

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)

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:

1. Determining what is known about the HFE gene and protein (using Entrez Gene).
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? 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. Currently, how many missense (non-synonymous) SNPs are placed on the longest hemochromatosis transcript variant, NM_000410? How many of these have links to OMIM (Clinically Associated)? 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 GENPEPT link for NP_000401 under the section “Genomic Region, Transcripts and products”. Then select “Related Structure” from the Links menu. The output contains a list of similar proteins with known 3D structures. The entry 1A6Z chain A provides the structure of part of human hemochromatosis protein. Click on the first arrow representing the related structure and then on the “Get 3D-structure data” button. This downloads its 3D structure and the 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 structure image 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.

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What does NCBI do? **Hot Spots**

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

  *Entrez, The Life Sciences Search Engine.*

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Search across databases **GO** [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

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

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All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

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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"[organ] OR "Mus musculus"[organ])
chromosome and symbol	11[chr] OR 2[chr] AND adh*[sym]
associated sequence accession number	M11313[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	1.0.2.1[sc]

NCBI Entrez Gene

Search Gene for hfe Go Clear Save Search

Display Summary Show 20 Send to

All: 35 Current Only: 35 Genes Genomes: 31 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
 Annotation: Chromosome 6, NC_000006.10 (26195427..26205038)
 MIM: 235200
 GeneID: 3077

2: [Hfe](#)
 Official Symbol Hfe and Name: hemochromatosis [*Mus musculus*]
 Other Aliases: RP23-480B19.9, MGC151121, MGC151123, MR2
 Chromosome: 13; Location: 13 15.0 cM
 Annotation: Chromosome 13, NC_000079.5 (23795710..23802680, complement)
 GeneID: 15216

3: [Hfe](#)
 Official Symbol Hfe and Name: hemochromatosis [*Rattus norvegicus*]
 Chromosome: 17; Location: 17p11-q11
 Annotation: Chromosome X, NC_005120.2 (40298542..40315963, complement)
 GeneID: 29199

NCBI Entrez Gene

Search Gene for HFE Go Clear

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

1: **HFE hemochromatosis** [*Homo sapiens*]
 GeneID: 3077 updated 28-Oct-2007

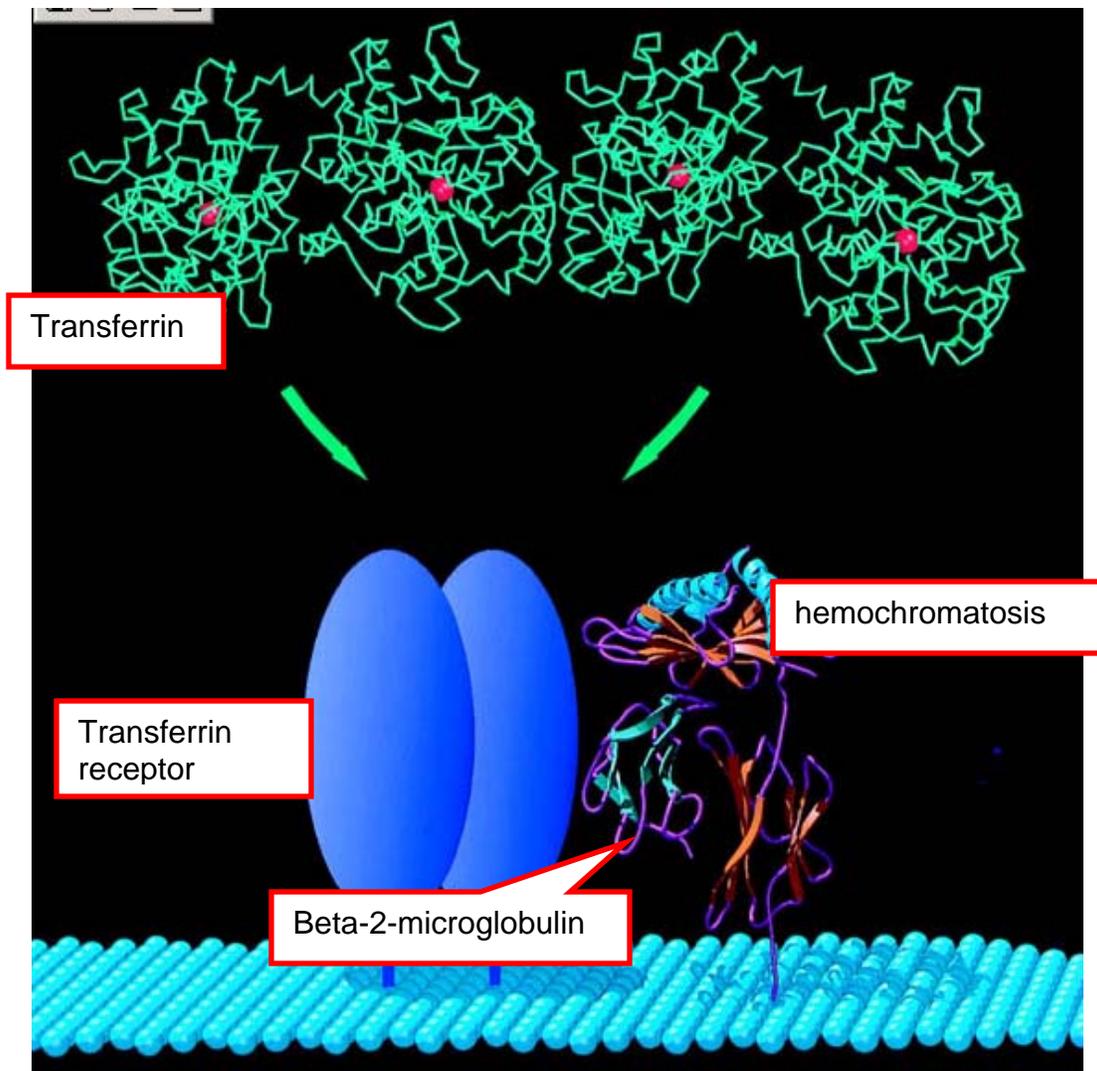
Summary

Official Symbol	HFE	provided by HGNC
Official Full Name	hemochromatosis	provided by HGNC
Primary source	HGNC:4886	provided by HGNC
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

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 SNP



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.

Genomic regions, transcripts, and products

Go to [reference sequence details](#)

Genomic context

chromosome: 6; Location: 6p21.3

See [HFE in MapViewer](#)

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- SNP: GeneView
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- UniSTS
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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](#)

cd00098 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
pfam00129 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.

[PubMed](#) links

GeneRIFs: Gene References Into Function

[What's a GeneRIF?](#)

important to recognise the symptoms of iron overloading at an early stage because hereditary haemochromatosis needs to be treated immediately.

151. 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.

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

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

154. 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.

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

156. 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.

157. 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	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

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

1: HFE hemochromatosis [*Homo sapiens*]

GeneID: 3077 updated 28-Oct-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](#)

■ - coding region ■ - untranslated region

NM_139815.2
 NM_139912.2
 NC_018169.3
 NM_139814.2
 NC_018169.3
 NM_139819.2
 NM_139912.2
 NM_139819.2
 NM_139914.2
 NM_139816.2
 NP_628774.1 Isoform 5 precursor
 NP_628771.1 Isoform 2 precursor
 NP_628771.1 Isoform 1 precursor
 CC014577.1
 NP_628773.1 Isoform 4 precursor
 CC014577.1
 NP_628772.1 Isoform 3 precursor
 NP_628776.1 Isoform 9 precursor
 CC014588.1
 NP_628777.1 Isoform 8 precursor
 NP_628779.1 Isoform 10 precursor
 CC014581.1
 NP_628780.1 Isoform 11 precursor
 CC014581.1
 NP_628775.1 Isoform 6 precursor

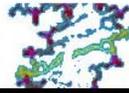
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- HGMD
- HGNC
- HPRD



Search for SNP on NCBI Reference Assembly
 Search Entrez for

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

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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
NM_139007	plus strand	NP_620576	forward	NT_007592	reference	View snp on GeneModel
NM_139007	plus strand	NP_620576	forward	NW_922984	Celera	View snp on GeneModel
NM_139008	plus strand	NP_620577	forward	NT_007592	reference	View snp on GeneModel
NM_139008	plus strand	NP_620577	forward	NW_922984	Celera	View snp on GeneModel

Region	Contig position	mRNA pos	dbSNP rs#	dbSNP cluster id	Heterozygosity	Validation	3D	Clinically Associated	Function	dbSNP allele	Protein residue	Codon pos	Amino acid pos
exon_1	16945920	161							start codon				1
exon_2	16949347	264	rs2242956	N.D.	H	Yes	Yes	Yes	missense	C	Thr [T]	2	35
									contig reference	T	Met [M]	2	35
	16949430	347	rs1799245	0.123	H	Yes	Yes	Yes	missense	G	Asp [D]	1	63
									contig reference	C	His [H]	1	63
	16949436	353	rs1800730	N.D.		Yes	Yes	Yes	missense	T	Cys [C]	1	65
									contig reference	A	Ser [S]	1	65
	16949520	437	rs28934597	N.D.		Yes	Yes	Yes	missense	C	Arg [R]	1	93
									contig reference	G	Gly [G]	1	93
	16949557	474	rs28934596	N.D.		Yes	Yes	Yes	missense	C	Thr [T]	2	105
									contig reference	T	Ile [I]	2	105
exon_3	16949833	541	rs28934595	N.D.		Yes	Yes	Yes	missense	C	His [H]	3	127
									contig reference	A	Gln [Q]	3	127
exon_4	16951197	810	rs4986950	N.D.	H	Yes	Yes	Yes	missense	T	Ile [I]	2	217
									contig reference	C	Thr [T]	2	217
									missense	A	Tyr [Y]	2	282
	16951392	1005	rs1800562	0.024	H	Yes	Yes	Yes	missense	G	Cys [C]	2	282
				0.024	H	Yes	Yes	Yes	contig reference				

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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. 🧐

Allelic Variants

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Creation Date

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Gene map

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+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

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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

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
Research and Innovation Padova, Italy Alberta Leon, BSc, PhD; Antonino D'Arrigo, BSc, PhD; Elda Del Giudice, BSc, PhD			•			
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			•			•
Acbadem Healthcare Group Acbadem 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 Boston, MA Aubrey Milunsky, MD, DSc			•	•	•	
Birc Molecular Genetics Diagnostic and Research Laboratory Istanbul, Turkey Dr. Gokul Pillai, MD, FCCMG, FACMG; Dr. Kalpal, MD, PhD			•			

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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](#)

Home Page	About GeneTests	GENEReviews	Laboratory Directory	Clinic Directory	Educational Materials
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www.genetests.org

HFE-Associated Hereditary Hemochromatosis

Summary
Diagnosis
Clinical Description
Prevalence
Differential Diagnosis
Management
Genetic Counseling
Molecular Genetics
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References
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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.

HFE-Associated Hereditary Hemochromatosis

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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
<i>HFE</i>	235200	<i>HFE</i>	<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.

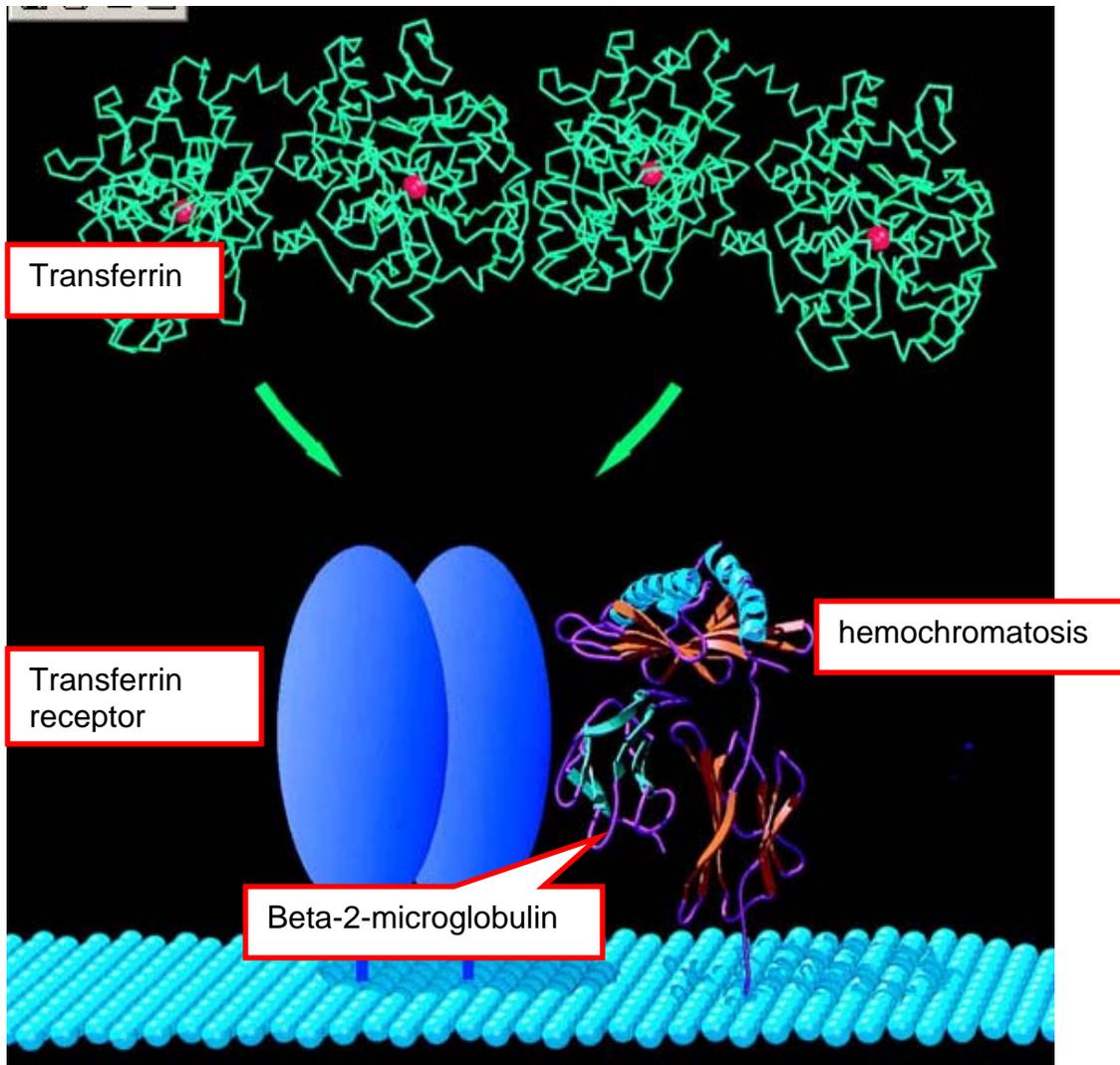
Pathologic allelic variants: At least 28 distinct mutations have been reported, most being missense or nonsense mutations. Two missense mutations account for the vast majority of disease-causing alleles in the population:

- 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

Search OMIM for Go Clear

Display Detailed Show 20 Send to

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. 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, it is now being diagnosed, this is a form of preventable cancer.

Links

- Books
- 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](#) [Try our new Sequence Viewer](#)

NC_000006.10

[26195427] 5' [26295038] 3'

■ - coding region ■ - untranslated region

NM_139005.2
 NM_139002.2
 NM_004109.3
 NM_139004.2
 NM_139003.2
 NM_139009.2
 NM_139007.2
 NM_139006.2
 NM_139010.2
 NM_139011.2
 NM_139008.2

NP_620574.1 isoform 5 precursor
 NP_620571.1 isoform 2 precursor
 NP_000401.1 isoform 1 precursor (CCN345726.1)
 NP_620573.1 isoform 1
 NP_620572.1 isoform 1
 NP_620575.1 isoform 1
 NP_620576.1 isoform 1
 NP_620577.1 isoform 1
 NP_620579.1 isoform 1
 NP_620580.1 isoform 1
 NP_620578.1 isoform 1

Links

- FASTA
- GENPEPT
- Blink
- Conserved Domains

PubMed (general)
 SNP
 SNP: Genotype
 SNP: GeneView
 Taxonomy
 UniSTS
 AceView
 CCDS
 Ensembl
 Evidence Viewer
 GDB
 GeneTests for MIM: 235200
 HGMD
 HGNC
 HPRD
 KEGG
 MGC
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Entrez Gene Info
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PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Books

Search Protein for

Limits Preview/Index History Clipboard Details

Display GenPept Show 5 Send to

Range: from begin to end Features: SNP CDD

1: NP_000401. Reports hemochromatosis p...[gi:4504377] BLink, Conserved Domains.

[Comment](#) [Features](#) [Sequence](#)

LOCUS NP_000401 348 aa linear PRI 24-FEB-2008
 DEFINITION hemochromatosis protein isoform 1 precursor [Homo sapiens].
 ACCESSION NP_000401
 VERSION NP_000401.1 GI:4504377
 DBSOURCE REFSEQ: accession [NH_000410.3](#)
 KEYWORDS .
 SOURCE Homo sapiens (human)
 ORGANISM [Homo sapiens](#)
 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
 Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
 Catarrhini; Hominidae; Homo.
 REFERENCE 1 (residues 1 to 348)
 AUTHORS Allen,K.J., Gurrin,L.C., Constantine,C.C., Osborne,N.J.,
 Delatycki,M.B., Nicoll,A.J., McLaren,C.E., Bahlo,M., Nisselle,A.E.,
 Vulpe,C.D., Anderson,G.J., Southey,M.C., Giles,G.G., English,D.R.,
 Hopper,J.L., Olynyk,J.K., Powell,L.W. and Gertig,D.M.
 TITLE Iron-overload-related disease in HFE hereditary hemochromatosis
 JOURNAL N. Engl. J. Med. 358 (3), 221-230 (2008)
 PUBMED [18199861](#)
 REMARK GeneRIF: In persons who are homozygous for the C282Y mutation,
 iron overload-related disease developed in a substantial proportion

Links

- Gene
- Genome Project
- HomoloGene
- CoreNucleotide
- Full text in PMC
- Protein (UniProtKB)
- PubMed (RefSeq)
- Gene Genotype
- GeneView in dbSNP
- Related Structure
- UniGene
- Related Sequences
- Domain Relatives
- Genome
- Map Viewer
- OMIM
- PubMed
- SNP
- Taxonomy
- LinkOut

NCBI **Related Structures**

HOME SEARCH SITE MAP PubMed Blast Entrez Structure Help

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

List All MMDB sequences, sort by Blast E value and display as Graphic

Show Page 1 at 50 structures per page

2608 hits with known structures found

Page 1 of 53 [Next >>](#)

Query

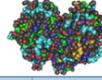
CDs HHC_I IGc

Structure

[1A6Z_A](#) 1e-125

[1A6Z_C](#) 1e-125

E Value



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

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

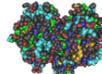
Reference: [MMDb] [PubMed]

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

E-value = 1e-125, Bit score = 588, Aligned length = 275, Sequence Identity = 100%

		10	20	30	40	50	60	70	80	
gi 4504377	23*********
1A6Z A	1*********
		90	100	110	120	130	140	150	160	
gi 4504377	103*********
1A6Z A	81*********
		170	180	190	200	210	220	230	240	
gi 4504377	183*********
1A6Z A	161*********
		250	260	270						
gi 4504377	263*********
1A6Z A	241*********

Reference:
Wang Y, Address KJ, Chen J, Geer LY, He J, He S, Lu S, Madej T, Marchler-Bauer A, Thiessen PA, Zhang N, Bryant SH (2007), *MMDb: annotating protein sequences with Entrez's 3D-structure database*, *Nucleic Acids Res.* **35**(D):298-300.



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

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

Reference: [MMDB] [PubMed]

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

E-value = 1e-125, Bit score = 588, Aligned length = 275, Sequence Identity = 100%

		0	20	30	40	50	60	70	80	
gi 4504377	23	RLLRSHSLHYLFGASEQDLGLSLFEALGVYDQLFVFDHESRRVEPTPWSSRISSQMWLQSLKQWDHMFVDF	102							
1A6Z A	1	RLLRSHSLHYLFGASEQDLGLSLFEALGVYDQLFVFDHESRRVEPTPWSSRISSQMWLQSLKQWDHMFVDF	80							
		90	100	110	120	130	140	150	160	
gi 4504377	103	WTIMENHNHSHKESHTLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPDTLDURAAEPRAWPTKLEWERHKIRARQNRAY	182							
1A6Z A	81	WTIMENHNHSHKESHTLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPDTLDURAAEPRAWPTKLEWERHKIRARQNRAY	160							
		170	180	190	200	210	220	230	240	
gi 4504377	183	LERDCPAQLQQLLELGRGVLDQQVPLVRYTHVTSVYTLRCRALNYPQNIHKWLKDKOPMDAKEFEKDVLPNGDG	262							
1A6Z A	161	LERDCPAQLQQLLELGRGVLDQQVPLVRYTHVTSVYTLRCRALNYPQNIHKWLKDKOPMDAKEFEKDVLPNGDG	240							
		250	260	270						
gi 4504377	263	TYOGWITLAVPPGEGRYTCQVEHPGLDQPLIVIV	297							
1A6Z A	241	TYOGWITLAVPPGEGRYTCQVEHPGLDQPLIVIV	275							

Reference:

Wang Y, Address KJ, Chen J, Gear LV, He J, He S, Lu S, Madaj T, Marchler-Bauer A, Thiessen PA, Zhang N, Bryant SH (2007), *MMDB: annotating protein sequences with Entrez's 3D-structure database*, *Nucleic Acids Res.* 35(D):298-300.



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.

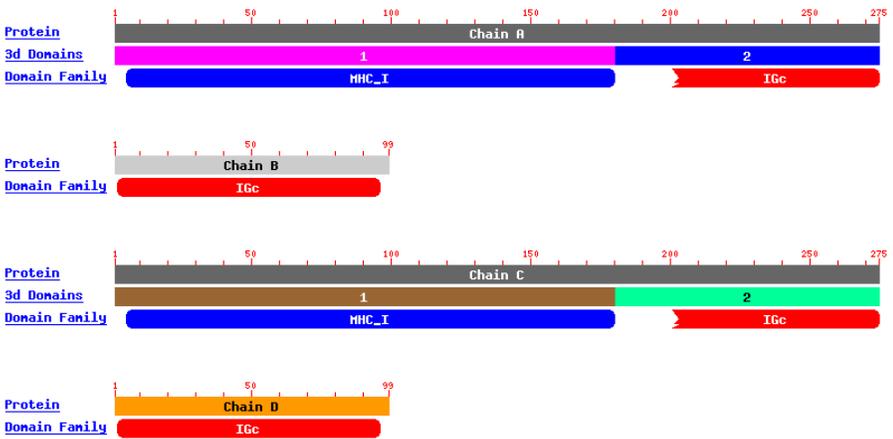
Deposition: 1998/3/4

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.



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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 ₁ 2 ₁ 2 ₁

Unit Cell

Length [Å]	a	b	c
68.80	100.10	147.60	
Angles [°]	alpha	beta	gamma
90.00	90.00	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** Common Name: **Human**

Images and Visualization

Biological Molecule

Display Options

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- WebMol
- MBT SimpleViewer*
- MBT Protein Workshop
- QuickPDB
- All Images

* Capable of displaying biological molecules

Quick Tips: RCSB has a new Web Services API for software developers and tutorials for developers using C/C++, Java, Python and Perl. Click here.

NCBI

Structure Summary
MMDB

PubMed | BLAST | Structure | Taxonomy | OMLM | Help? | Cn3d

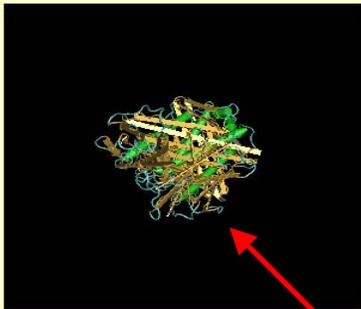
Reference: Lebron JA, Bennett MJ, Vaughn DE, Chirino AJ, Snow PM, Mintier GA, Feder JN, Bjorkman PJ [Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor](#) *Cell* v93, p. 111-123

Description: Hfe (Human) Hemochromatosis Protein.

Deposition: 1998/3/4

Taxonomy: [Homo sapiens](#)
MMDB: [9816](#) PDB: [1A6Z](#)

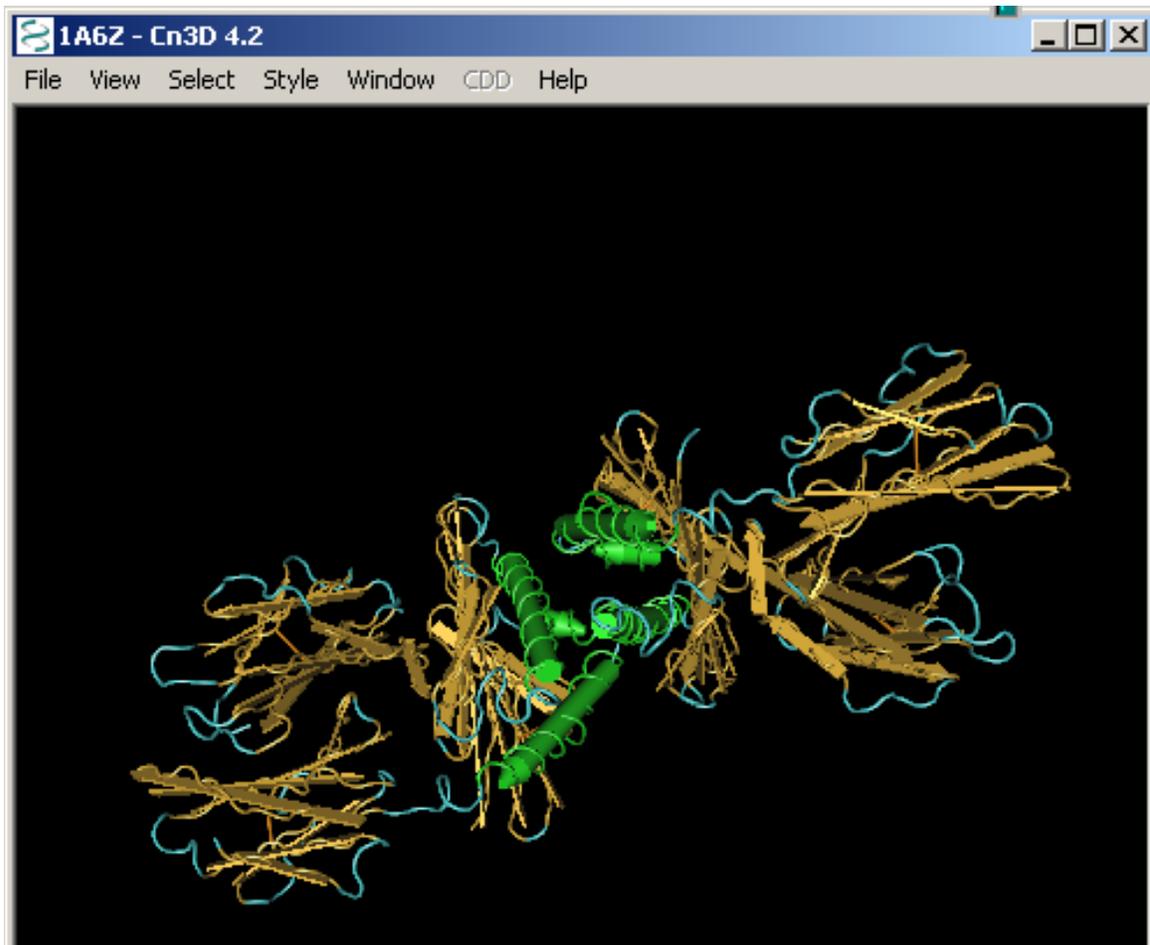
Molecular components in the MMDB structure are listed below. The icons indicate macromolecular chains, 3D domains, protein classifications and ligands. Please hold the mouse over each icon for more information on the component. You may also click the thumbnails below to view corresponding chains and domains in Cn3D.

Protein  **3d Domains** **Domain Family**

Sequence A

1 50 100 150 200 250 275

1 HHC_1 2 IgC



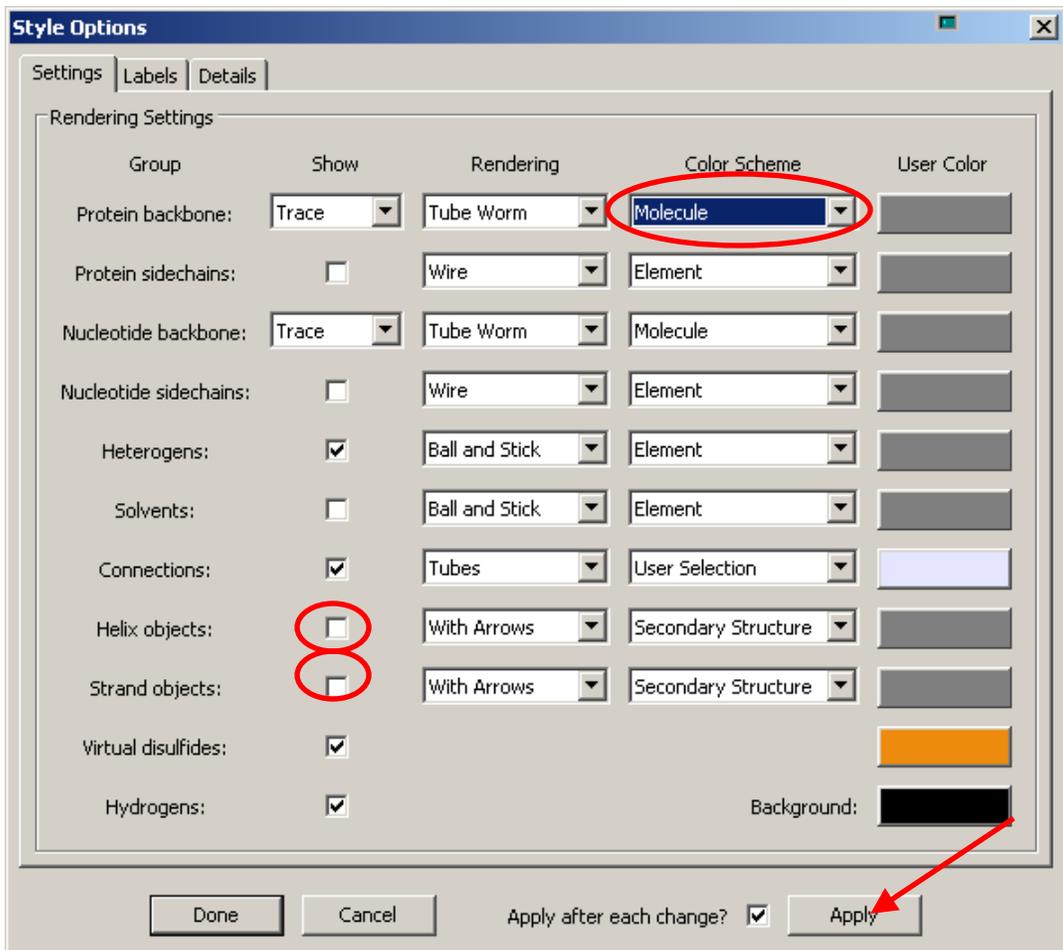
1A6Z - Sequence/Alignment Viewer

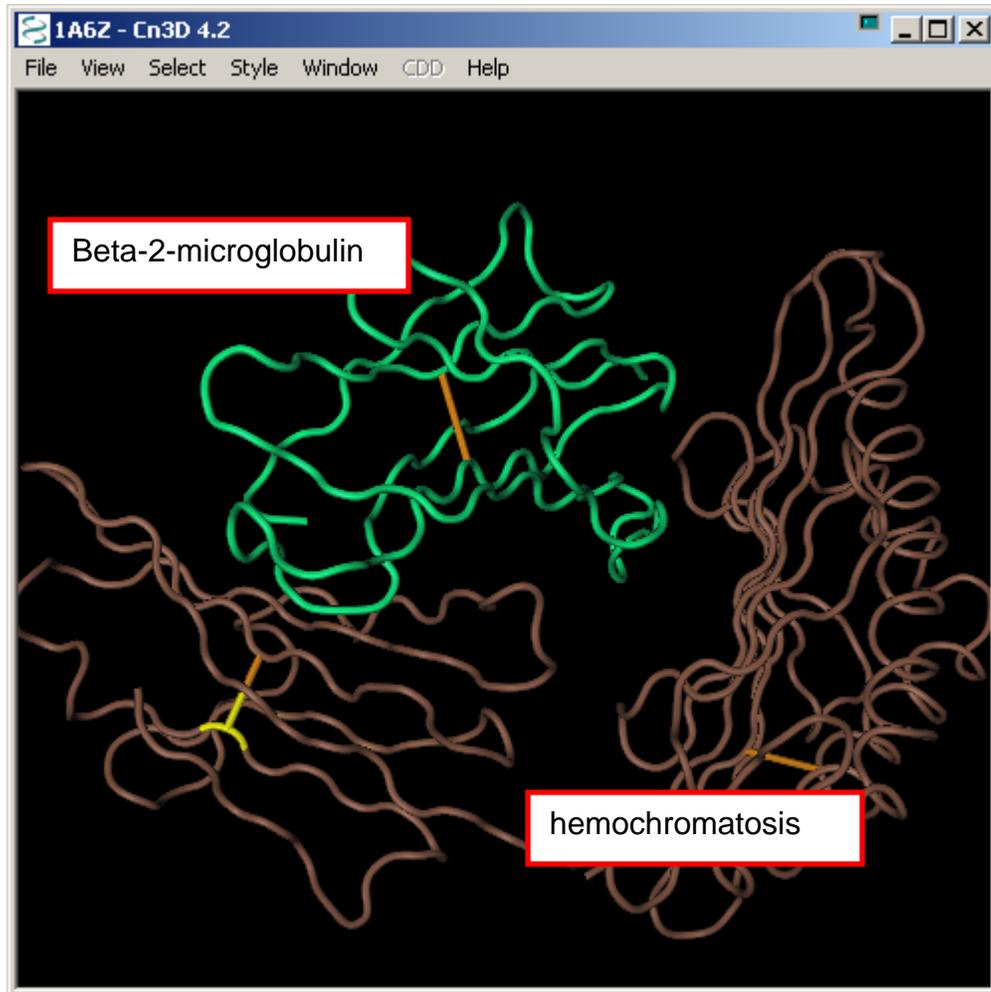
View Edit Mouse Mode Unaligned Justification Imports

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1A6Z_A rllrshslhyifmgaseeqdligslfealgyvddqlfvfydhessrveprtpwvssrissqmwlqlsqsikgwdhmfvtvdfwtimenhnhskeshl
1A6Z_B iqrtpkiqvysrhpaeangkfnlncyvsghpsdievdllkngeriekvehsdlsfskdwsfylllytftptekdeyacrnhvtlsqpkivkw
1A6Z_C rllrshslhyifmgaseeqdligslfealgyvddqlfvfydhessrveprtpwvssrissqmwlqlsqsikgwdhmfvtvdfwtimenhnhskeshl
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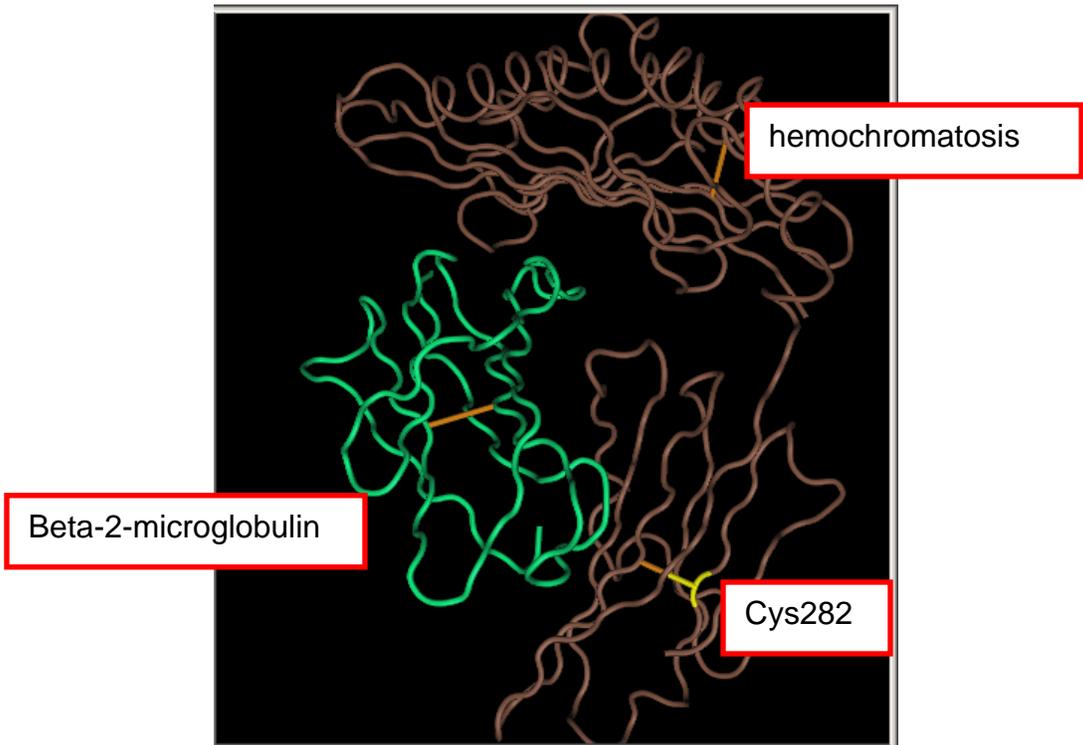
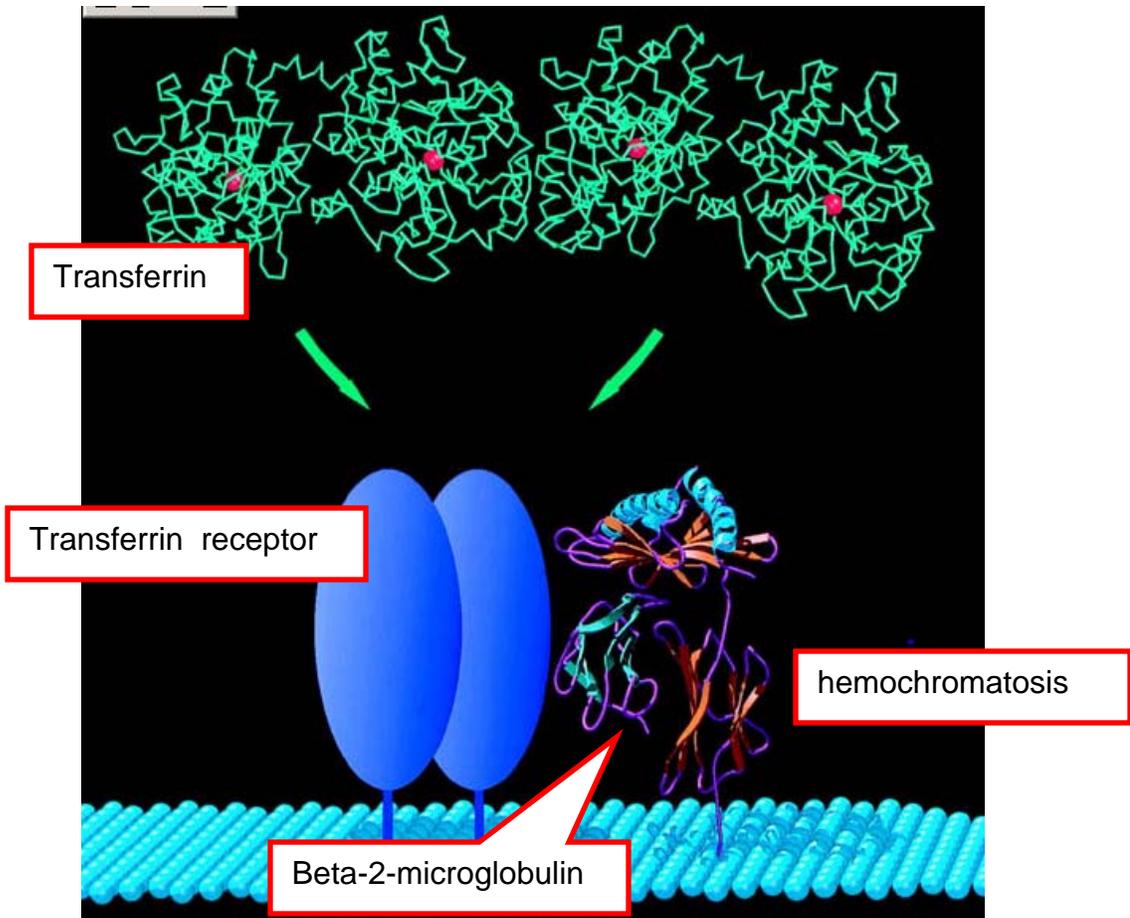


```

IA62 - Sequence/Alignment Viewer
View Edit Mouse Mode Unaligned Justification Imports
IA62_A v i s s v t t l r c r a l n y y p q n i t m k w l k d k q p m d a k e f e p k d v l p n g d g t y q g w i l 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
IA62_B
IA62_C v t s s v t t l r c r a l n y y p q n i t m k w l k d k q p m d a k e f e p k d v l p n g d g t y q g w i l 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
IA62_D
IA62_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. 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? 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" link in the left blue bar 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.

Let us first take a look at the structure of the wild type protein. Click on the NP_000509 protein link and select GENPEPT. Click on "Related Structure" from the Links menu. The output contains a list of similar proteins with 3D structures known. The entry, 1DXT_B, represents the structure of deoxyhemoglobin chain B. Click on the arrow next to 1DXT_B to get the sequence alignment of the query protein to the B chain of 1DXT. 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 structure image.

Search for the structure of the mutant (deoxyhemoglobin S) in the structure database, if available. 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 the structure image on the MMDB page. 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 residue

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.