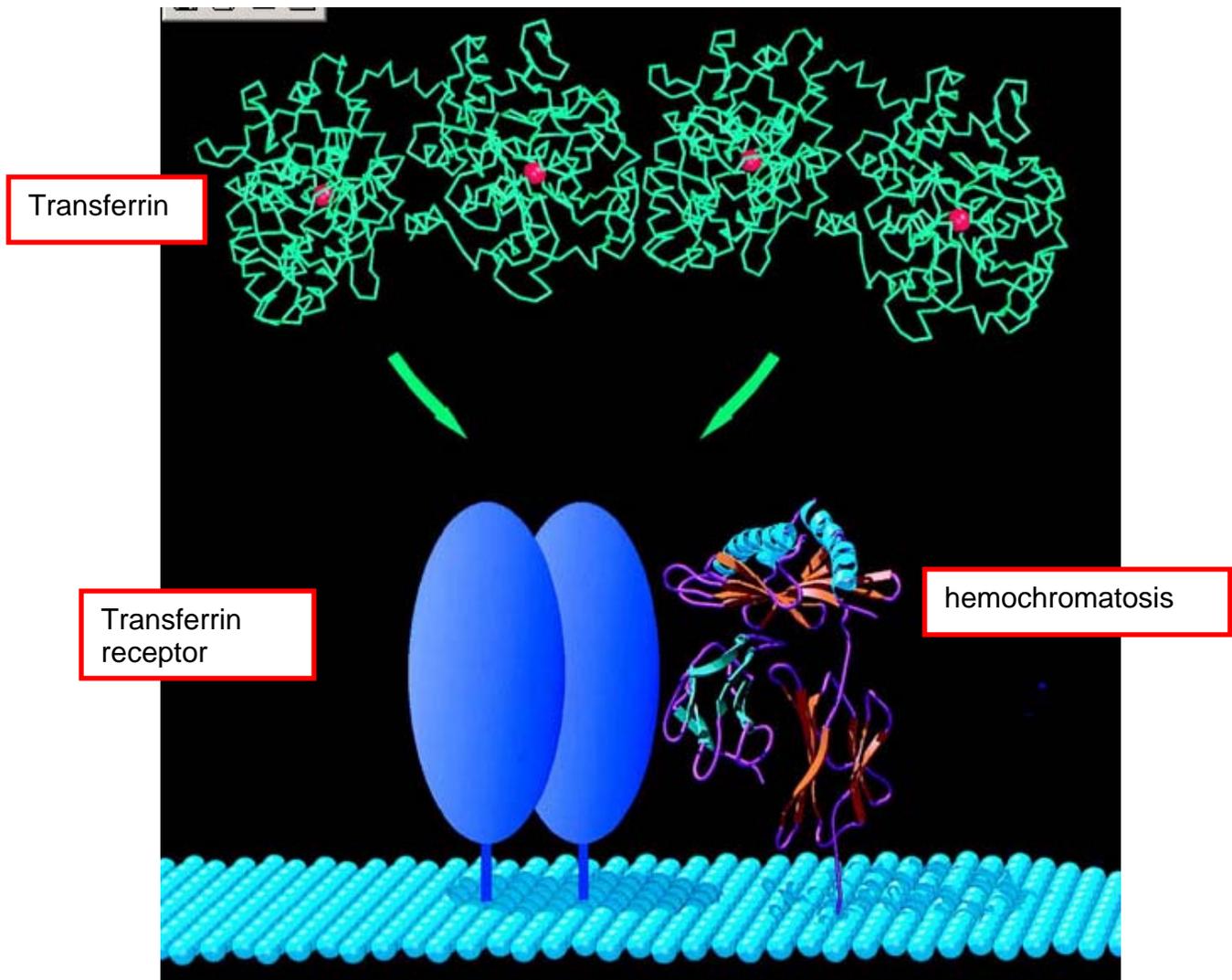
Pathologic allelic variants: At least 28 distinct mutations have been reported, most being missense or nonsense mutations. missense mutations account for the vast majority of disease-causing alleles in the population:

- Cys282Tyr (p.C282Y; nucleotide 845G>A). This missense mutation removes a highly conserved cysteine residue that normally forms an intermolecular disulfide bond with beta-2-microglobulin, and thereby prevents the protein from being expressed on the cell surface.
- His63Asp (p.H63D; nucleotide 187C>G). This missense mutation may alter a pH-dependent intramolecular salt bridge, possibly affecting interaction of the HFE protein with the transferrin receptor.

Normal gene product: The largest predicted primary translation product is 348 amino acids, which gives rise to a mature protein of about 321 amino acids after cleavage of the signal sequence. The HFE protein is similar to HLA Class I molecules at the primary [Feder et al 1996] and tertiary structure [Lebron et al 1998] levels. The mature protein is expressed on the cell surface as a heterodimer with beta-2-microglobulin, and this interaction is necessary for normal presentation on the cell surface. The normal HFE protein binds to transferrin receptor 1 on the cell surface and may reduce cellular iron uptake; however, the exact means by which the HFE protein regulates iron uptake is as yet unclear [Fleming et al 2004].

Abnormal gene product: The p.C282Y mutation destroys a key cysteine residue that is required for disulfide bonding with beta-2-microglobulin. As a result, the HFE protein does not mature properly and becomes trapped in the endoplasmic reticulum and Golgi apparatus, leading to decreased cell-surface expression. The mechanistic basis for the phenotypic effect of other HFE mutations is not clear at present.

Resources



Bacon et al. *Gastroenterology*, 116:193-207, Figure 4

The hemochromatosis protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin.

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+235200
HEMOCHROMATOSIS; HFE

Alternative titles; symbols

HLAH
HEMOCHROMATOSIS, HEREDITARY; HH
HFE GENE, INCLUDED; HFE, INCLUDED

Gene map locus [6p21.3](#)

TEXT

DESCRIPTION

The clinical features of hemochromatosis include cirrhosis of the liver, diabetes, hypermelanotic pigmentation of the skin, and heart failure. Predisposing to hepatocellular carcinoma (HCC; [114550](#)), complicating cirrhosis, is responsible for about one-third of deaths in affected homozygotes. Since hemochromatosis is a relatively common disease, this is a form of preventable cancer.

Links

- PubMed
- Gene
- GEO Profiles
- HomoloGene
- OMIA
- Free in PMC
- PubMed (calculated)
- PubMed (cited)
- Gene Genotype
- GeneView in dbSNP
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All: 34 Current Only: 34 Genes Genomes: 30 SNP GeneView: 25

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1: **HFE**

Official Symbol: HFE and Name: hemochromatosis [*Homo sapiens*]
 Other Aliases: HFE1, HH, HLA-H, MGC103790, dJ221C16.10.1
 Other Designations: MHC class I-like protein HFE; hemochromatosis protein; hereditary hemochromatosis protein HLA-H
 Chromosome: 6; Location: 6p21.3
 MIM: 235200
 GeneID: 3077

Genomic regions, transcripts, and products

Go to [reference sequence details](#)

NC_000006.10

[26195427] 5' [26205038] 3'

NM_139805.2
 NM_139802.2
 NM_00410.3
 NM_139804.2
 NM_139803.2
 NM_139809.2
 NM_139807.2
 NM_139808.2
 NM_139810.2
 NM_139811.2
 NM_139806.2

NP_620574 isoform 5 precursor
 NP_620571 isoform 2 protein
 NP_009401 isoform 1 protein
 NP_620573 isoform 4 protein
 NP_620572 isoform 3 protein
 NP_620578 isoform 9 protein
 NP_620576 isoform 7 protein
 NP_620577 isoform 8 protein
 NP_620579 isoform 10 protein
 NP_620580 isoform 11 protein
 NP_620575 isoform 6 protein

Links

- FASTA
- GENEPT
- Blink
- Conserved Domains

Genomic context

chromosome: 6; Location: 6p21.3

[26153610] [26216343]

HIST1H3C HIST1H3C HFE HIST1H3C HIST1H1T

Map Viewer
 Nucleotide
 OMIA
 OMIM
 Full text in PMC
 Probe
 Protein
 PubMed
 PubMed (GeneRIF)
 SNP
 SNP: Genotype
 ✓ SNP: GeneView
 Taxonomy
 UniSTS
 AceView
 CCDS
 Evidence Viewer
 GDB
 GeneTests for MIM: 235200
 HGMD
 HGNC
 HPRD
 KEGG
 MGC
 ModelMaker
 UniGene
 LinkOut

Entrez Gene Info
 Feedback

NCBI

BLAST Protein Structure PubMed Taxonomy
Genome Nucleotide 3D-Domains Books Help

Query: gi:4504377 hemochromatosis protein isoform 1 precursor [Homo sapiens]
Matching gi: 1469790, 22854810, 83323630, 20250786, 80748852, 1890180, 2088551, 2370111, 2497915, 119575928, 15115850, 38502807, 109658506, 109658670, 112053064, 112088318, 14100030, 57114069, 29709343, 11094315

Hide identical Best hits Common Tree Taxonomy Report 3D structures CDD-Search Gl list Run BLAST

200 BLAST hits to 21 unique species Sort by taxonomy proximity

Archaea 0 Bacteria 199 Metazoa 0 Fungi 0 Plants 0 Viruses 0 Other Eukaryotae

Keep only [] Cut-Off 100 Select Reset New search by GI: 4504377 Go

348 aa

SCORE	E	ACCESSION	GI	PROTEIN DESCRIPTION
<u>Conserved Domain Database hits</u>				
1870	31	AAC51823	1469790	HLA-H
1870	29	AAN09793	22854810	hereditary hemochromatosis [Pan troglodytes]
1870	31	CAB07442	1890180	HFE [Homo sapiens]
1870	31	AAB82083	2088551	hereditary hemochromatosis [Homo sapiens]
1870	31	CAA70934	2370111	HFE [Homo sapiens]
1870	31	Q30201	2497915	Hereditary hemochromatosis protein precursor (HLA-H)
1870	31	EAWS5524	119575928	hemochromatosis, isoform CRA_i [Homo sapiens]
1870	29	P60018	38502807	Hereditary hemochromatosis protein homolog precursor (HLA-H)
1870	31	AA117204	109658506	Hemochromatosis [Homo sapiens]
1870	31	AA117202	109658670	Hemochromatosis [Homo sapiens]
1870	29	NP_001...	57114069	hemochromatosis protein [Pan troglodytes]
1870	31	AAQ29572	11094315	hemochromatosis termination variant terE6; HFE [Homo sapiens]
1776	31	AAH74721	50960016	HFE protein [Homo sapiens]
1772	31	AAC62646	3695107	hemochromatosis splice variant del14E4 [Homo sapiens]
1772	31	EAWS5523	119575927	hemochromatosis, isoform CRA_h [Homo sapiens]
1772	31	NP_620575	21040347	hemochromatosis protein isoform 6 precursor [Homo sapiens]
1713	31	CAC67792	15485419	hemochromatosis protein [Homo sapiens]
1713	31	NP_620578	21040353	hemochromatosis protein isoform 9 precursor [Homo sapiens]
1713	31	EAWS5521	119575925	hemochromatosis, isoform CRA_f [Homo sapiens]
1694	26	XP_001...	109069866	PREDICTED: hemochromatosis protein isoform 9 [Macaca mulatta]
1681	26	XP_001...	109069868	PREDICTED: hemochromatosis isoform 7 [Macaca mulatta]

NCBI

BLAST Protein Structure PubMed Taxonomy
Genome Nucleotide 3D-Domains Books Help

Query: gi:4504377 hemochromatosis protein isoform 1 precursor [Homo sapiens]
Matching gi: 1469790, 22854810, 83323630, 20250786, 80748852, 1890180, 2088551, 2370111, 2497915, 119575928, 15115850, 38502807, 109658506, 109658670, 29709343, 11094315

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200 BLAST hits to 4 unique species Sort by taxonomy proximity

Archaea 0 Bacteria 200 Metazoa 0 Fungi 0 Plants 0 Viruses 0 Other Eukaryotae

Keep only [] Cut-Off 100 Select Reset New search by GI: 4504377 Go

348 aa

SCORE	E	ACCESSION	GI	PROTEIN DESCRIPTION
<u>Conserved Domain Database hits</u>				
1517	•	1A62C	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	•	1DE4A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Transfer
1517	•	1DE4D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Transfer
1517	•	1DE4G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Transfer
1517	•	1A62A	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
525	•	1B1IA	3891929	Chain A, The Crystal Structure Of H-2dd Mhc Class I In Compl
507	•	1S7RA	48425592	Chain A, Crystal Structures Of The Murine Class I Major Histo
507	•	1S7RD	48425595	Chain D, Crystal Structures Of The Murine Class I Major Histo
507	•	1S7SA	48425598	Chain A, Crystal Structures Of The Murine Class I Major Histo
507	•	1S7TA	48425601	Chain A, Crystal Structures Of The Murine Class I Major Histo
507	•	1S7TD	48425604	Chain D, Crystal Structures Of The Murine Class I Major Histo
507	•	1S7QA	48425589	Chain A, Crystal Structures Of The Murine Class I Major Histo

NCBI **Related Structures**

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Query: hemochromatosis protein isoform 1 precursor [Homo sapiens]
[gi: [4504377](#)]

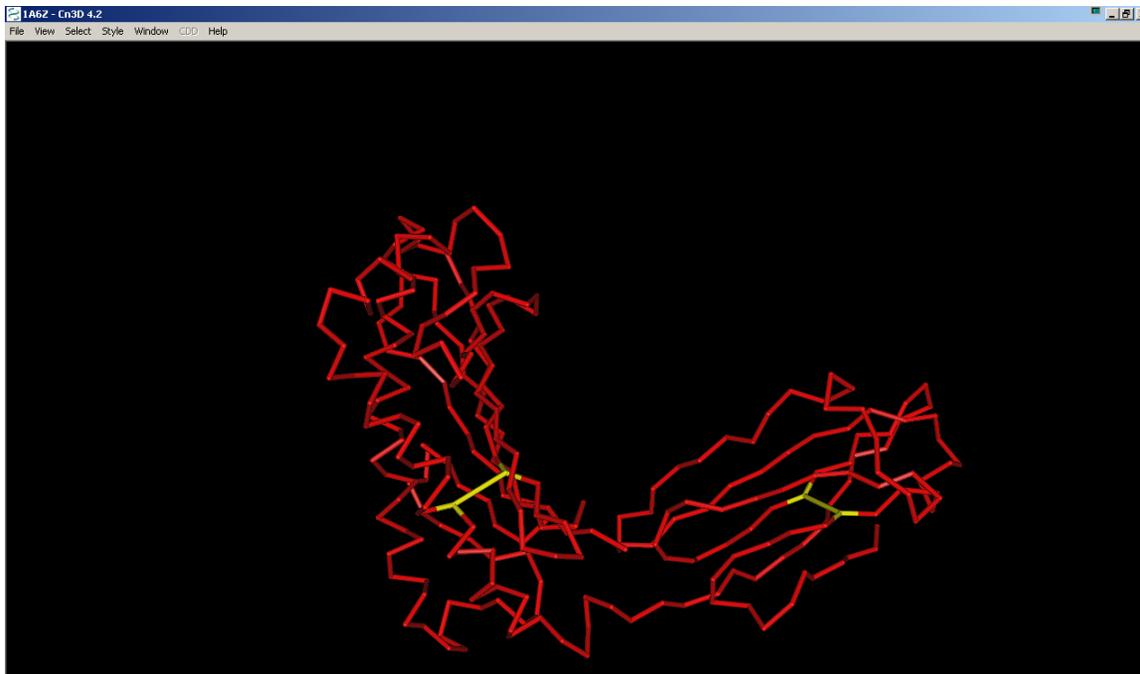
Structure: 1A6Z Chain C, Hfe (Human) Hemochromatosis Protein

Reference: [MMDB] [PubMed]

Get 3D Structure data to: **View in Cn3D** (To display structure, download [Cn3D](#))

E-value = 7e-168, Bit score = 588, Aligned length = 275, Sequence Identity = 100%

		10	20	30	40	50	60	70	80	
gi_4504377	23	RLLRSHSLHYLFMGASEQDLGLSLFEALGYVDDQLFVFDHESRRVEPRTPWVSSRISSQMWLQLS	QSLKGN	DMFTVDF	102					
1A6Z_C	1	RLLRSHSLHYLFMGASEQDLGLSLFEALGYVDDQLFVFDHESRRVEPRTPWVSSRISSQMWLQLS	QSLKGN	DMFTVDF	80					
		90	100	110	120	130	140	150	160	
gi_4504377	103	WTIMENHNHKSESH TLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPDTLDWRAAEPRAWPTKLEWERH	KIRARQ	NRAY	182					
1A6Z_C	81	WTIMENHNHKSESH TLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPDTLDWRAAEPRAWPTKLEWERH	KIRARQ	NRAY	160					



1A6Z - Sequence/Alignment Viewer

View Edit Mouse Mode Unaligned Justification Imports

1A6Z_C	KDKQPMDAKEFEFKDVL P NGDGT YQGWI T L AV P P GEEQR Y T Q V E H P G L D Q P L I V I W ~ ~ ~ ~ ~
gi_4504377	KDKQPMDAKEFEFKDVL P NGDGT YQGWI T L AV P P GEEQR Y T C Q V E H P G L D Q P L I V I W e p s p s g t l v i g v i s g i a v f v v i l f i g

gi_4504377, loc 282 block 1, Row 2

Problem 2:

<http://www.ncbi.nlm.nih.gov/Class/minicourses/pheno2.html>

Mutations in the HBB gene are associated with sickle cell anemia. A laboratory working on sickle cell anemia wants to elucidate the biochemical and structural basis for the function of the mutant HBB protein.

Step 1. Determining what is known about the HBB gene and protein (using Entrez Gene):

Search for 'HBB' in [Entrez Gene](#). One entry is for the human HBB gene. Retrieve the entry by clicking on the HBB link.

What is the location and orientation of the HBB gene on the human genome? List the genes adjacent to it. How many alternatively spliced products have been annotated for the HBB gene when the RefSeq mRNA entries were reviewed? List some of the HBB gene aliases. What are the phenotypes associated with the mutations in the HBB gene? Where are the mouse and rat HBB genes located?

What is the name and function of the protein encoded by the HBB gene? What is the conserved domain in the protein? To which cellular component(s) is the protein localized? Beta hemoglobin is a subunit of which protein? Name other subunit(s) in that protein.

Obtain the locations of exons and introns for each transcript by choosing "Gene Table" from the Display pull down menu. Go back to the description page.

Step 2. Determining other identified SNPs and their locations in the HBB gene:

From the Links menu on the top right hand side of the page, click on the "SNP: GeneView" to access a list of the known SNPs (reported in dbSNP). By default, the SNPs in the coding region of a gene are reported. Additional SNPs such as in the upstream region or the introns can be viewed by clicking on the "in gene region" button. Currently, how many **coding** SNPs are placed on the beta hemoglobin transcript NM_000518? How many of these have links to OMIM? We will concentrate on the Glu7Val mutant in the following analysis.

Step 3. Learning more about sickle cell anemia disease and its genetic testing:

Go back to the Entrez Gene report. Click on the OMIM link and then HBB link. What are the phenotypes caused by mutations in HBB, the absence of HBB and reduced amounts of HBB? What is the clinical synopsis of sickle cell anemia? What is its prominent feature? What is its mode of inheritance? How many allelic variants of the HBB gene have been reported? As mentioned in the OMIM report, the allelic variants are listed for the mature beta hemoglobin protein which lacks

an initiator methionine. Hence, the allelic variants in the OMIM report are off by one amino acid compared to the precursor protein in NP_000509. Click on the Allelic Variant “View list” to get information about the mutant proteins from patients. Is the Glu6Val variant mentioned in the list? (It is the variant number 0243). Which phenotype does it cause? What is the name of the mutant hemoglobin (hemoglobin S).

Click on the Gene Tests link at top of the page. Identify some of the laboratories performing the clinical testing for sickle cell anemia. Now refer to the Reviews section for Sickle Cell Disease, Mutation analysis is available for which of the HBB alleles? List one explanation for the sickle cell anemia phenotype caused by the Glu7Val mutant beta hemoglobin.

Step 4. Elucidating the biochemical and structural basis for the function of the wild type and mutant proteins, if possible:

A. Information about the wild type protein

Go back to the OMIM report by clicking the back button on the web browser. Go to the Gene report through the Links menu. Based on the RefSeq summary and the PubMed articles, describe the biochemical functions of beta hemoglobin and hemoglobin S. PubMed articles in the Entrez Gene report indicate that the 3-D structure of hemoglobin S is available.

Let us first take a look at the structure of the wild type protein. Click on the NP_000509 protein link and select Blink. Click on the “Show identical” button and then on the “3D structures” button. The output contains a list of similar proteins with 3D structures known. The entry, 1DXTD, represents the structure of deoxyhemoglobin chain D. Click on the blue dot next to 1DXTD to get the sequence alignment of the query protein to the D chain of 1DXTD. To view the 3D structure of dexoxyhemoglobin (all chains, 2 alpha and 2 beta), click on the MMDB link. That takes us to the MMDB structure summary page for 1DXT. Access the PDB entry, by clicking on 1DXT. Note that the chains A and C in the structure represent alpha chains, and B and D represent beta chains. Go back to the MMDB summary page. View the deoxyhemoglobin tetramer by clicking on the "View 3D Structure button".

Search for the structure of the mutant (deoxyhemoglobin S) in the structure database. Two entries, 1HBS and 2HBS, are retrieved. Click on the 2HBS link. Then click on the PubMed link from the MMDB and PDB entries (under Reference). The abstracts indicate that the mutated valine residue of the beta chain contacts with another hemoglobin tetramer molecule to form hemoglobin polymers which are building blocks for the sickle cell fiber.

B. To show the side chains of the mutant residue and view its interaction with another hemoglobin molecule: Download the structure 2HBS by clicking on View 3D Structure. For easier viewing, remove the helix and strand objects using Style--Edit global style, and unclick the boxes next to the Helix objects and Strand objects. Highlight valine 6 from the H chain (one of the beta chains). To show the side chains of the residue, use the Structure window--Style--Annotate--new. Give a name to this annotation such as "valine" and then click on Edit Style. Change the protein backbone "Rendering" to "Space Fill", Color Scheme to "charge" or "hydrophobicity". Repeat these steps for the Protein Sidechains row and click the Protein Sidechains on. To show the amino acid number, choose the Labels panel, and change the Protein Backbone spacing to 1. Click on the "Done", "OK" then "Done" buttons. The valine interacts with a pocket between the two helices on another tetramer. Identify the residues from other molecules within 4 angstroms of the valine, use Show/Hide--Select by distance--other molecules. To unselect the highlighted residues, click on the white portion of the sequence window.

You can now easily explain why the Glu7Val mutant has an altered function.

Summary:

This mini-course describes how to obtain information about the HBB gene, known SNPs in it, and elucidate the biochemical and structural basis for the function of the wild type and Glu7Val mutant protein.

Summary: 1. The HBB gene is located on chromosome 11 and has no alternatively spliced products annotated.
2. Currently, there are 301 coding SNPs annotated on the protein NP_000509.
3. The Glu7Val mutant is associated with the sickle cell anemia disease and the site of mutation is used in sickle cell anemia genetic testing.
4. The HBB gene encodes beta hemoglobin which is a part of hemoglobin along with alpha hemoglobin. Hemoglobin is a tetramer consisting of 2 beta and 2 alpha chains. Mutation of the 7th negatively charged amino acid, glutamic acid, to hydrophobic valine leads to polymerization of hemoglobin forming a sickle fiber that changes the shape of red blood cells leading to sickle cell anemia.

NCBI Entrez Gene

Search: Gene for HBB [Go] [Clear]

Entrez Gene is a searchable database of genes, from RefSeq genomes, and defined by sequence and/or located in the NCBI Map Viewer

News Query by accession with version number. [News archives...](#)

Sample Searches

Find genes by...	Search text
free text	human muscular dystrophy
partial name and multiple species	transporter[title] AND ("Drosophila melanogaster"[orgn] OR "Mus musculus"[orgn])
chromosome and symbol	(H[chr] OR 2[chr]) AND adh*[sym]
associated sequence accession number	M11313[accn]
gene name (symbol)	BRCA1[sym]

NCBI Entrez Gene

Search: Gene for HBB [Go] [Clear] [Save Search]

Display: Summary Show: 20 Send to:

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- 1: [Hbb](#) Links
Official Symbol: Hbb and **Name:** hemoglobin beta chain complex [*Mus musculus*]
Chromosome: 7; **Location:** 7 50.0 cM
GeneID: 15127
- 2: [HBB](#) Order cDNA clone, Links
Official Symbol: HBB and **Name:** hemoglobin, beta [*Homo sapiens*]
Other Aliases: CD113t-C, HBD
Other Designations: beta globin; beta globin chain
Location: 11p15.5
Chromosome: 11 **Annotation:** NC_000011.8 (5204876..5203271, complement)
MIM: 141900
GeneID: 3043
- 3: [Hbb](#) Order cDNA clone, Links
Official Symbol: Hbb and **Name:** hemoglobin beta chain complex [*Rattus norvegicus*]
Other Designations: Hemoglobin, beta, III beta-1 globin, III beta-2 globin
Location: 1q22
Chromosome: 1 **Annotation:** NC_005100.2 (161620192..161618781, complement)
GeneID: 24440

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All: 1 Current Only: 1 Genes Genomes: 1 SNP GeneView: 1

1: HBB hemoglobin, beta [Homo sapiens]

GeneID: 3043 updated 12-May-2007

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SNP

SNP: Genotype

SNP: GeneView

Taxonomy

UniSTS

AcView

CCDS

Evidence Viewer

GDB

GeneTests for MIM: 141900

Globin Gene Server

HGMD

HGNC

HPRD

KSCC

Official Symbol HBB provided by HGNC

Official Full Name hemoglobin, beta provided by HGNC

Primary source HGNC:4827

See related HPRD:00786; MIM:141900

Gene type protein coding

RefSeq status Reviewed

Organism Homo sapiens

Lineage Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

Also known as HBD; CD113t-C

Summary The alpha (HBA) and beta (HBB) loci determine the structure of the 2 types of polypeptide chains in adult hemoglobin, Hb A. The normal adult hemoglobin tetramer consists of two alpha chains and two beta chains. Mutant beta globin causes sickle cell anemia. Absence of beta chain causes beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. The order of the genes in the beta-globin cluster is 5'-epsilon -- gamma-G -- gamma-A -- delta -- beta--3'.

Genomic regions, transcripts, and products

(minus strand) Go to [reference sequence details](#)

Genomic context

chromosome: 11; Location: 11p15.5

See HBB in MapViewer

Bibliography

Related Articles in PubMed

PubMed links

GeneRIFs: Gene References Into Function

What's a GeneRIF?

incapable of overcoming the intrinsic mechanisms governing gamma-gene silencing in this context

43. multiple interactions between the locus control region and the beta-globin gene are required to maintain the appropriate spatial configuration in vivo

44. undecamer quasi-palindromic sequence d(TGGGGACCCCA) (HPA11) and its reported polymorphic (SNP) version d(TGGGGACCCCA) (HPG11) exist in hairpin-duplex equilibria

45. in a study of 918 chromosomes for mutations leading to beta-thalassemia and sickle cell anemia in postnatal and prenatal cases, one new Hb variant and one new mutation, Cod 3 (+T) were found. Chromosome abnormalities in fetuses were also documented.

46. Sickle hemoglobin polymer stability probed by triple and quadruple mutant hybrids (Hemoglobin S)

47. Results report a detailed analysis of replicator sequences that dictate initiation of DNA replication from the human beta-globin locus.

48. genotypes in Albanian patients affected by beta-globin gene disorders

49. developmentally related activation of human beta-like globin genes in human and transgenic mice hematopoietic progenitor cells is preceded by a wave of gene-specific histone H3 hyperacetylation and K4 dimethylation

Submit: [New GeneRIF](#) [Correction](#)

KEGG

MGC

ModelMaker

PharmGKB

UniGene

LinkOut

Entrez Gene Info

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Interactions				
Orc2 interacts with beta-globin origin.				
NC_000011.8	NP_006181.1	ORC2L	BIND	PubMed
Beta-globin interacts with pol II.				
NC_000011.8	NP_000928.1	POLR2A	BIND	PubMed
Ku80 interacts with beta-globin origin.				
NC_000011.8	NP_066964.1	XRCC5	BIND	PubMed
NP_000509.1	NP_000508.1	HBA2	HPRD	PubMed
NP_000509.1	NP_000509.1	HBB	HPRD	PubMed
NP_000509.1	Hemoglobin zeta	HBZ	HPRD	PubMed
NP_000509.1	Haptoglobin	HP	HPRD	PubMed
Affinity Capture-MS; in vitro				
BioGRID:109293	BioGRID:109290	HBA2	BioGRID	PubMed
Affinity Capture-MS; in vitro				
BioGRID:109293	BioGRID:109293	HBB	BioGRID	PubMed
Affinity Capture-MS; in vitro				
BioGRID:109293	BioGRID:109300	HBZ	BioGRID	PubMed
in vivo				
BioGRID:109293	BioGRID:109480	HP	BioGRID	PubMed
in vitro				
BioGRID:109293	BioGRID:109487	HPR	BioGRID	PubMed

General gene information
Markers
<p>STS-L48931(e-PCR) Links: UniSTS:16426 Alternate names: RH39984; sts-L48931</p> <p>RH41842(e-PCR) Links: UniSTS:41617 Alternate names: STS-F17257; sts-F17257</p> <p>RH69634(e-PCR) Links: UniSTS:50848 Alternate name: N57637</p> <p>D11F194S1E(e-PCR) Links: UniSTS:58277 Alternate names: D11F1941E; GDB:451709; RH27396</p> <p>D11S1382(e-PCR) Links: UniSTS:148642 Alternate name: GDB:216826</p> <p>GDB:177071(e-PCR) Links: UniSTS:154822</p> <p>GDB:177422(e-PCR)</p>
Phenotypes
<p>Erythremias, beta- MIM: 141900</p> <p>Heinz body anemias, beta- MIM: 141900</p> <p>HPFH, deletion type MIM: 141900</p> <p>Methemoglobinemias, beta- MIM: 141900</p> <p>Sickle cell anemia MIM: 141900</p> <p>Thalassemia-beta, dominant inclusion-body MIM: 603902</p> <p>Thalassemias, beta- MIM: 141900</p>

GeneOntology Provided by GOA

Function	Evidence
heme binding	IEA
hemoglobin binding	IDA PubMed
iron ion binding	IEA
metal ion binding	IEA
molecular_function	ND
oxygen binding	IEA
oxygen binding	IDA PubMed
oxygen transporter activity	NAS PubMed
oxygen transporter activity	IEA
selenium binding	IDA PubMed

Process	Evidence
biological_process	ND
nitric oxide transport	NAS PubMed
oxygen transport	IEA
oxygen transport	NAS PubMed
oxygen transport	TAS PubMed
positive regulation of nitric oxide biosynthetic process	NAS PubMed
transport	IEA

Component	Evidence
hemoglobin complex	IEA
hemoglobin complex	NAS PubMed
hemoglobin complex	TAS PubMed

General protein information ↑ ?

Names
 beta globin
 beta globin chain

NCBI Reference Sequences (RefSeq) ↑ ?

RefSeqs maintained independently of Annotated Genomes

These reference sequences exist independently of genome builds. [Explain](#)

Genomic

1. **NG_000007.3 Reference**

Range	70545..72150
Download	GenBank FASTA

mRNA and Protein(s)

1. **NM_000518.4--NP_000509.1 beta globin**

Source sequence(s)	L48217
Consensus CDS	CCDS7753.1
Conserved Domains (1)	summary
cd01040	globin; Globins are heme proteins, which bind and transport oxygen.
Location:5-142	
Blast Score:277	

RefSeqs of Annotated Genomes: Build 36.2

The following sections contain reference sequences that belong to a specific genome build. [Explain](#)

Reference assembly

Genomic

1. **NC_000011.8 Reference assembly**

Range	5204877..5203272, complement
Download	GenBank FASTA

2. **NT_009237.17**

Range	4035542..4033937, complement
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Genomes: 1 SNP GeneView: 1

Homo sapiens] updated 12-May-2007 Entrez Gene Home

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Display Gene Table Show 5 Send to

All: 1 Current Only: 1 Genes Genomes: 1 SNP GeneView: 1

1: HBB hemoglobin, beta [Homo sapiens]

GeneID: 3043 updated 12-May-2007

RefSeq status: Reviewed
total gene size: 1606 bp

Genomic regions, transcripts, and products

(minus strand) Go to reference sequence details

mRNA bp exons Protein aa exons
NM_000518.4 626 3 NP_000509.1 148 3

Exon information:
NM_000518.4 length: 626 bp, number of exons: 3
NP_000509.1 length: 147 aa, number of exons: 3

EXON		Coding EXON		INTRON	
coords	length	coords	length	coords	length
1 - 142	142 bp	51 - 142	92 bp	143 - 272	130 bp
273 - 495	223 bp	273 - 495	223 bp	496 - 1345	850 bp
1346 - 1606	261 bp	1346 - 1474	129 bp		

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- KEGG
- MGC
- ModelMaker
- PharmKB
- UniGene
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Entrez Gene Info

Feedback

NCBI Single Nucleotide Polymorphism

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

Search for SNP on NCBI Reference Assembly

Search Entrez SNP for Go

BUILD 127 SNP linked to Gene **HBB** (geneID:3043) Via Contig Annotation

Send rs# on all gene models to Batch Query Download all rs# to file: [GENE GENOTYPE REPORT](#)

Gene Model (mRNA alignment) information from genome sequence

Total gene model (contig mRNA transcript): 2

mRNA	transcript	protein	mRNA orientation	Contig	Contig Label	List SNP
NM_000518	minus strand	NP_000509	reverse	NT_009237	reference	<- currently shown
NM_000518	minus strand	NP_000509	reverse	NW_925006	Celera	View snp on GeneModel

in gene region cSNP has frequency double hat haplotype tagged

gene model	Contig Label	Contig	mRNA	protein	mRNA orientation	transcript	snp count
(contig mRNA transcript):	reference	NT_009237	NM_000518	NP_000509	reverse	minus strand	301, coding

Region	Contig position	mRNA pos	dbSNP rs# cluster id	Heterozygosity	Validation	3D	OMIM	Function	dbSNP allele	Protein residue	Codon pos	Amino acid pos
exon_3	4034072	491	rs33985739	N.D.				nonsynonymous	A	Gln [Q]	3	147
								nonsynonymous	G	Gln [Q]	3	147
								contig reference	C	His [H]	3	147
	4034073	490	rs33954264	N.D.				nonsynonymous	C	Pro [P]	2	147
								nonsynonymous	G	Arg [R]	2	147
								nonsynonymous	T	Leu [L]	2	147
	4034074	489	rs33961444	N.D.				contig reference	A	His [H]	2	147
								nonsynonymous	G	Asp [D]	1	147
								nonsynonymous	T	Tyr [Y]	1	147

	4035471	72	rs34948328	N.D.				nonsynonymous	A	Lys [K]	1	8
				N.D.				contig reference	G	Glu [E]	1	8
	4035473	70	rs3334	0.068	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	Yes	nonsynonymous	C	Ala [A]	2	7
				0.068	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	Yes	nonsynonymous	T	Val [V]	2	7
				0.068	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	Yes	contig reference	A	Glu [E]	2	7
	4035474	69	rs33920162	N.D.				nonsynonymous	A	Lys [K]	1	7
				N.D.				nonsynonymous	C	Gln [Q]	1	7
				N.D.				contig reference	G	Glu [E]	1	7
	4035475	67	rs33920098	N.D.				nonsynonymous	C	Ala [A]	5	6

NCBI Entrez Gene

Search Gene for Go Clear

Display Gene Table Show 5 Send to

All: 1 Current Only: 1 Genes Genomes: 1 SNP GeneView: 1

1: **HBB hemoglobin, beta** [*Homo sapiens*]

GeneID: 3043 updated 12-May-2007 Entrez Gene Home

Summary

Official Symbol HBB provided by HGNC

Official Full Name hemoglobin, beta provided by HGNC

Primary source HGNC:4827

See related HPRD:00786; MIM:141900

Gene type protein coding

RefSeq status Reviewed

Organism [Homo sapiens](#)

Lineage Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorhini; Catarrhini; Hominoidea; Homo

Also known as HBD; CD113t-C

Summary The alpha (HBA) and beta (HBB) loci determine the structure of the 2 types of polypeptide chains in adult hemoglobin, Hb A. The normal adult hemoglobin tetramer consists of two alpha chains and two beta chains. Mutant beta globin causes sickle cell anemia. Absence of beta chain causes beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. The order of the genes in the beta-globin cluster is 5'-epsilon -- gamma-G -- gamma-A -- delta -- beta--3'.

Genomic regions, transcripts, and products

(minus strand) Go to [reference sequence details](#)

NC_000011.8

52046777 5' 52032721 3'

NM_000518.4 SP_000589.1 CC037253.1

■ - coding region ■ - untranslated region

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Links: Order cDNA clone, Books, Conserved Domains, Genome, GEO Profiles, HomoloGene, Map Viewer, Nucleotide, OMIM, Full text in PMC, Probe, Protein, PubMed, PubMed (GeneRIF), SNP, SNP: Genotype, SNP: GeneView, Taxonomy, UniSTS, AceView, CCDS, Evidence Viewer, GDB, GeneTests for MIM: 141900, Globin Gene Server, HGMD, HGNC, HPRD, KEGG

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+141900 GeneTests, Links

HEMOGLOBIN-BETA LOCUS; HBB

Alternative titles; symbols

BETA-THALASSEMIA, INCLUDED

METHEMOGLOBINEMIA, BETA-GLOBIN TYPE, INCLUDED

ERYTHREMIA, BETA-GLOBIN TYPE, INCLUDED

Gene map locus [11p15.5](#)

TEXT

The alpha and beta loci determine the structure of the 2 types of polypeptide chains in adult hemoglobin, Hb A. Mutant beta globin that sickles causes sickle cell anemia (603903). Absence of beta chain causes beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. For clinical purposes, beta-thalassemia is divided into thalassemia major (transfusion dependent), thalassemia intermedia (of intermediate severity), and thalassemia minor (asymptomatic).

Patients with thalassemia major present in the first year of life with severe anemia; they are unable to maintain a hemoglobin level about 5 gm/dl. Clinical details of this disorder have been detailed extensively in numerous monographs and are summarized by Weatherall et al. (1995). Modell et al. (2000) found that about 50% of U.K. patients with beta-thalassemia major die before the age of 35 years, mainly because conventional iron-chelation therapy is too burdensome for full adherence.

To gain insight into the cellular and structural alterations of thalassaemic bone, Mahachoklertwattana et al. (2003) studied bone histomorphometry and biochemical and hormonal profiles in children and adolescents with suboptimally treated beta-thalassemia disease. Seventeen patients underwent iliac crest bone biopsy for histomorphometric analyses. Most patients had growth retardation and delayed bone age. Bone mineral density (BMD) was low especially at the lumbar spine. Serum IGF1 (147440) levels were almost always low. Bone histomorphometry revealed increased osteoid thickness, osteoid maturation time, and mineralization lag time, which indicate impaired bone matrix maturation and defective mineralization. In addition, iron deposits appeared along mineralization fronts and osteoid surfaces.

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- Allelic Variants
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- HomoloGene Links
- Nucleotide Links
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- PubChem BioAssay Links
- PMC Links
- Protein Links
- PubMed (calculated) Links
- PubMed (cited) Links

Gene m

TEXT

The alpha structure of the 2 types of polypeptide chains in adult hemoglobin, Hb A. Mutant beta globin that anemia (603903). Absence of beta chain causes beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thal purposes, beta-thalassemia is divided into thalassemia major (transfusion dependent), thalassemia intermedia (of intermediate severity).

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Display Clinical Synopsis Show 20 Send to

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HEMOGLOBIN--BETA LOCUS: HBB

Clinical Synopsis

Heme :

- Beta polypeptide hemoglobin chain
- Anemia
- Microcytosis
- Hypochromia
- Congenital dyserythropoietic anemia (Irish type)
- Mild hemolytic anemia (e.g. Hb Extremadura [141900.0074](#))
- Hemolytic microcytic anemia in compound heterozygosity with Hb C (e.g. Hb Korle-bu [141900.0153](#))
- Macrocytic hemolytic disease (e.g. Hb Redondo [141900.0404](#))
- Erythrocytosis (e.g. Hb Brigham [141900.0028](#))
- Congenital Heinz body anemia (e.g. Hb Bruxelles [141900.0033](#))
- Sickle cell anemia (homozygous Hb SS [141900.0243](#))
- Painful crises
- Aplastic crises
- Acute splenic sequestration
- Splenomegaly
- Dactylitis
- Ischemia
- Avascular necrosis
- Leg ulcers
- Cholelithiasis

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[CORIELL](#)
[HGMD](#)
[GAD](#)

- [0232 HEMOGLOBIN KAMIKI](#) [HBB, TRP140CTG]
- [0233 HEMOGLOBIN RALEIGH](#) [HBB, VAL1ALA]
- [0234 HEMOGLOBIN RANDWICK](#) [HBB, TRP15GLY]
- [0235 HEMOGLOBIN REGINA](#) [HBB, LEU96VAL]
- [0236 HEMOGLOBIN RICHMOND](#) [HBB, ASN102LYS]
- [0237 HEMOGLOBIN RIO GRANDE](#) [HBB, LYS8THR]
- [0238 HEMOGLOBIN RIVERDALE-BRONX](#) [HBB, GLY24ARG]
- [0239 HEMOGLOBIN RIYADH](#) [HBB, LYS120ASN]
- [HEMOGLOBIN KARATSU](#)
- [0240 HEMOGLOBIN ROSEAU-POINTE A PITRE](#) [HBB, GLU90GLY]
- [0241 HEMOGLOBIN ROTHSCHILD](#) [HBB, TRP07ARG]
- [0242 HEMOGLOBIN RUSH](#) [HBB, GLU101GLN]
- [0243 HEMOGLOBIN S](#) [HBB, GLU6VAL]
- [0244 HEMOGLOBIN S \(ANTILLES\)](#) [HBB, GLU6VAL AND VAL23ILE]
- [0245 HEMOGLOBIN S \(OMAN\)](#) [HBB, GLU6VAL AND GLU121LYS]
- [HEMOGLOBIN S/O \(ARAB\)](#)
- [0246 HEMOGLOBIN S \(PROVIDENCE\)](#) [HBB, GLU6VAL AND LYS82ASX]
- [0247 HEMOGLOBIN S \(TRAVIS\)](#) [HBB, GLU6VAL AND ALA142VAL]
- [0248 HEMOGLOBIN SABINE](#) [HBB, LEU91PRO]
- [0249 HEMOGLOBIN SAINT JACQUES](#) [HBB, ALA140THR]
- [0250 HEMOGLOBIN SAITAMA](#) [HBB, HIS117PRO]
- [0251 HEMOGLOBIN SAKI](#) [HBB, LEU14PRO]
- [0252 HEMOGLOBIN SAN DIEGO](#) [HBB, VAL109MET]
- [0253 HEMOGLOBIN SANTA ANA](#) [HBB, LEU88PRO]

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 Johns Hopkins University

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Search: OMIM for Go Clear

Limits Preview/Index History Clipboard Details

Display: Allelic Variants Show: 20 Send to:

All: 1 OMIM dbSNP: 0 OMIM UniSTS: 0

+141900 **HEMOGLOBIN--BETA LOCUS; HBB** [GeneTests, Links](#)

ALLELIC VARIANTS
 (selected examples)

- [0001 HEMOGLOBIN AALBORG](#) [HBB, GLY74ARG]
- [0002 HEMOGLOBIN ABRUZZO](#) [HBB, HIS143ARG]
- [0003 HEMOGLOBIN AGENOGI](#) [HBB, GLU90LYS]
- [0004 HEMOGLOBIN ALABAMA](#) [HBB, GLU39LYS]

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The result of your search (below) includes a group of related disorders with your search term in **bold** or an alphabetical listing of the individual entries that match your search term. For more information about search results, see [Interpreting Your Search Results](#).

Search Result for OMIM# 141900

Beta-Thalassemia [Testing](#) [Research](#) [Reviews](#) [Resources](#)
 Thalassemia Intermedia
 Thalassemia Major
 Thalassemia Minor

Hemoglobin E [Testing](#) [Resources](#)

Sickle Cell Disease [Reviews](#) [Resources](#)
Hemoglobin S Beta-Thalassemia [Testing](#)
 Hemoglobin SC [Testing](#)
 Hemoglobin SD [Testing](#)
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Hemoglobin S Beta-Thalassemia						
Select all clinical laboratories						
Laboratories offering clinical testing:						
	Analysis of the entire coding region: Sequence analysis	Analysis of the entire coding region: Mutation scanning	Targeted mutation analysis	Prenatal diagnosis	Clinical confirmation of mutations identified in a research lab	Carrier testing
ARUP Laboratories Molecular Genetics Laboratory Salt Lake City, UT Elaine Lyon, PhD; Rong Mao, MD; Edward R. Ashwood, MD; Marzia Pasquali, PhD; Pinar Bayrak-Toydemir, MD, PhD	•		•	•		•
Alberta Children's Hospital Molecular Diagnostic Laboratory Calgary, Alberta, Canada Peter Bridge, PhD, FCCMG, FACMG; Jillian Parboosingh, PhD, FCCMG	•		•			
Ambry Genetics Corp. Ambry Genetics Aliso Viejo, CA James Thompson, MD, PhD	•			•	•	•
Hamilton Regional Laboratory Medicine Program Molecular Diagnostic Genetics Hamilton, Ontario, Canada John S. Wavre, PhD						
Johns Hopkins Hospital DNA Diagnostic Laboratory Baltimore, MD Garry R. Cutting, MD; Steven J. Steinberg, PhD	•			•		
McGill University Health Centre - Montreal Children's Hospital Molecular Genetics Unit Montreal, Quebec, Canada Patrick Scott, PhD, FCCMG			•	•		•
Medizinisch Genetisches Zentrum Munich, Germany Elke Holinski-Feder, MD		•		•		
The Children's Hospital of Philadelphia Molecular Genetics Laboratory	•					

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Search Result for OMIM# 141900					
Beta-Thalassemia Testing Research Reviews Resources Thalassemia Intermedia Thalassemia Major Thalassemia Minor					
Hemoglobin E Testing Resources					
Sickle Cell Disease Reviews Resources Hemoglobin S Beta-Thalassemia Testing Hemoglobin SC Testing Hemoglobin SD Testing Hemoglobin SO Testing Hemoglobin SS Testing Research					
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Sickle Cell Disease

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Sickle Cell Disease

Author: MA Bender, MD, PhD
[About the Author / Author History](#)

Initial Posting: 15 September 2003 **Last Update:** 7 March 2006

Summary

Disease characteristics. Sickle cell disease (SCD) is characterized by variable degrees of hemolysis and intermittent episodes of vascular occlusion resulting in tissue ischemia and acute and chronic organ dysfunction. Pain and/or swelling of the hands or feet are often the earliest manifestations of sickle cell disease and usually occur in infants and young children. Consequences of hemolysis include chronic anemia, jaundice, predisposition to aplastic crisis, cholelithiasis, and delayed growth and sexual maturation. Vascular occlusion and tissue ischemia can result in acute and chronic injury to virtually every organ of the body, most significantly the spleen, brain, lungs, and kidneys.

Diagnosis/testing. The term **sickle cell disease** encompasses a group of symptomatic disorders associated with **mutations** in the **HBB gene** and defined by the presence of hemoglobin S (Hb S). Sickle cell anemia (Hb SS) accounts for 60-70% of sickle cell disease in the United States. The other forms of sickle cell disease result from co-inheritance of

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Data are compiled from the following standard references: Gene symbol from [HUGO](#); chromosomal locus, locus name, critical region, complementation group from [OMIM](#); protein name from [Swiss-Prot](#).

Sickle Cell Disease

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OMIM Entries for Sickle Cell Disease

141900	HEMOGLOBIN--BETA LOCUS; HBB
603903	SICKLE CELL ANEMIA

Genomic Databases for Sickle Cell Disease

Gene Symbol	Locus Specific	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
HBB	HBB	141900	HBB	HBB	119297	HBB

For a description of the genomic databases listed, [click here](#).

Molecular Genetic Pathogenesis

Hemoglobin S results from the substitution of valine for glutamic acid in the second **nucleotide** of the sixth **codon** of the β -globin chain. In deoxygenated sickle hemoglobin, an interaction between the β^6 valine and the complementary regions on adjacent molecules can result in the formation of highly ordered molecular polymers that aggregate and distort the shape of the red blood cells, making them brittle and poorly deformable. Sickle hemoglobin is also injurious to the red cell membrane, resulting in cellular dehydration, oxidative damage, and increased adherence to endothelial cells [[Gladwin & Rodgers 2000](#) , [Heibel 2000](#) , [Nagel 2001](#)]. Other factors contributing to the pathophysiology of sickle cell include leukocytosis, resulting in increased production of injurious cytokines and altered blood flow, coagulation abnormalities, and abnormal vascular regulation. The net result of these abnormalities is shortened red cell lifespan or hemolysis and intermittent vascular occlusion and a state of chronic inflammation.

Normal allelic variants: The **HBB gene**, which spans 1.6 kb, contains three **exons** and both 5' and 3' untranslated regions. The **HBB gene** is regulated by an adjacent 5' promoter, which contains a TATA, CAAT, and duplicated CACCC boxes, and an upstream regulatory element dubbed the **locus control region (LCR)**. A number of **transcription factors** regulate the function of the **HBB gene** including the erythroid Kruppel-like factor (EKLF) which binds the proximal CACCC box and whose knockout in the mouse leads to a thalassemia-like clinical picture. Many other factors are critical, but their **deletion** results in milder **phenotypes** because of compensation by other factors. The **HBB gene** is contained within the **HBB gene** cluster, which also includes the **genes** encoding the delta globin chain, A gamma and G gamma chains, and a pseudo **HBB gene** and epsilon.

Click on [defined terms](#); definition displays here.

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+141900
HEMOGLOBIN--BETA LOCUS; HBB

Alternative titles: symbols

BETA-THALASSEMIAS, INCLUDED
 METHEMOGLOBINEMIA, BETA-GLOBIN TYPE, INCLUDED
 ERYTHREMA, BETA-GLOBIN TYPE, INCLUDED

Gene map locus [11p15.5](#)

TEXT

The alpha and beta loci determine the structure of the 2 types of polypeptide chains in adult hemoglobin, Hb A. Mutant beta globin that sickles causes (603903). Absence of beta chain causes beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. For clinical

GeneTests Links

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- PubMed (cited)
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- GeneView in dbSNP
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Display Summary Show 20 Send to

All: 1 Current Only: 1 Genes Genomes: 1 SNP GeneView: 1

1: **HBB**

Official Symbol: HBB and Name: hemoglobin, beta [*Homo sapiens*]

Other Aliases: CD113t-C, HED

Other Designations: beta globin, beta globin chain

Location: 11p15.5

Chromosome: 11 Annotation: NC_000011.8 (5204876..5203271, complement)

MIM: 141900

GeneID: 3043

Order cDNA clone, Links

RefSeq status Reviewed

Organism [Homo sapiens](#)

Lineage *Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo*

Also known as HBD; CD113t-C

Summary The alpha (HBA) and beta (HBB) loci determine the structure of the 2 types of polypeptide chains in adult hemoglobin, Hb A. The normal adult hemoglobin tetramer consists of two alpha chains and two beta chains. Mutant beta globin causes sickle cell anemia. Absence of beta chain causes beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. The order of the genes in the beta-globin cluster is 5'-epsilon -- gamma-G -- gamma-A -- delta -- beta--3'.

Genomic regions, transcripts, and products

(minus strand) Go to [reference sequence details](#)

Genomic context

NC_000011.8

5204877 5' 5203272 3'

NP_000549.1 CC037753.1

■ - coding region ■ - untranslated region

Links

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- UniSTS
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- CCDS
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- GDB
- GeneTests for MIM: 141900
- Globin Gene Server
- HGMD
- HGNC
- HPRD
- KEGG
- MGC
- ModelMaker
- PharmGKB

PROTEIN LINKS

- FASTA
- GENE
- Blink
- Conserved Domains

NCBI

BLAST Protein Structure PubMed Taxonomy
Genome Nucleotide 3D-Domains Books Help

Query: gi|4504349 beta globin [Homo sapiens]
 Matching gi: 455997, 532506, 532507, 532508, 532509, 532510, 532511, 532512, 532513, 532514, 532515, 532516, 532517, 532518, 532519, 532520, 532521, 532522, 1066768, 1066771, 1066774, 1066777, 1066780, 22094827, 49168544, 49456781, 123992967, 123999887, 133711987, 30349217, 61361760, 13937929, 117645526, 117646600, 55635219, 56749856, 56749857, 56749858, 29437, 29441, 183830, 442846, 442848, 71727161, 71727163, 71727165, 71727167, 71727169, 71727171, 71727173, 71727175, 71727177, 71727179, 71727181, 71727183, 71727185, 71727187, 71727189, 71727191, 71727193, 71727195, 71727197, 71727199, 71727201, 71727203, 71727205, 71727207, 71727209, 71727211, 71727213, 71727215, 71727217, 71727219, 71727221, 71727223, 71727225, 71727227, 71727229, 2253432, 3993885, 119589212

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200 BLAST hits to 5 unique species [Sort by taxonomy proximity](#)

0 Archaea 0 Bacteria 193 Metazoa 0 Fungi 0 Plants 0 Viruses 0 Other Eukaryotae

Keep only Cut-Off 100 Select Reset New search by GI: 4504349 Go

147 aa

SCORE	P	ACCESSION	GI	PROTEIN DESCRIPTION
Conserved Domain Database hits				
780	31	AAA16334	455997	beta-globin [Homo sapiens]
780	31	AAA21100	532506	beta-globin
780	31	AAA21101	532507	beta-globin
780	31	AAA21103	532508	beta-globin
780	31	AAA21104	532509	beta-globin
780	31	AAA21105	532510	beta-globin
780	31	AAA21106	532511	beta-globin
780	31	AAA21107	532512	beta-globin
780	31	AAA21108	532513	beta-globin
780	31	AAA21102	532514	beta-globin
780	31	AAA21109	532515	beta-globin
780	31	AAA21110	532516	beta-globin
780	31	AAA21111	532517	beta-globin
780	31	AAA21112	532518	beta-globin
780	31	AAA21113	532519	beta-globin
780	31	AAA21114	532520	beta-globin
780	31	AAA21115	532521	beta-globin
780	31	AAA21116	532522	beta-globin

NCBI

BLAST Protein Structure PubMed Taxonomy
Genome Nucleotide 3D-Domains Books Help

Query: gi|4504349 beta globin [Homo sapiens]
 Matching gi: 455997, 532506, 532507, 532508, 532509, 532510, 532511, 532512, 532513, 532514, 532515, 532516, 532517, 532518, 532519, 532520, 532521, 532522, 1066768, 1066771, 1066774, 1066777, 1066780, 22094827, 49168544, 49456781, 123992967, 123999887, 133711987, 30349217, 61361760, 13937929, 117645526, 117646600, 55635219, 56749856, 56749857, 56749858, 29437, 29441, 183830, 442846, 442848, 71727161, 71727163, 71727165, 71727167, 71727169, 71727171, 71727173, 71727175, 71727177, 71727179, 71727181, 71727183, 71727185, 71727187, 71727189, 71727191, 71727193, 71727195, 71727197, 71727199, 71727201, 71727203, 71727205, 71727207, 71727209, 71727211, 71727213, 71727215, 71727217, 71727219, 71727221, 71727223, 71727225, 71727227, 71727229, 2253432, 3993885, 119589212

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200 BLAST hits to 1 unique species [Sort by taxonomy proximity](#)

0 Archaea 0 Bacteria 200 Metazoa 0 Fungi 0 Plants 0 Viruses 0 Other Eukaryotae

Keep only Cut-Off 100 Select Reset New search by GI: 4504349 Go

147 aa

SCORE	P	ACCESSION	GI	PROTEIN DESCRIPTION
Conserved Domain Database hits				
780	•	1DXTB	442846	Chain B, Hemoglobin (Deoxy) Mutant With Additional Met At The N-Terminus Of The Beta Cha
780	•	1DXTD	442848	Chain D, Hemoglobin (Deoxy) Mutant With Additional Met At The N-Terminus Of The Beta Cha
775	•	1G2XD	2218694	Chain D, Oxy T State Hemoglobin: Oxygen Bound At All Four Heme
775	•	1B8BB	493851	Chain B, Hemoglobin Thionville Alpha Chain Mutant With Val 1 Replaced By Glu And An Acet-
775	•	1B8BD	493853	Chain D, Hemoglobin Thionville Alpha Chain Mutant With Val 1 Replaced By Glu And An Acet-
775	•	1HBBE	494075	Chain B, Hemoglobin A (Deoxy, Low Salt, 100mM Cl)
775	•	1HBBD	494077	Chain D, Hemoglobin A (Deoxy, Low Salt, 100mM Cl)
775	•	1HGAB	494096	Chain B, Hemoglobin (T State, Deoxygenated)
775	•	1HGAD	494098	Chain D, Hemoglobin (T State, Deoxygenated)
775	•	1HGBE	494100	Chain B, Hemoglobin (T State, Aquomet)
775	•	1HGBD	494102	Chain D, Hemoglobin (T State, Aquomet)
775	•	1HGCE	494104	Chain B, Hemoglobin (T State, Alpha-Oxy)
775	•	1HGCD	494106	Chain D, Hemoglobin (T State, Alpha-Oxy)
775	•	1CBLA	576037	Chain A, Deoxy-Beta4 Hemoglobin ("r-Like" Quaternary Structure)
775	•	1CBLB	576038	Chain B, Deoxy-Beta4 Hemoglobin ("r-Like" Quaternary Structure)
775	•	1CBLC	576039	Chain C, Deoxy-Beta4 Hemoglobin ("r-Like" Quaternary Structure)
775	•	1CBLD	576040	Chain D, Deoxy-Beta4 Hemoglobin ("r-Like" Quaternary Structure)
775	•	1CBWA	576041	Chain A, Carboxymoxy-Beta4 Hemoglobin ("r-Like" Quaternary Structure)

NCBI **Related Structures**

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Query: beta globin [Homo sapiens]
[gi: 4504349]

Structure: 1DXT Chain D, Hemoglobin (Deoxy) Mutant With Additional Met At The N-Terminus Of The Beta Chains

Reference: [MMDB] [PubMed]

Get 3D Structure data to: View in Cn3D (To display structure, download Cn3D)

E-value = 6e-03, Bit score = 305, Aligned length = 147, Sequence Identity = 100%

		10	20	30	40	50	60	70	80
gi_4504349	1	MVHLTPEEKSAVTALWGRVNVDEVGGEALGRLLLVVYPTQRFESFGDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHL	80						
1DXT_D	1	MVHLTPEEKSAVTALWGRVNVDEVGGEALGRLLLVVYPTQRFESFGDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHL	80						

		90	100	110	120	130	140
gi_4504349	81	NLKGTFATLSELHCDKLRHVDPENFRLLGNVLCVLAHHPGKEFTPPVQAAAYQKVVAGVANALAHKYH	147				
1DXT_D	81	NLKGTFATLSELHCDKLRHVDPENFRLLGNVLCVLAHHPGKEFTPPVQAAAYQKVVAGVANALAHKYH	147				

NCBI **MMDB Structure Summary**

PubMed BLAST Structure Taxonomy OMIM Help? Cn3d

Reference: Kavanaugh JS, Rogers PH, Amone A [High-resolution X-ray study of deoxy recombinant human hemoglobins synthesized from beta-globins having mutated amino termini](#) *Biochemistry* v31, p.8640-8647
[All References](#)

Description: Hemoglobin (Deoxy) Mutant With Additional Met At The N-Terminus Of The Beta Chains.

Deposition: 1992/5/6

Taxonomy: [Homo sapiens](#)

MMDB: [815](#) PDB: [1DXT](#) Structure Neighbors: [VAST](#)

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Molecular components in the MMDB structure are listed below. The icons indicate macromolecular chains, 3D domains, protein classifications and ligands. Please hold the mouse over each icon for more information on the component.

Protein	Chain A	141
Domain Family	globin	

Protein	Chain B	147
Domain Family	globin	

Protein	Chain C	141
Domain Family	globin	

Protein	Chain D	147
Domain Family	globin	


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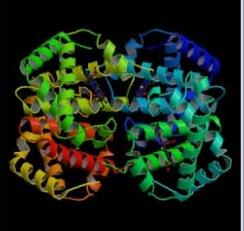
1DXT   Learn more: [M] DOI 10.2210/pdb1dxt/pdb

Red - Derived Information

Title	HIGH-RESOLUTION X-RAY STUDY OF DEOXY RECOMBINANT HUMAN HEMOGLOBINS SYNTHESIZED FROM BETA-GLOBINS HAVING MUTATED AMINO TERMINI						
Authors	Kavanaugh, J.S., Arnone, A.						
Primary Citation	Kavanaugh, J.S., Rogers, P.H., Arnone, A. High-resolution X-ray study of deoxy recombinant human hemoglobins synthesized from beta-globins having mutated amino termini. <i>Biochemistry</i> v31 pp.8640-8647, 1992 [Abstract]						
History	Deposition	1992-05-06	Release 1993-10-31				
Experimental Method	Type	X-RAY DIFFRACTION Data [EDS]					
Parameters	Resolution [Å]	R-Value	R-Free				
	1.70	0.160 (obs.)	n/a				
			Space Group P 2 ₁ (P 1 2 ₁ 1)				
Unit Cell	Length [Å]	a	63.20	b	83.60	c	53.80
	Angles [°]	alpha	90.00	beta	90.00	gamma	90.00
Molecular Description Asymmetric Unit	Polymer: 1 Molecule: HEMOGLOBIN (DEOXY) (ALPHA CHAIN) Chains: A,C Polymer: 2 Molecule: HEMOGLOBIN (DEOXY) (BETA CHAIN) Chains: B,D						
Classification	Oxygen Transport						

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MMDB
Structure Summary

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Reference: Kavanaugh JS, Rogers PH, Arnone A [High-resolution X-ray study of deoxy recombinant human hemoglobins synthesized from beta-globins having mutated amino termini](#) *Biochemistry* v31, p.8640-8647
[All References](#)

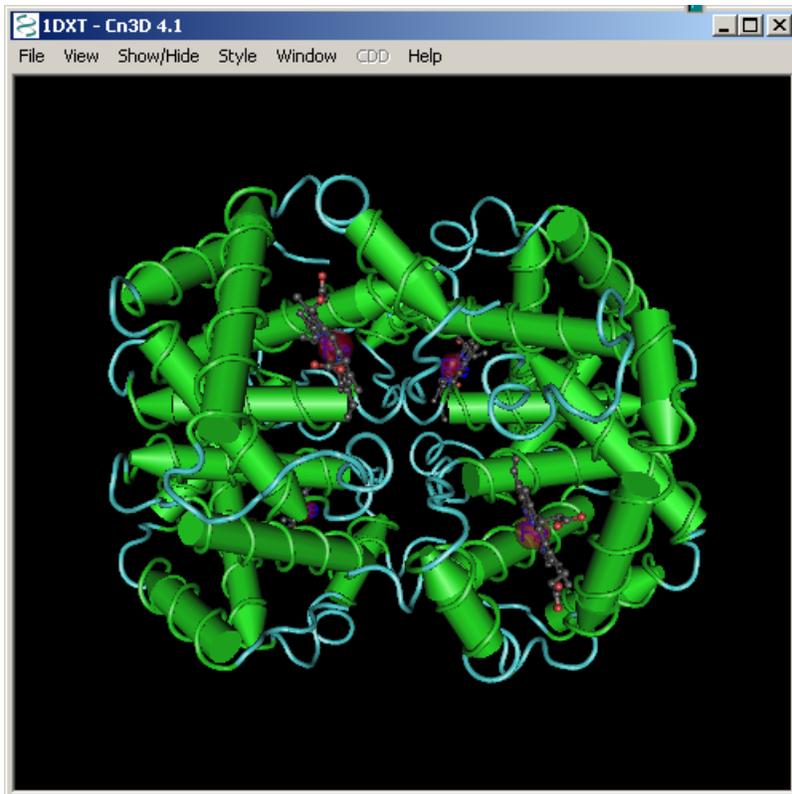
Description: Hemoglobin (Deoxy) Mutant With Additional Met At The N-Terminus Of The Beta Chains.
Deposition: 1992/5/6
Taxonomy: [Homo sapiens](#)
MMDB: [815](#) **PDB:** [1DXT](#) **Structure Neighbors:** [VAST](#)

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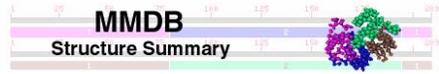
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Protein Chain A
Domain Family globin





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Reference: [Kavanaugh JS, Rogers PH, Arnone A High-resolution X-ray study of deoxy recombinant human hemoglobins synthesized from beta-globins having mutated amino termini Biochemistry v31, p.8640-8647](#)
[All References](#)

Description: Hemoglobin (Deoxy) Mutant With Additional Met At The N-Terminus Of The Beta Chains.

Deposition: 1992/5/6

Taxonomy: [Homo sapiens](#)
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Protein  [chain B](#)
Domain Family  [globin](#)


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Search: All Databases for deoxyhemoglobin S Go

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Protein Clusters
 Entrez Protein Clusters database
 The Entrez Protein Clusters database is a collection of sequence (RefSeq) proteins, from the complete genomes of prokaryotes, plasmids, and organelles, that have been grouped and annotated based on sequence similarity and protein function. Click here to find out more about the [Protein Clusters database](#).

Hot Spots

- Assembly Archive
- Clusters of orthologous groups
- Coffee Break, Genes & Disease, NCBI Handbook
- Electronic PCR
- Entrez Home
- Entrez Tools
- Gene expression omnibus (GEO)
- Human genome

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All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy

Search: Structure for deoxyhemoglobin S Go Clear Save Search

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About Entrez

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Structure Research The NCBI Structure group
 MMDB About Entrez's structure database
 CDD Conserved Domain Database
 PDBeast

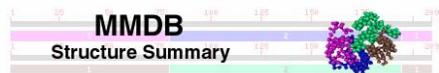
Display: Summary Show 20 Send to

All: 2 Bacterial: 0 Eukaryotic: 2 Ligand: 2 NMR: 0 X-ray: 2

Items 1 - 2 of 2

1: [2HBS](#)
 The High Resolution Crystal Structure Of Deoxyhemoglobin S [mmdbId:6228]

2: [1HBS](#)
 Hemoglobin S (Deoxy) [mmdbId:1118]

PubMed BLAST Structure Taxonomy OMIM Help? Cn3d

Reference: Harrington DJ, Adachi K, Royer WE Jr [The high resolution crystal structure of deoxyhemoglobin S](#). *J. Mol. Biol.* v272, p.398-407
[All References](#)

Description: The High Resolution Crystal Structure Of Deoxyhemoglobin S.

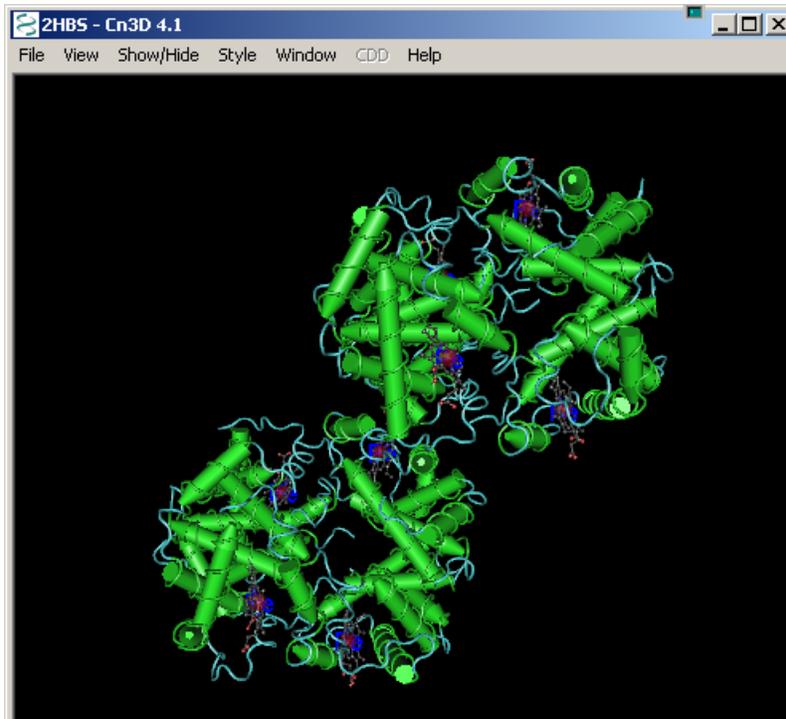
Deposition: 1997/5/6

Taxonomy: [Homo sapiens](#)
 MMDB: [6228](#) PDB: [2HBS](#) Structure Neighbors: [VAST](#)

of [Download Cn3D!](#)

Molecular components in the MMDB structure are listed below. The icons indicate macromolecular chains, 3D domains, protein classifications and ligands. Please hold the mouse over each icon for more information on the component.

Protein  [Chain A](#)
Domain Family  [globin](#)



2HBS - Sequence/Alignment Viewer

View Edit Mouse Mode Unaligned Justification Imports

```

2HBS_A v l s p a d k t n v k a a w g k v g a h a g e y g a e a l e r m f l s f p t t k t y f p h f d l s h g s a q v k g h g k k v a d a l t n a v a h v d d m p n a l s a l
2HBS_B v h l t p v e k s a v t a l w g k v n v d e v g g e a l g r i l l v y p w t q r f f e s f g d l s t p d a v m g n p k v k a h g k k v l g a f s d g l a h l d n l k g
2HBS_C v l s p a d k t n v k a a w g k v g a h a g e y g a e a l e r m f l s f p t t k t y f p h f d l s h g s a q v k g h g k k v a d a l t n a v a h v d d m p n a l s a l
2HBS_D v h l t p v e k s a v t a l w g k v n v d e v g g e a l g r i l l v y p w t q r f f e s f g d l s t p d a v m g n p k v k a h g k k v l g a f s d g l a h l d n l k g
2HBS_E
  
```

User Annotations

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Selection:

Description:

