

## 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 literature, expression and structure databases 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. This handout contains the screenshots of the overview.

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

Course Developed by Medha Bhagwat ([bhagwat@ncbi.nlm.nih.gov](mailto:bhagwat@ncbi.nlm.nih.gov))

## 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:**

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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? Which is the longest splice variant? 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?

### **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:***

#### **A. Visualization of cysteine 282 on the structure of the hemochromatosis protein**

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 entry 1A6Z chain C provides the structure of 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 to the area of the disulphide bridges (colored in tan) by pressing "z" on the keyboard. Select the cysteine residues forming the disulphide bridges by double clicking on them. Mouse over the corresponding cysteine residues on the query line in the Alignment Viewer and read 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 that is mutated to tyrosine causing the hemochromatosis phenotype.

#### **B. Visualization of hemochromatosis protein and beta-2-microglobulin complex**

Return to the sequence alignment (Related Structures) page and select the link to MMDB (the Molecular Modeling Database). The graphic representation of the structure lists four chains. The PDB record, which can be accessed through the "1A6Z" link on the MMDB page, indicates that chains A and C represent the human hemochromatosis protein, while chains B and D represent human beta-2-microglobulin. Download the structure of the complex by clicking on the "View 3D

Structure” button on the MMDB page. For easier viewing, remove the helix and strand objects using Style→Edit Global Style -- unclick the boxes next to the Helix objects and Strand objects. To distinguish between the individual chains, select “Molecule” as the Color Scheme for the protein backbone. Click on the “Apply”, then “Done” buttons.

***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

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

PubMed All Databases BLAST OMIM Books TaxBrowser Structure

Search All Databases 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

**NCBI** 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.

**NCBI** Entrez Gene

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

Search Gene for nfe **Go** **Clear**

Limits Preview/Index History Clipboard Details

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

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 Page 1 of 2 Next

1: **HFE** Order cDNA clone, Links

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  
 Annotation: Chromosome 6, NC\_000006.10 (26195426..26205037)  
 MIM: 235200  
 GeneID: 3077

NCBI Entrez Gene

Search Gene for Go Clear

Display Full Report Show 20 Send to

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

1: **HFE hemochromatosis** [*Homo sapiens*]  
 GeneID: 3077 updated 09-Sep-2007

Summary

**Official Symbol** HFE provided by HGNC

**Official Full Name** hemochromatosis provided by HGNC

**Primary source** HGNC:4886

**See related** Ensembl:ENSG0000010704; HPRD:01993; MIM:235200

**Gene type** protein coding

**RefSeq status** Reviewed

**Organism** *Homo sapiens*

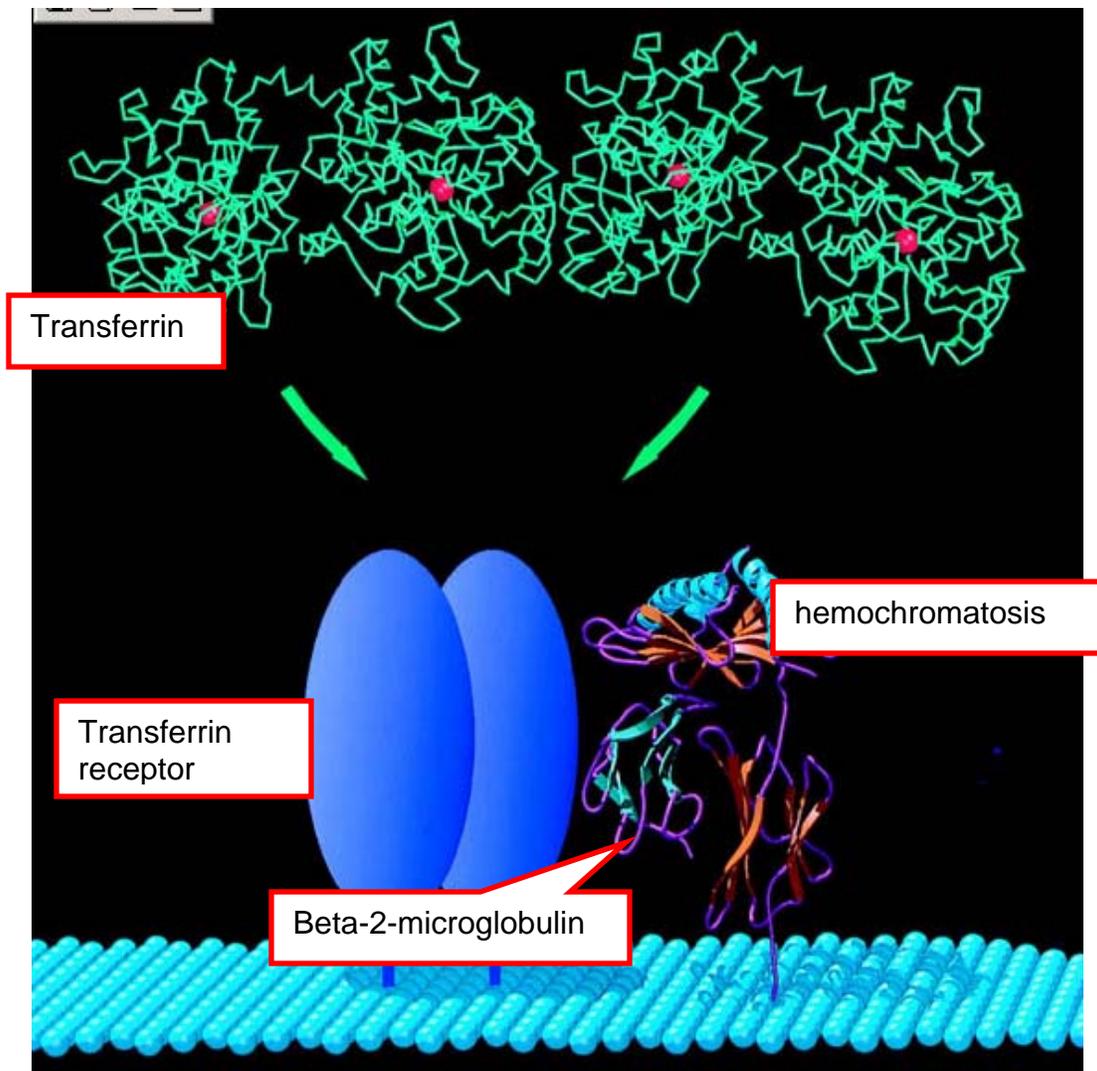
**Lineage** Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo

**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 nine alternatively spliced variants have been described for this gene. Additional variants have been found but their full-length nature has not been determined.

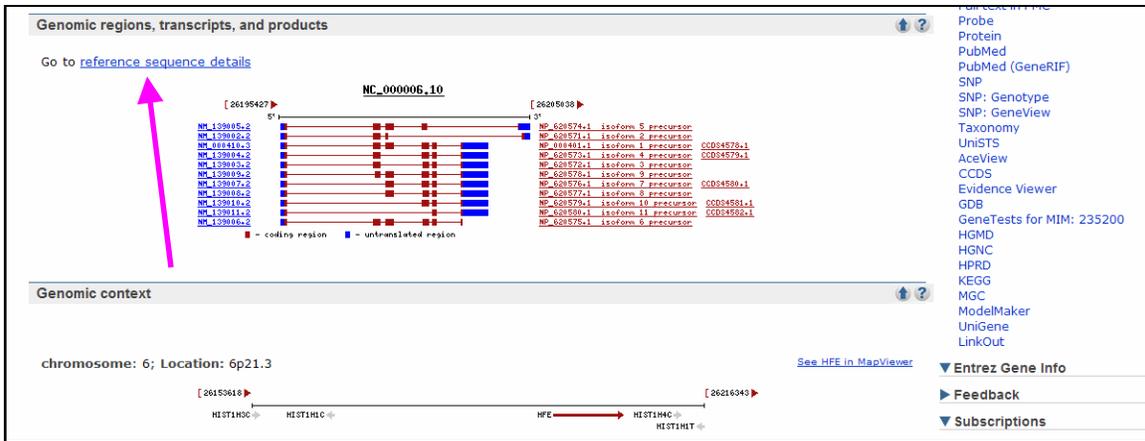
**Genomic regions, transcripts, and products**

Go to [reference sequence details](#)



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

**The interaction of hemochromatosis protein with beta-2-microglobulin allows cell surface presentation of the complex. Once on cell surface, the hemochromatosis protein regulates iron absorption by regulating the interaction of the transferrin receptor with transferrin.**



**General protein information**

**Names**

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

**NCBI Reference Sequences (RefSeq)**

**Genomic**

- NG\_001335.1 Reference**  
Range: 71162..80773  
Download: [GenBank](#), [FASTA](#)

**mRNA and Protein(s)**

- 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\\_A1249337\\_U91328](#)  
Consensus CDS: [CCDS4578.1](#)  
Conserved Domains (2) [summary](#)

<b>cd00098</b> Location:223-298 Blast Score:169	IG; 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
<b>pfam00129</b> Location:27-202 Blast Score:314	MHC_I; Class I Histocompatibility antigen, domains alpha 1 and 2
- NM\_139002.2~NP\_620571.1 hemochromatosis protein isoform 2 precursor**  
Description: Transcript Variant: This variant (2) lacks a large 3' region including the 3' CDS and UTR but has an alternate 3' exon, as compared to variant 1. The resulting protein (isoform 2) has a unique carboxy terminus.

**Bibliography** ↑ ?

**Related Articles in PubMed**

[PubMed](#) links

**GeneRIFs: Gene References Into Function** [What's a GeneRIF?](#)

124. determined race-specific frequencies of the HFE mutations, C282Y and H63D

125. the homozygous Cys282Tyr missense mutation and high levels of serum ferritin. It is important to recognise the symptoms of iron overloading at an early stage because hereditary haemochromatosis needs to be treated immediately.

126. The effect of particulate air pollution on cardiac autonomic function was shielded in subjects with at least 1 copy of an HFE variant compared with wild-type subjects.

127. Our data suggest that the HFE gene is not a major disease gene for migraine.

128. analysis of the localisation and functional effects of the HFE and its chaperone protein beta2M

129. Prevalence of epsilon dA was significantly higher in specimens of alcoholic fatty liver and fibrosis patients but not in hepatitis samples. The prevalence in alcohol fibrosis was as high as in the liver from Wilson's disease and hemochromatosis patients.

130. The Ala176Val mutation may have a possible role on the cause of hemochromatosis in a Japanese case

131. 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.

132. 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](#)

**Interactions** ↑ ?

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

NCBI Entrez Gene

Search: Gene for [ ] Go Clear

Display: Full Report Show 20 Send to

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

1: HFE hemochromatosis [ *Homo sapiens* ] updated 09-Sep-2007

GeneID: 3077

**Summary**

**Official Symbol** HFE provided by HGNC

**Official Full Name** hemochromatosis provided by HGNC

**Primary source** HGNC:4886

**See related** [Ensembl:ENSG00000010704](#); [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 nine alternatively spliced variants have been described for this gene. Additional variants have been found but their full-length nature has not been determined.

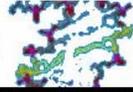
**Genomic regions, transcripts, and products**

Go to [reference sequence details](#)

NC\_000006.10

■ coding region ■ untranslated region

SNP: Genotype  
SNP: GeneView



Search for SNP on NCBI Reference Assembly  
 Search Entrez  for

SNP linked to Gene [HFE\(geneID:3077\)](#) Via Contig Annotation

Send  on all gene models to Batch Query  all rs# to file.

**BUILD 127**  
 Have a question about dbSNP? Try searching the SNP FAQ Archive!

- GENERAL**
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- DOCUMENTATION**
- SEARCH**
- HAPLOTYPE**
- RELATED SITES**

**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
<a href="#">NM_000410</a>	plus strand	<a href="#">NP_000401</a>	forward	<a href="#">NT_007592</a>	reference	<- currently shown
<a href="#">NM_000410</a>	plus strand	<a href="#">NP_000401</a>	forward	<a href="#">NW_922984</a>	Celera	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139002</a>	plus strand	<a href="#">NP_620571</a>	forward	<a href="#">NT_007592</a>	reference	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139002</a>	plus strand	<a href="#">NP_620571</a>	forward	<a href="#">NW_922984</a>	Celera	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139003</a>	plus strand	<a href="#">NP_620572</a>	forward	<a href="#">NT_007592</a>	reference	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139003</a>	plus strand	<a href="#">NP_620572</a>	forward	<a href="#">NW_922984</a>	Celera	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139004</a>	plus strand	<a href="#">NP_620573</a>	forward	<a href="#">NT_007592</a>	reference	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139004</a>	plus strand	<a href="#">NP_620573</a>	forward	<a href="#">NW_922984</a>	Celera	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139005</a>	plus strand	<a href="#">NP_620574</a>	forward	<a href="#">NT_007592</a>	reference	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139005</a>	plus strand	<a href="#">NP_620574</a>	forward	<a href="#">NW_922984</a>	Celera	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139006</a>	plus strand	<a href="#">NP_620575</a>	forward	<a href="#">NT_007592</a>	reference	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139006</a>	plus strand	<a href="#">NP_620575</a>	forward	<a href="#">NW_922984</a>	Celera	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139007</a>	plus strand	<a href="#">NP_620576</a>	forward	<a href="#">NT_007592</a>	reference	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139007</a>	plus strand	<a href="#">NP_620576</a>	forward	<a href="#">NW_922984</a>	Celera	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139008</a>	plus strand	<a href="#">NP_620577</a>	forward	<a href="#">NT_007592</a>	reference	<a href="#">View snp on GeneModel</a>
<a href="#">NM_139008</a>	plus strand	<a href="#">NP_620577</a>	forward	<a href="#">NW_922984</a>	Celera	<a href="#">View snp on GeneModel</a>

gene model (contig mRNA transcript):	Contig Label	Contig	mrna	protein	mrna orientation	transcript	snp count
	reference	<a href="#">NT_007592</a>	<a href="#">NM_000410</a>	<a href="#">NP_000401</a>	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	<a href="#">rs2242956</a>	N.D.		Yes		nonsynonymous	C	Thr [T]	2	35
				N.D.		Yes		contig reference	T	Met [M]	2	35
	16949430	347	<a href="#">rs1799945</a>	0.127		Yes		nonsynonymous	G	Asp [D]	1	63
				0.127		Yes		contig reference	C	His [H]	1	63
	16949436	353	<a href="#">rs1800730</a>	N.D.		Yes		nonsynonymous	T	Cys [C]	1	65
				N.D.		Yes		contig reference	A	Ser [S]	1	65
	16949520	437	<a href="#">rs28934597</a>	N.D.		Yes		nonsynonymous	C	Arg [R]	1	93
				N.D.		Yes	Yes	contig reference	G	Gly [G]	1	93
	16949557	474	<a href="#">rs28934596</a>	N.D.		Yes		nonsynonymous	C	Thr [T]	2	105
				N.D.		Yes	Yes	contig reference	T	Ile [I]	2	105
exon_3	16949833	541	<a href="#">rs28934595</a>	N.D.		Yes		nonsynonymous	C	His [H]	3	127
				N.D.		Yes	Yes	contig reference	A	Gln [Q]	3	127
exon_4	16951197	810	<a href="#">rs4986950</a>	N.D.		Yes		nonsynonymous	T	Ile [I]	2	217
				N.D.		Yes		contig reference	C	Thr [T]	2	217
	16951392	1005	<a href="#">rs1800562</a>	0.024		Yes		nonsynonymous	A	Tyr [Y]	2	282
				0.024		Yes	Yes	contig reference	G	Cys [C]	2	282
exon_6	16952684	1186	<a href="#">rs55201683</a>	0.053				synonymous	T	Tyr [Y]	3	342
				0.053				contig reference	C	Tyr [Y]	3	342

NCBI **OMIM** Online Mendelian Inheritance in Man Johns Hopkins University

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Display Detailed Show 20 Send to

**+235200** GeneTests, Links

**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. Primary hepatocellular carcinoma (HCC; [114550](#)), complicating cirrhosis, is responsible for about one-third of deaths in affected homozygotes. Since hemochromatosis is a relatively easily treated disorder if diagnosed, this is a form of preventable cancer. ☹

NCBI menu: MIM +235200, Description, Clinical Features, Other Features, Inheritance, Mapping, Heterogeneity, Molecular Genetics, Genotype/Phenotype Correlations, Diagnosis, Clinical Management, Population Genetics, Pathogenesis, Cloning, Biochemical Features, Gene Structure, Gene Function, Nomenclature, Animal Model, History, Allelic Variants, View List, See Also, References, Contributors, Creation Date, Edit History, Clinical Synopsis, Gene map.

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All: 1 OMIM dbSNP: 1 OMIM UniSTS: 1

**+235200** GeneTests, Links

**HEMOCHROMATOSIS; HFE**

**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 ]

Entrez Gene

<a href="#">Home Page</a>	<a href="#">About GeneTests</a>	<a href="#">GENEReviews</a>	<a href="#">Laboratory Directory</a>	<a href="#">Clinic Directory</a>	<a href="#">Educational Materials</a>
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Funded by the National Institutes of Health 

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# 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	Analysis of the entire coding region: Mutation scanning	Targeted mutation analysis	Prenatal diagnosis	Clinical confirmation of mutations identified in a research lab	Carrier testing
<a href="#">Research and Innovation</a> Padova, Italy Alberta Leon, BSc, PhD; Antonino D'Arrigo, BSc, PhD; Elda Del Giudice, BSc, PhD			•			
<a href="#">ARUP Laboratories</a> <a href="#">Molecular Genetics Laboratory</a> Salt Lake City, UT Elaine Lyon, PhD; Rong Mao, MD; Edward R Ashwood, MD; Marzia Pasquali, PhD; Pinar Bayrak-Toydemir, MD, PhD			•			•
<a href="#">Acibadem Healthcare Group</a> <a href="#">Acibadem Genetic Diagnostic Center</a> Istanbul, Turkey Ender Altioik, MD, PhD			•			•
<a href="#">Alberta Children's Hospital</a> <a href="#">Molecular Diagnostic Laboratory</a> Calgary, Alberta, Canada Peter Bridge, PhD, FCCMG, FACMG; Jillian Parboosingh, PhD, FCCMG			•			
<a href="#">Baylor College of Medicine</a> <a href="#">Medical Genetics Laboratories</a> Houston, TX Christine M Eng, MD, FACMG; William E O'Brien, PhD; Lee-Jun Wong, PhD; Sau W. Cheung, PhD			•			
<a href="#">BioLab spol. s.r.o.</a> <a href="#">Molecular Biology Laboratory</a> Klatovy, Czech Republic Frantisek Musil, MUDr			•			
<a href="#">BloodCenter of Wisconsin</a> <a href="#">Molecular Diagnostics Laboratory</a> Milwaukee, WI Daniel B Bellissimo, PhD			•			
<a href="#">Boston University School of Medicine</a> <a href="#">Center for Human Genetics</a> Boston, MA Aubrey Milunsky, MD, DSc			•	•	•	
<a href="#">Birc Molecular Genetics Diagnostic and Research Laboratory</a> Istanbul, Turkey Dr. Ceylan Bilik, MD; Dr. Vedat Kalkan, MD, PhD						

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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# 235200**

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**HFE-Associated Hereditary Hemochromatosis**

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## HFE-Associated Hereditary Hemochromatosis

**Authors:** Kris V Kowdley, MD  
Jonathan F Tait, MD, PhD  
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.

**OMIM Entries for HFE-Associated Hereditary Hemochromatosis**

235200	HEMOCHROMATOSIS; HFE
--------	----------------------

**Genomic Databases for HFE-Associated Hereditary Hemochromatosis**

Gene Symbol	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
HFE	235200	HFE	HFE	119309	HFE

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.

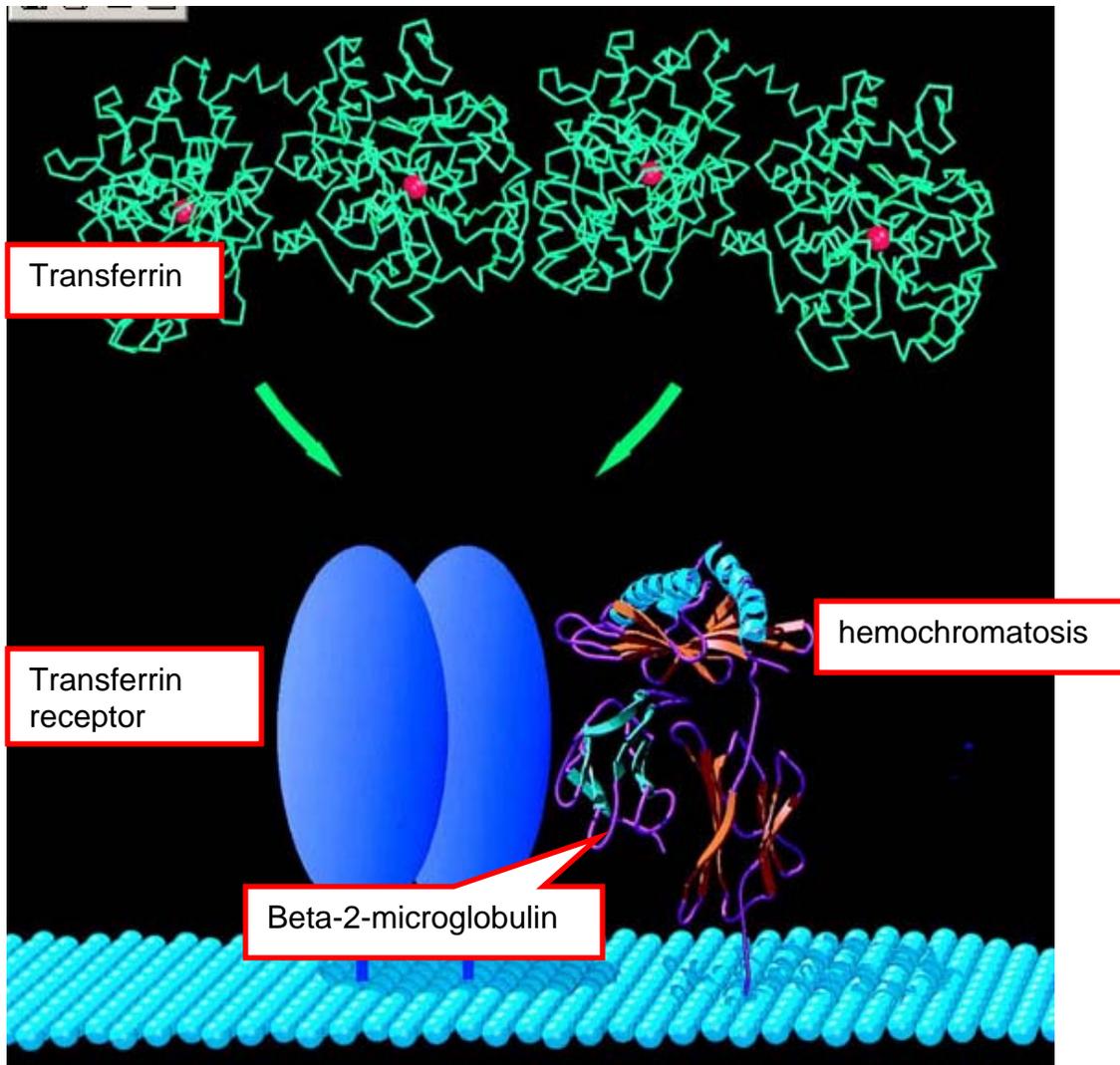
**Pathologic allelic variants:** At least 28 distinct mutations have been reported, most being missense or nonsense mutations. Two missense mutations account for the vast majority of disease-causing alleles in the population:

- 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 interaction of hemochromatosis protein with beta-2-microglobulin allows cell surface presentation of the complex. Once on cell surface, the hemochromatosis protein regulates iron absorption by regulating the interaction of the transferrin receptor with transferrin.**

NCBI OMIM Online Mendelian Inheritance in Man Johns Hopkins University

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All: 1 OMIM dbSNP: 1 OMIM UniSTS: 1

**+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. Prr (HCC; [114550](#)), complicating cirrhosis, is responsible for about one-third of deaths in affected homozygotes. Since hemochromatosis is a relatively rare 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
- UniGene
- Related Entries
- Nucleotide
- Protein
- SNP
- Structure

Genomic regions, transcripts, and products

Go to [reference sequence details](#)

**NC\_000006.10**

[ 26195427 ] 5' [ 26205038 ] 3'

NM\_139005.2  
 NM\_139002.2  
 NM\_001010.3  
 NM\_139014.2  
 NM\_139003.2  
 NM\_139009.2  
 NM\_139007.2  
 NM\_139008.2  
 NM\_139010.2  
 NM\_139011.2  
 NM\_139006.2

NP\_620574 isoform 5 precursor  
 NP\_620571 isoform 2 precu  
 NP\_620570 isoform 1 precu  
 NP\_620573 isoform 4 precu  
 NP\_620572 isoform 3 precu  
 NP\_620578 isoform 9 precu  
 NP\_620576 isoform 7 precu  
 NP\_620577 isoform 8 precu  
 NP\_620579 isoform 10 precu  
 NP\_620580 isoform 11 precu  
 NP\_620575 isoform 6 precu

■ - coding region ■ - untranslated region

**Links**

- FASTA
- GENEPT
- Blink
- Conserved Domains

**Genomic context**

chromosome: 6; Location: 6p21.3 [See HFE in MapViews](#)

[ 26153618 ] [ 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  
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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

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200 BLAST hits to 23 unique species [Sort by taxonomy proximity](#)

0 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
<b>Conserved Domain Database hits</b>				
1870	31	AAC51823	1469790	HLA-H
1870	29	AAM09793	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	EAW55524	119575928	hemochromatosis, isoform CRA_1 [Homo sapiens]
1870	29	F60018	38502807	Hereditary hemochromatosis protein homolog precursor (HLA-H)
1870	31	AAI17204	109658506	Hemochromatosis (Homo sapiens)
1870	31	AAI17202	109658670	Hemochromatosis (Homo sapiens)
1870	29	NF_001111	57114069	hemochromatosis protein [Pan troglodytes]
1870	31	AAQ29572	11094315	hemochromatosis termination variant terE6; HFE [Homo sapiens]
1776	31	AAM74721	50960016	HFE protein [Homo sapiens]
1772	31	AAC62646	3695107	hemochromatosis splice variant dell4E4 [Homo sapiens]
1772	31	EAW55523	119575927	hemochromatosis, isoform CRA_h [Homo sapiens]
1772	31	NF_620575	21040347	hemochromatosis protein isoform 6 precursor [Homo sapiens]
1713	31	CAC67792	15485419	hemochromatosis protein [Homo sapiens]
1713	31	NF_620578	21040353	hemochromatosis protein isoform 9 precursor [Homo sapiens]
1713	31	EAW55521	119575925	hemochromatosis, isoform CRA_f [Homo sapiens]
1517	31	1A62C	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	31	1DE4A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	1DE4D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	1DE4G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	1A62A	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
1495	21	Q9GL42	24418418	Hereditary hemochromatosis protein homolog precursor
1495	21	AAQ23703	10945692	HFE protein [Diceros bicornis sumatrensis]
1495	21	Q9GK20	24418446	Hereditary hemochromatosis protein homolog precursor
1495	21	AAQ23701	10945688	HFE protein [Ceratotherium simum]
1492	21	Q9GL43	24418449	Hereditary hemochromatosis protein homolog precursor
1492	21	AAQ23702	10945690	HFE protein [Diceros bicornis]
1491	31	NF_620574	21040345	hemochromatosis protein isoform 5 precursor [Homo sapiens]
1491	31	EAW55527	119575931	hemochromatosis, isoform CRA_l [Homo sapiens]
1489	21	AAQ23704	10945694	HFE protein [Rhinoceros unicornis]
1489	21	Q9GL41	24418447	Hereditary hemochromatosis protein homolog precursor
1463	31	AAQ47091	28800982	hemochromatosis [Homo sapiens]
1412	21	AAQ39940	11692703	HFE [Diceros bicornis]
1303	22	NF_445753	25742631	hemochromatosis [Rattus norvegicus]

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

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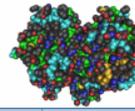
200 BLAST hits to 3 unique species [Sort by taxonomy proximity](#)

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: 4504377 Go

348 aa

SCORE	E	ACCESSION	GI	PROTEIN DESCRIPTION
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1517	31	1A62C	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	31	1DE4A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	1DE4D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	1DE4G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	1A62A	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
525	31	1B71A	3891929	Chain A, The Crystal Structure Of H-2dd Mhc Class I In Complex With The Hiv-1 Derived Peptide P18-11
507	31	1S7RA	48425592	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	31	1S7RD	48425595	Chain D, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	31	1S7SA	48425598	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	31	1S7TA	48425601	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	31	1S7TD	48425604	Chain D, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	31	1S7TB	48425599	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
502	31	1X84D	49258567	Chain D, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	31	1X70C	49258567	Chain A, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	31	1X70D	49258567	Chain D, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	31	2HN7A	119389933	Chain A, Hla-A1101 In Complex With Hbv Peptide Homologue
502	31	1X70A	73535522	Chain A, Crystal Structure Of Hla-A1101 With Sars Nucleocapsid Peptide
502	31	1Q94A	49258564	Chain A, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	31	2BCKD	88192434	Chain D, Crystal Structure Of Hla-A2402 Complexed With A Telomerase Peptide
502	31	2BCKA	88192431	Chain A, Crystal Structure Of Hla-A2402 Complexed With A Telomerase Peptide



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

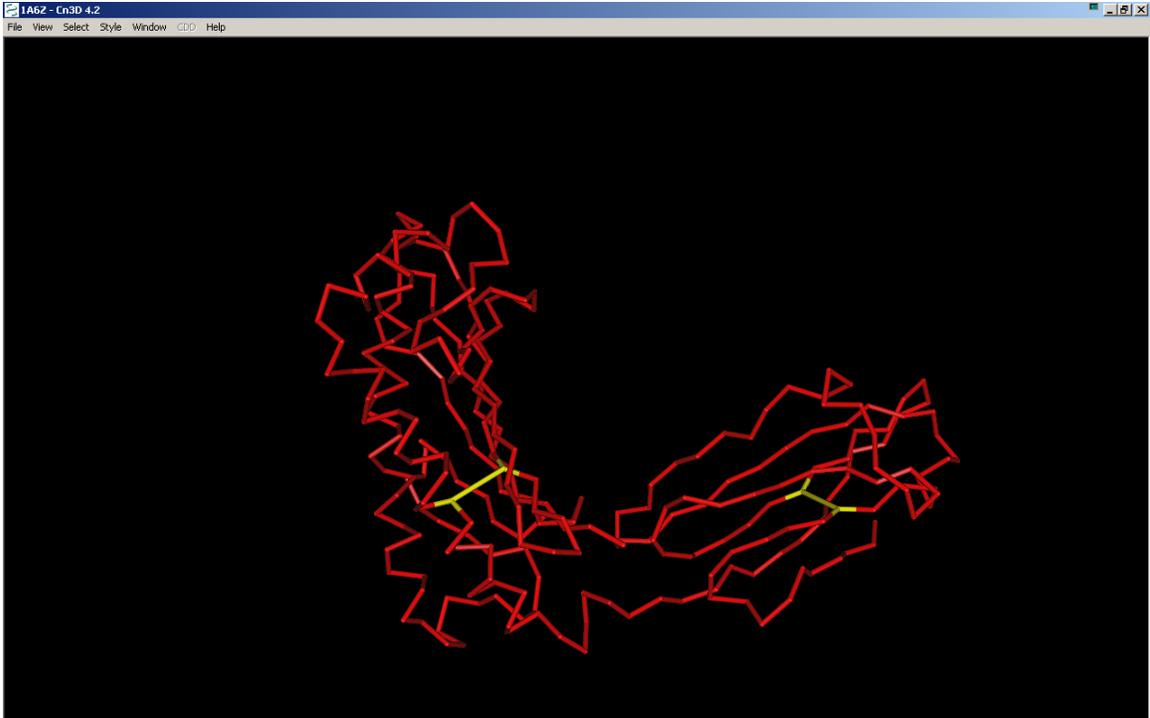
**Structure:** 1A6Z Chain C, Hfe (Human) Hemochromatosis Protein

**Reference:** [[MMDB](#)] [[PubMed](#)]

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

		10	20	30	40	50	60	70	80
<a href="#">gi_4504377</a>	23	RLLRSHSLHYLFMGASEQDLGSLFEALGYVDDQLFVFDHESRRVEPRTPWVSSRISSQMWLQLSQSLKGNHDMFTVDF	102						
<a href="#">1A6Z_C</a>	1	RLLRSHSLHYLFMGASEQDLGSLFEALGYVDDQLFVFDHESRRVEPRTPWVSSRISSQMWLQLSQSLKGNHDMFTVDF	80						
		90	100	110	120	130	140	150	160
<a href="#">gi_4504377</a>	103	WTIMENHNHKSESHILQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPDTLDWRAAEPRAWPTKLEWERHKIRARQNRAY	182						
<a href="#">1A6Z_C</a>	81	WTIMENHNHKSESHILQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPDTLDWRAAEPRAWPTKLEWERHKIRARQNRAY	160						
		170	180	190	200	210	220	230	240
<a href="#">gi_4504377</a>	183	LERDCPAQLQQLLELGRGVLDQQVPLVKVTHHVTSSVITLRCRALNYYPQNITMKWLKDKQPMDAKEFEPKDVLPNGDG	262						
<a href="#">1A6Z_C</a>	161	LERDCPAQLQQLLELGRGVLDQQVPLVKVTHHVTSSVITLRCRALNYYPQNITMKWLKDKQPMDAKEFEPKDVLPNGDG	240						
		250	260	270					
<a href="#">gi_4504377</a>	263	TYQGWITLAVPPGEEQRYTCQVEHPGLDQPLIVI	297						
<a href="#">1A6Z_C</a>	241	TYQGWITLAVPPGEEQRYTCQVEHPGLDQPLIVI	275						



1A6Z - Sequence/Alignment Viewer  
View Edit Mouse Mode Unaligned Justification Imports

1A6Z_C	LNYY PQNI TMKWLKDKQPM DAK E F E P K D V L P N G D G T Y Q G W I T L A V P P G E E Q R Y T C Q V E H P G L D Q P L I V I W ~ ~ ~ ~ ~
gi 4504377	LNYY PQNI TMKWLKDKQPM DAK E F E P K D V L P N G D G T Y Q G W I T L A V P P G E E Q R Y T Q V E H P G L D Q P L I V I W e p s p g t l v i g v i

gi 4504377, loc 282 | Block 1, Row 2

The image shows a sequence alignment viewer window. The top part displays the protein name '1A6Z\_C' and its sequence. Below it, a reference sequence from 'gi 4504377' is shown. The two sequences are aligned, with a yellow highlight under the 'Q' residue in the reference sequence. At the bottom, a status bar shows 'gi 4504377, loc 282' and 'Block 1, Row 2'. A red circle highlights the 'gi 4504377, loc 282' text in the status bar.

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]

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

		10	20	30	40	50	60	70	80
gi_4504377	23	RLLRSHSLHYLFGASEQDLGLSLFEALGYVDDQLFVFDHESRRVEPRTPWVSSRISSQMWLQLSQSLKGDHMFVDF	102						
1A6Z_C	1	RLLRSHSLHYLFGASEQDLGLSLFEALGYVDDQLFVFDHESRRVEPRTPWVSSRISSQMWLQLSQSLKGDHMFVDF	80						

NCBI **MMDB Structure Summary**

PubMed BLAST Structure Taxonomy OMM Help? Cn3d

**Reference:** Lebron JA, Bennett MJ, Vaughn DE, Chirino AJ, Snow PM, Mintier GA, Feder JN, Bjorkman PJ *Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor Cell v93, p. 111-123*

**Description:** Hfe (Human) Hemochromatosis Protein.

**Deposition:** 1998/3/4

**Taxonomy:** [Homo sapiens](#)

MMDB: [9816](#) PDB: [1A6Z](#) 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.

**Chain A**

Protein Chain A

3d Domains 1 2

Domain Family HHC\_I IGc

**Chain B**

Protein Chain B

Domain Family IGc

**Chain C**

Protein Chain C

3d Domains 1 2

Domain Family HHC\_I IGc

**Chain D**

Protein Chain D

Domain Family IGc

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Help Structure Summary Biology & Chemistry Materials & Methods Sequence Details Geometry

**1a6z** Learn more: [M] [M] DOI 10.2210/pdb1a6z/pdb

Red - Derived Information

**Title** HFE (HUMAN) HEMOCHROMATOSIS PROTEIN

**Authors** Lebron, J.A., Bennett, M.J., Vaughn, D.E., Chirino, A.J., Snow, P.M., Mintier, G.A., Feder, J.N., Bjorkman, P.J.

**Primary Citation** Lebron, J.A., Bennett, M.J., Vaughn, D.E., Chirino, A.J., Snow, P.M., Mintier, G.A., Feder, J.N., Bjorkman, P.J. Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor. *Cell* v93, pp.111-123, 1998 [Abstract]

**History** Deposition 1998-03-04 Release 1999-03-23

**Experimental Method** Type X-RAY DIFFRACTION Data N/A

**Parameters** Resolution[Å] R-Value R-Free Space Group  
2.60 0.233 (obs.) 0.277 P 2<sub>1</sub> 2<sub>1</sub> 2<sub>1</sub>

**Unit Cell** Length [Å] a 68.80 b 100.10 c 147.60  
Angles [°] alpha 90.00 beta 90.00 gamma 90.00

**Molecular Description Asymmetric Unit** Polymer: 1 Molecule: HFE Chains: A,C  
Polymer: 2 Molecule: BETA-2-MICROGLOBULIN Chains: B,D

**Classification** Mhc Class I Complex

**Source** Polymer: 1 Scientific Name: **Homo sapiens** Common Name: **Human** Expression system: **Chinese hamster ovary cells (cho), cricetus griseus** Polymer: 2 Scientific Name: **Homo sapiens** Name: **Human** Human

**Images and Visualization** Biological Molecule

**Display Options** KING Jmol WebMol MBT SimpleViewer\* MBT Protein Workshop QuickPDB All Images \* Capable of displaying biological mol

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NCBI

**MMDB**  
Structure Summary

PubMed BLAST Structure Taxonomy OMIM Help? Cn3d

**Reference:** Lebron JA, Bennett MJ, Vaughn DE, Chirino AJ, Snow PM, Mintier GA, Feder JN, Bjorkman PJ [Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor](#) *Cell* v93, p. 111-123

**Description:** Hfe (Human) Hemochromatosis Protein.

**Deposition:** 1998/3/4

**Taxonomy:** [Homo sapiens](#)

MMDB: [9816](#) PDB: [1A6Z](#) Structure Neighbors: [VAST](#)

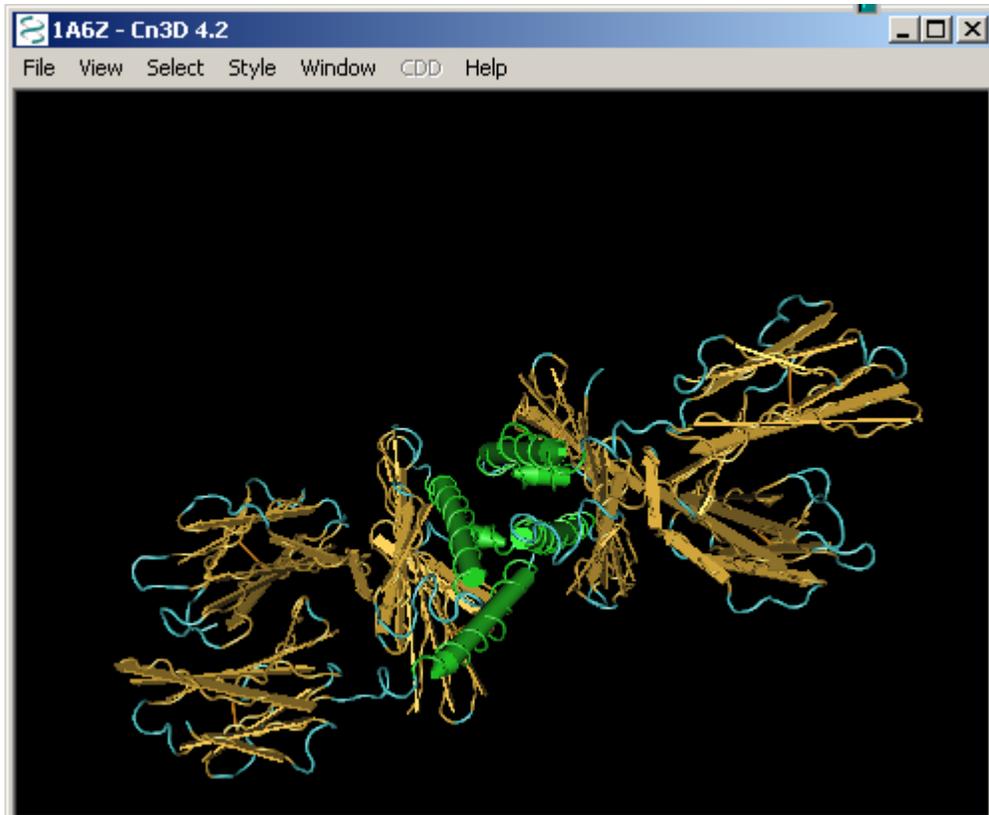
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Molecular components in the MMDB structure are listed below. The icons indicate macromolecular chains, 3D domains, protein classifications and ligands. Please hold the mouse over each icon for more information on the component.

**Protein** Chain A

**3d Domains** 1 2

**Domain Family** MHC\_I IGc



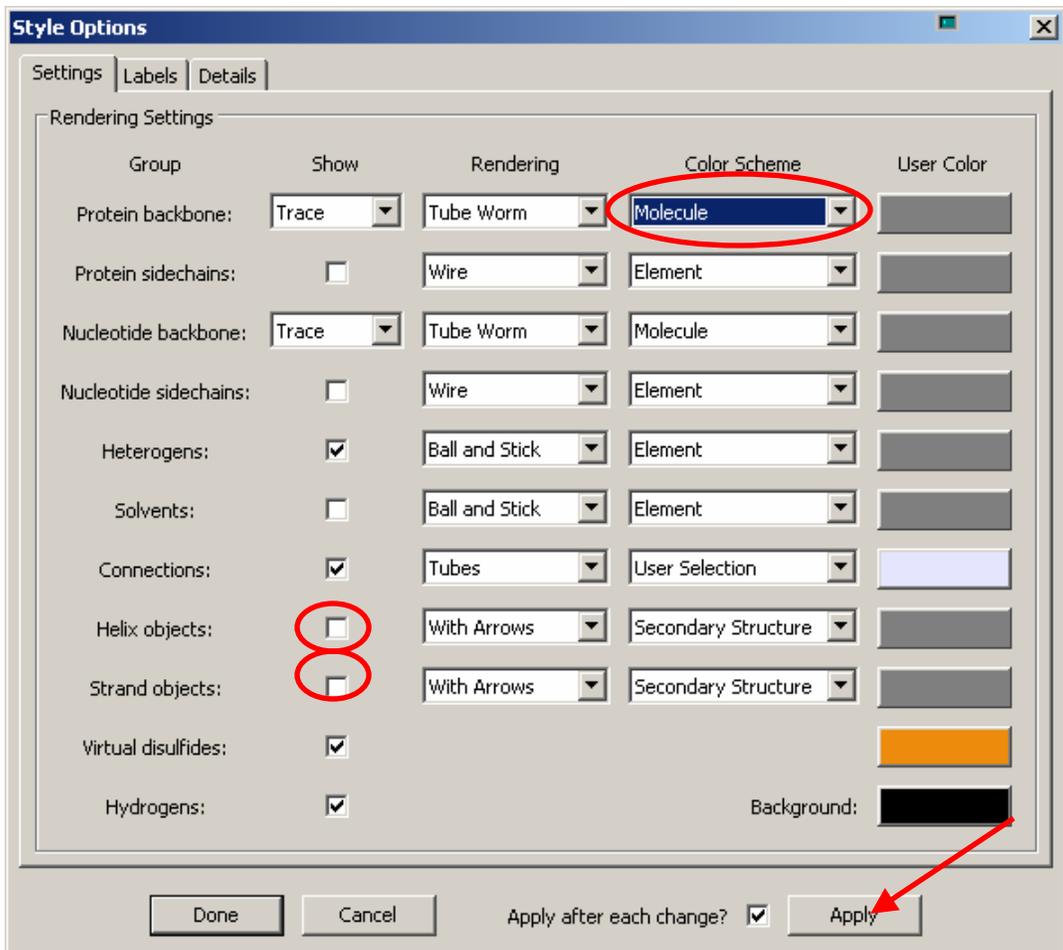
1A6Z - Sequence/Alignment Viewer

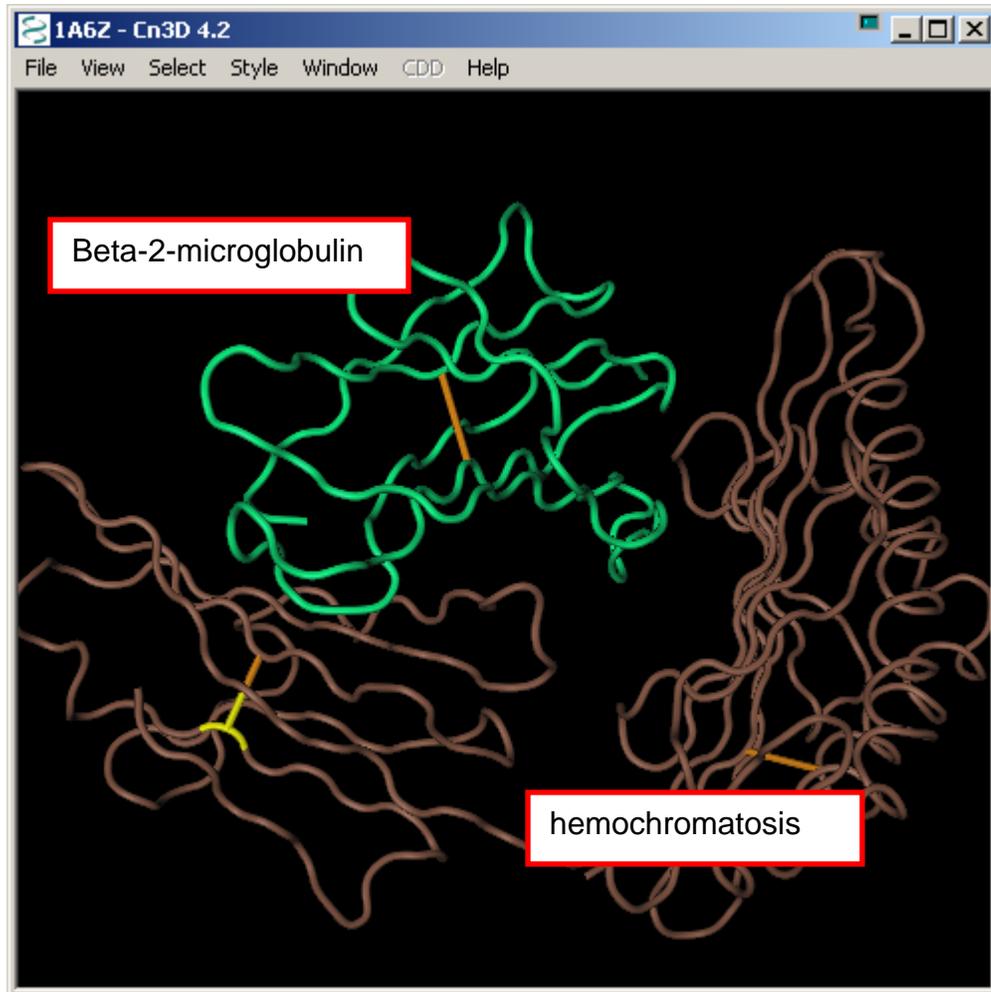
View Edit Mouse Mode Unaligned Justification Imports

```

1A6Z_A r l l r s h s l h y l f m g a s e q d l g l s l f e a l g y v d d q l f v f y d h e s r r v e p r t p w v s s r i s s q m w l q l s q s l k g w d h m f t v d f w t i m e n h n h s k e s h t
1A6Z_B i q r t p k i q v y s r h p a e n g k s n f l n c y v s g f h p s d i e v d l l k n g e r i e k v e h s d l s f s k d w s f y l l y t e f t p t e k d e y a c r v n h v t l s q p k i v k w
1A6Z_C r l l r s h s l h y l f m g a s e q d l g l s l f e a l g y v d d q l f v f y d h e s r r v e p r t p w v s s r i s s q m w l q l s q s l k g w d h m f t v d f w t i m e n h n h s k e s h t
1A6Z_D i q r t p k i q v y s r h p a e n g k s n f l n c y v s g f h p s d i e v d l l k n g e r i e k v e h s d l s f s k d w s f y l l y t e f t p t e k d e y a c r v n h v t l s q p k i v k w

```





1A6Z - Sequence/Alignment Viewer

View Edit Mouse Mode Unaligned Justification Imports

1A6Z\_A vtssvtllrcralnyppqnitmkwlkdkqpmcakefepkdvlpngdgyqgwitlavppgeeqrytcqvehpgldqplivw

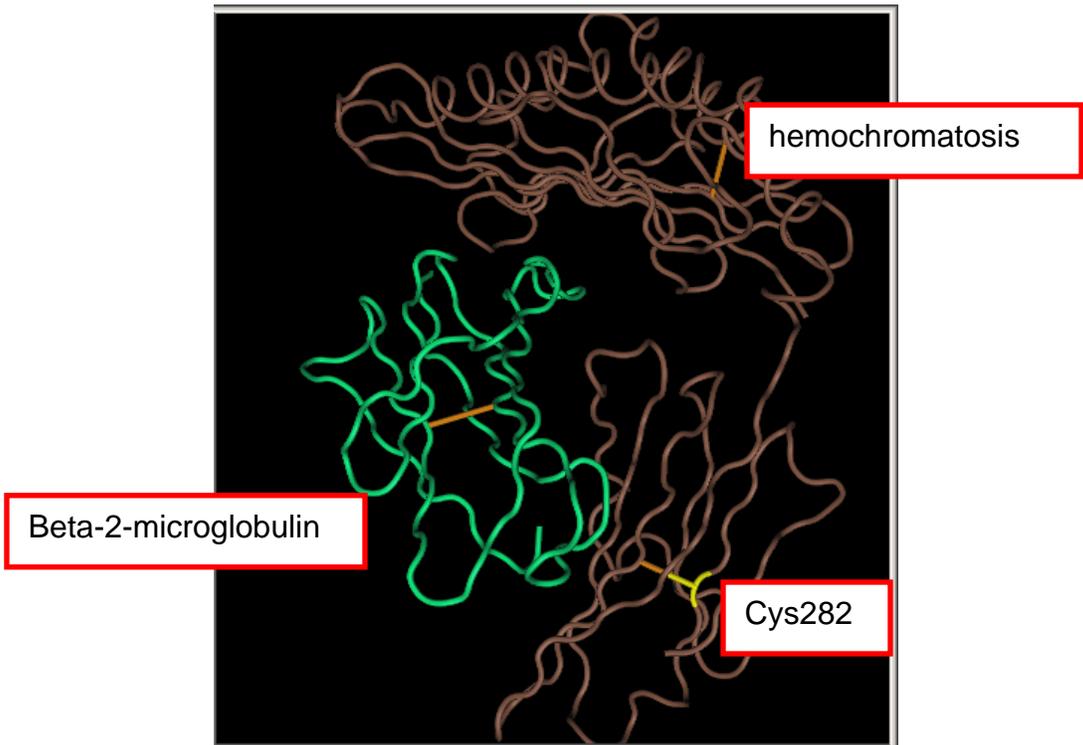
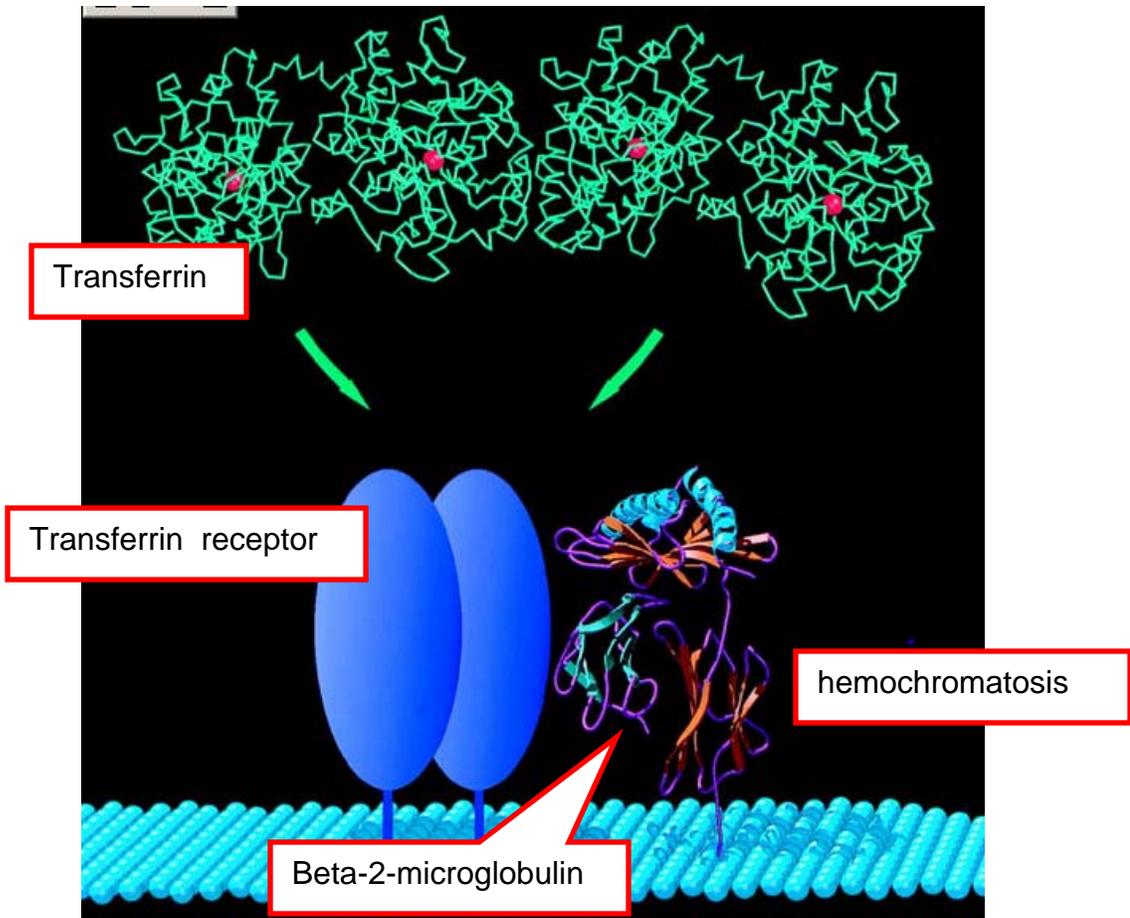
1A6Z\_B

1A6Z\_C vtssvtllrcralnyppqnitmkwlkdkqpmcakefepkdvlpngdgyqgwitlavppgeeqrytqvehpgldqplivw

1A6Z\_D

1A6Z\_C, loc 260 (PDB 260)

**The interaction of hemochromatosis protein with beta-2-microglobulin allows cell surface presentation of the complex. Once on cell surface, the hemochromatosis protein regulates iron absorption by regulating the interaction of the transferrin receptor with transferrin.**



## 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?

What is the name and function of the protein encoded by the HBB gene? Beta globin is a subunit of which protein? Name other subunit(s) in that protein.

### **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 deoxyhemoglobin (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.