Mini Courses NCBI Resources one course at a time

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.

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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. 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? 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.

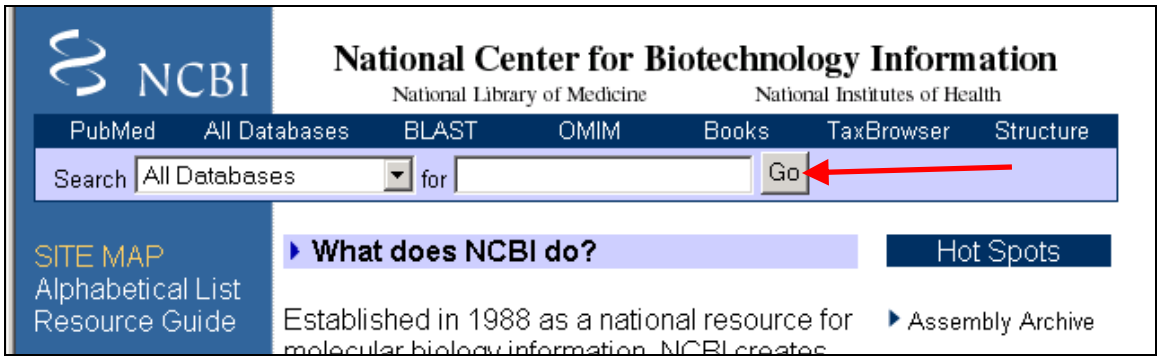
B. Visualization of hemochromatosis protein and beta-2-microglobulin complex

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 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 cystenie 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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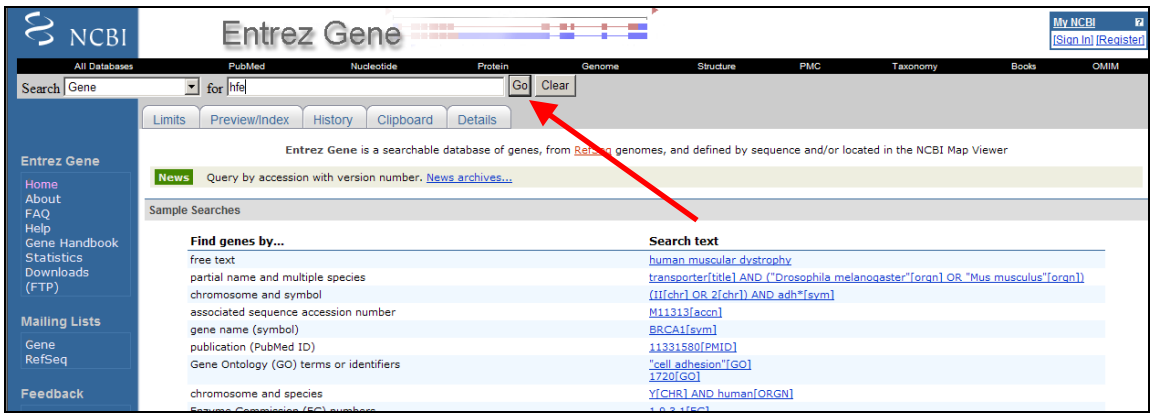
OMIA: online Mendelian Inheritance in Animals
CoreNucleotide: Core subset of nucleotide sequence records
EST: Expressed Sequence Tag records
GSS: Genome Survey Sequence records
Protein: sequence database
Genome: whole genome sequences
Structure: three-dimensional macromolecular structures
Taxonomy: organisms in GenBank
SNP: single nucleotide polymorphism
Gene: gene-centered information
HomoloGene: eukaryotic homology groups
PubChem Compound: unique small molecule chemical structures
PubChem Substance: deposited chemical substance records
Genome Project: genome project information
dbGaP: genotype and phenotype
UniGene: gene-oriented clusters of transcript sequences
CDD: conserved protein domain database
3D Domains: domains from Entrez Structure
UniSTS: markers and mapping data
PopSet: population study data sets
GEO Profiles: expression and molecular abundance profiles
GEO DataSets: experimental sets of GEO data
Cancer Chromosomes: cytogenetic databases
PubChem BioAssay: bioactivity screens of chemical substances
GENSAT: gene expression atlas of mouse central nervous system
Probe: sequence-specific reagents
Protein Clusters: a collection of related protein sequences
Journals: detailed information about the journals indexed in PubMed and other Entrez databases
NLM Catalog: catalog of books, journals, and audiovisuals in the NLM collections
MeSH: detailed information about NLM's controlled vocabulary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partial name and multiple species
transporter[title] AND ("Drosophila melanogaster"[orgn] OR "Mus musculus"[orgn])
chromosome and symbol
(II[chr] OR 2[chr]) AND adh*[sym]
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gene name (symbol)
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publication (PubMed ID)
11331580[PMID]
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"cell adhesion"[GO]
1720[GO]
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☐ 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 (26195427..26205038)
MIM: 235200
GeneID: 3077

☐ 2: Hfe — Order cDNA clone, Links

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 — Links

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

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☐ **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: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

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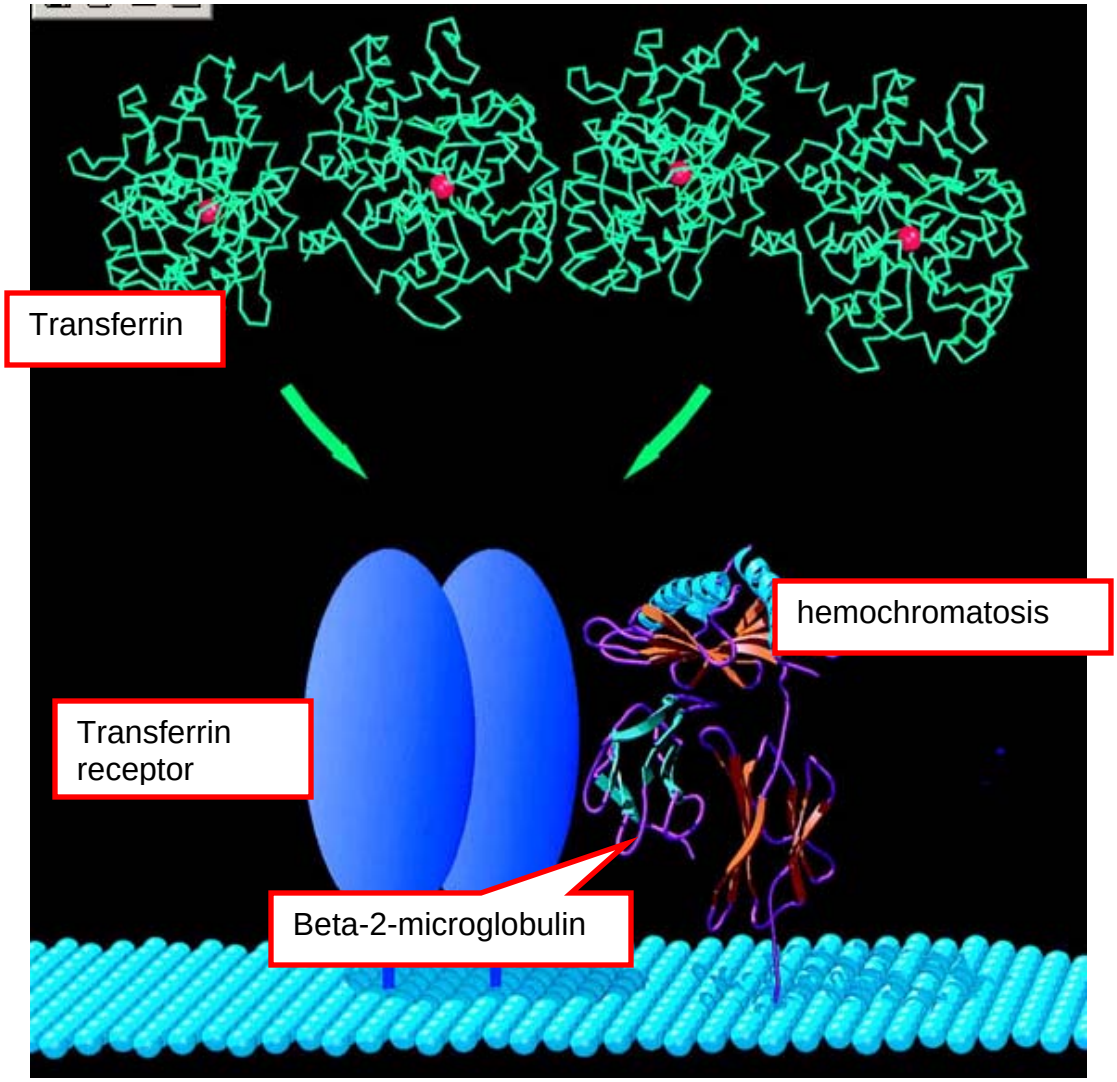
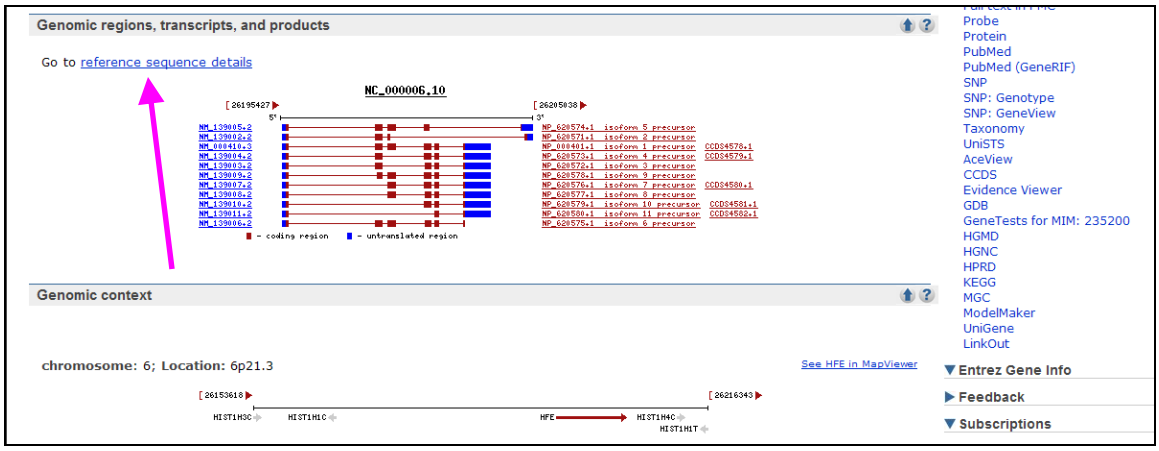


Bacon et al. Gastroenterology, 116:193-207, Figure 4

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.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Names
hemochromatosis protein
MHC class I-like protein HFE
hereditary hemochromatosis protein HLA-H
NCBI Reference Sequences (RefSeq)
Genomic
1. NG_001335.1 Reference
Range 71162..80773
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mRNA and Protein(s)
1. NM_000410.3→NP_000401.1 hemochromatosis protein isoform 1 precursor
Description Transcript Variant: This variant (1) encodes the longest isoform.
Source sequence(s) AF115265,AJ249337,U91328
Consensus CDS CCDS4578.1
Conserved Domains (2) summary
cd00098 Location:223-298 Blast Score:169
IGc; Immunoglobulin domain constant region subfamily; members of the IGc subfamily are components of immunoglobulins, T-cell receptors, CD1 cell surface glycoproteins, secretory glycoproteins A/C, and Major Histocompatibility Complex (MHC) class I/II molecules
pfam00129 Location:27-202 Blast Score:314
MHC_I; Class I Histocompatibility antigen, domains alpha 1 and 2
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 particlete 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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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: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.

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- coding region
- untranslated region

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

NCBI **Single Nucleotide Polymorphism**

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

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

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

Gene Model (mRNA alignment) information from genome sequence

Total gene model (contig mRNA transcript): 22

mrna	transcript	protein	mrna orientation	Contig	Contig Label	List SNP
NM_000410	plus strand	NP_000401	forward	NT_007592	reference	<- currently shown
NM_000410	plus strand	NP_000401	forward	NW_922984	Celera	View snp on GeneModel
NM_139002	plus strand	NP_620571	forward	NT_007592	reference	View snp on GeneModel
NM_139002	plus strand	NP_620571	forward	NW_922984	Celera	View snp on GeneModel
NM_139003	plus strand	NP_620572	forward	NT_007592	reference	View snp on GeneModel
NM_139003	plus strand	NP_620572	forward	NW_922984	Celera	View snp on GeneModel
NM_139004	plus strand	NP_620573	forward	NT_007592	reference	View snp on GeneModel
NM_139004	plus strand	NP_620573	forward	NW_922984	Celera	View snp on GeneModel
NM_139005	plus strand	NP_620574	forward	NT_007592	reference	View snp on GeneModel
NM_139005	plus strand	NP_620574	forward	NW_922984	Celera	View snp on GeneModel
NM_139006	plus strand	NP_620575	forward	NT_007592	reference	View snp on GeneModel
NM_139006	plus strand	NP_620575	forward	NW_922984	Celera	View snp on GeneModel
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# cluster id	Hetero-zygosity	Validation	3D	OMIM	Function	dbSNP allele	Protein residue	Codon pos	Amino acid pos
exon_1	16945920	161						start codon				1
exon_2	16949347	264	rs2242956	N.D.	H	Yes		missense	C	Thr [T]	2	35
				N.D.	H	Yes		contig reference	T	Met [M]	2	35
	16949430	347	rs1799945	0.123	H	Yes		missense	G	Asp [D]	1	63
				0.123	H	Yes	Yes	contig reference	C	His [H]	1	63
	16949436	353	rs1800730	N.D.		Yes		missense	T	Cys [C]	1	65
				N.D.		Yes	Yes	contig reference	A	Ser [S]	1	65
	16949520	437	rs28934597	N.D.		Yes		missense	C	Arg [R]	1	93
				N.D.		Yes	Yes	contig reference	G	Gly [G]	1	93
	16949557	474	rs28934596	N.D.		Yes		missense	C	Thr [T]	2	105
				N.D.		Yes	Yes	contig reference	T	Ile [I]	2	105
exon_3	16949833	541	rs28934595	N.D.		Yes		missense	C	His [H]	3	127
				N.D.		Yes	Yes	contig reference	A	Gln [Q]	3	127
exon_4	16951197	810	rs4986950	N.D.	H	Yes		missense	T	Ile [I]	2	217
				N.D.	H	Yes		contig reference	C	Thr [T]	2	217
	16951392	1005	rs1800562	0.024	H	Yes		missense	A	Tyr [Y]	2	282
				0.024	H	Yes	Yes	contig reference	G	Cys [C]	2	282
exon_6	16952684	1186	rs35201683	0.053				synonymous	T	Tyr [Y]	3	342
				0.053				contig reference	C	Tyr [Y]	3	342

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Online Mendelian Inheritance in Man
Johns Hopkins University

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Clinical Synopsis
Gene map

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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.

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Clinical Synopsis
Gene map

Entrez Gene

+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]

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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			•			•
Acibadem Healthcare Group Acibadem Genetic Diagnostic Center Istanbul, Turkey Ender Altiok, 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			•	•	•	
Burc Molecular Genetics Diagnostic and Research Laboratory Istanbul, Turkey						

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Search Result for OMIM# 235200

HFE- Associated Hereditary Hemochromatosis | Testing | Research | Reviews | Resources

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HFE-Associated Hereditary Hemochromatosis

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Title Index

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GeneReviews
www.genetests.org

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.

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
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.

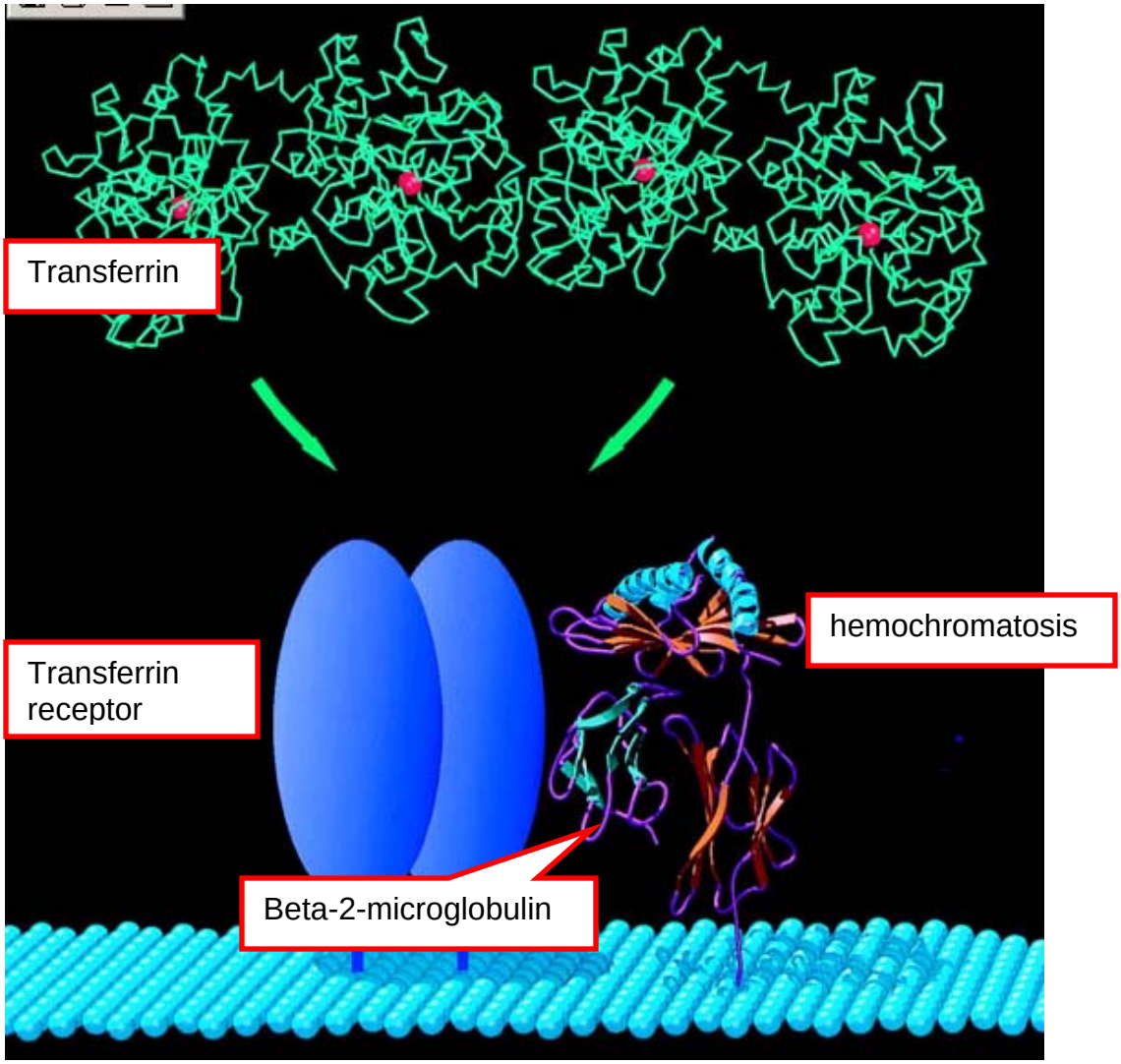
Pathologic allelic variants: At least 28 distinct mutations have been reported, most being missense or nonsense mutations. Two missense mutations account for the vast majority of disease-causing alleles in the population:

- 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.

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HEMOCHROMATOSIS, HEREDITARY; HH
HFE GENE, INCLUDED; HFE, INCLUDED
Gene map locus 6p21.3
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PubMed (calculated)
PubMed (cited)
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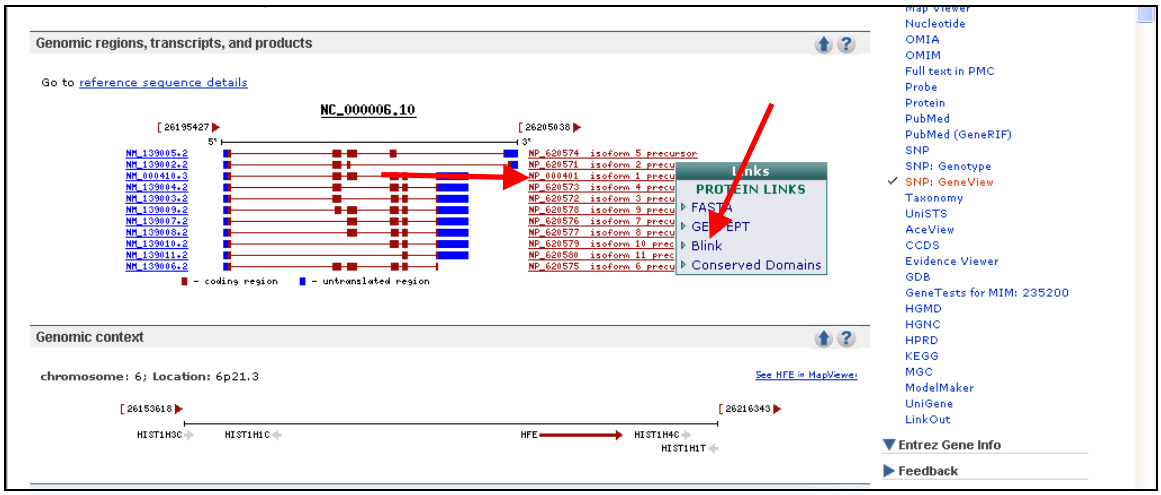
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Blink
Conserved Domains
Genomic context
chromosome: 6; Location: 6p21.3
See HFE in MapViewer
HFE
Nucleotide
OMIA
OMIM
Full text in PMC
Probe
Protein
PubMed
PubMed (GeneRIF)
SNP
SNP: Genotype
SNP: GeneView
Taxonomy
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AceView
CCDS
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Query: gi|4504377 hemochromatosis protein isoform 1 precursor [Homo sapiens]
Matching gi: 80748852, 20250786, 11094315, 109658506, 109658670, 1469790, 83323630, 22854810, 38502807, 15115850, 1890180, 2088551, 2370111, 2497915, 112053064, 112088318, 57114069, 119575928, 14100030, 29709343

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

200 BLAST hits to 20 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	P	ACCESSION	GI	PROTEIN DESCRIPTION
Conserved Domain Database hits				
1870	31	AAG29572	11094315	hemochromatosis termination variant terE6; HFE [Homo sapiens]
1870	31	AAI17204	109658506	Hemochromatosis [Homo sapiens]
1870	31	AAI17202	109658670	Hemochromatosis [Homo sapiens]
1870	31	AAC51823	1469790	HLA-H
1870	29	AAN09793	22854810	hereditary hemochromatosis [Pan troglodytes]
1870	29	P60018	38502807	Hereditary hemochromatosis protein homolog precursor (HLA-H)
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	29	NP_001...	57114069	hemochromatosis protein [Pan troglodytes]
1870	31	EAW55524	119575928	hemochromatosis, isoform CRA_i [Homo sapiens]
1776	31	AAH74721	50960016	HFE protein [Homo sapiens]
1772	31	AAC62646	3695107	hemochromatosis splice variant del14E4 [Homo sapiens]
1772	31	EAW55523	119575927	hemochromatosis, isoform CRA_h [Homo sapiens]
1772	31	NP_620575	21040347	hemochromatosis protein isoform 6 precursor [Homo sapiens]
1713	31	EAW55521	119575925	hemochromatosis, isoform CRA_f [Homo sapiens]
1713	31	CAC67792	15485419	hemochromatosis protein [Homo sapiens]
1713	31	NP_620578	21040353	hemochromatosis protein isoform 9 precursor [Homo sapiens]
1694	26	XP_001...	109069866	PREDICTED: hemochromatosis protein isoform 9 [Macaca mulatta]
1681	26	XP_001...	109069868	PREDICTED: hemochromatosis isoform 7 [Macaca mulatta]
1625	26	XP_001...	109069870	PREDICTED: hemochromatosis isoform 6 [Macaca mulatta]

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	P	ACCESSION	GI	PROTEIN DESCRIPTION
Conserved Domain Database hits				
1517	●	1A6ZC	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	●	1DE4A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	●	1DE4D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	●	1DE4G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	●	1A6ZA	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
525	●	1B71A	3891929	Chain A, The Crystal Structure Of H-2dd Mhc Class I In Complex With The Hiv-1 Derived Peptide P18-11
507	●	1S7RA	48425592	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	●	1S7RD	48425595	Chain D, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	●	1S7SA	48425598	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	●	1S7TA	48425601	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	●	1S7TD	48425604	Chain D, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	●	1S7QA	48425589	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
502	●	1Q94D	49258567	Chain D, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	●	1QVOA	49258584	Chain A, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	●	1QVOD	49258587	Chain D, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	●	2HN7A	119389933	Chain A, Hla-A1101 In Complex With Hbv Peptide Homologue
502	●	1X7QA	73535522	Chain A, Crystal Structure Of Hla-A1101 With Sars Nucleocapsid Peptide
502	●	1Q94A	49258564	Chain A, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	●	2BCKD	88192434	Chain D, Crystal Structure Of Hla-A2402 Complexed With A Telomerase Peptide
502	●	2BCKA	88192431	Chain A, Crystal Structure Of Hla-A2402 Complexed With A Telomerase Peptide

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

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

Reference: [MMDB] [PubMed]

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

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

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                      10        20        30        40        50        60        70        80
                ....*....|....*....|....*....|....*....|....*....|....*....|....*....|....*....|
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1A6Z_C        1 RLLRSHSLHYLFMGASEQDLGLSLFEALGYVDDQLFVFYDHESRRVEPRTPWVSSRISSQMWLQLSQSLKGWDHMFTVDF 80

                      90       100       110       120       130       140       150       160
                ....*....|....*....|....*....|....*....|....*....|....*....|....*....|....*....|
gi 4504377  103 WTIMENHNHSKESHTLQVILGCEMQEDNSTEGYWKYGYDGQDHLEFCPDTLDWRAAEPRAWPTKLEWERHKIRARQNRAY 182
1A6Z_C       81 WTIMENHNHSKESHTLQVILGCEMQEDNSTEGYWKYGYDGQDHLEFCPDTLDWRAAEPRAWPTKLEWERHKIRARQNRAY 160

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                ....*....|....*....|....*....|....*....|....*....|....*....|....*....|....*....|
gi 4504377  183 LERDCPAQLQQLLELGRGVLDQQVPPLVKVTHHVTSSVTTLRCRALNYYPQNITMKWLKDKQPMDAKEFEPKDVLPNGDG 262
1A6Z_C      161 LERDCPAQLQQLLELGRGVLDQQVPPLVKVTHHVTSSVTTLRCRALNYYPQNITMKWLKDKQPMDAKEFEPKDVLPNGDG 240

                     250       260       270
                ....*....|....*....|....*....|....*
gi 4504377  263 TYQGWITLAVPPGEEQRYTCQVEHPGLDQPLIVIW 297
1A6Z_C      241 TYQGWITLAVPPGEEQRYTCQVEHPGLDQPLIVIW 275
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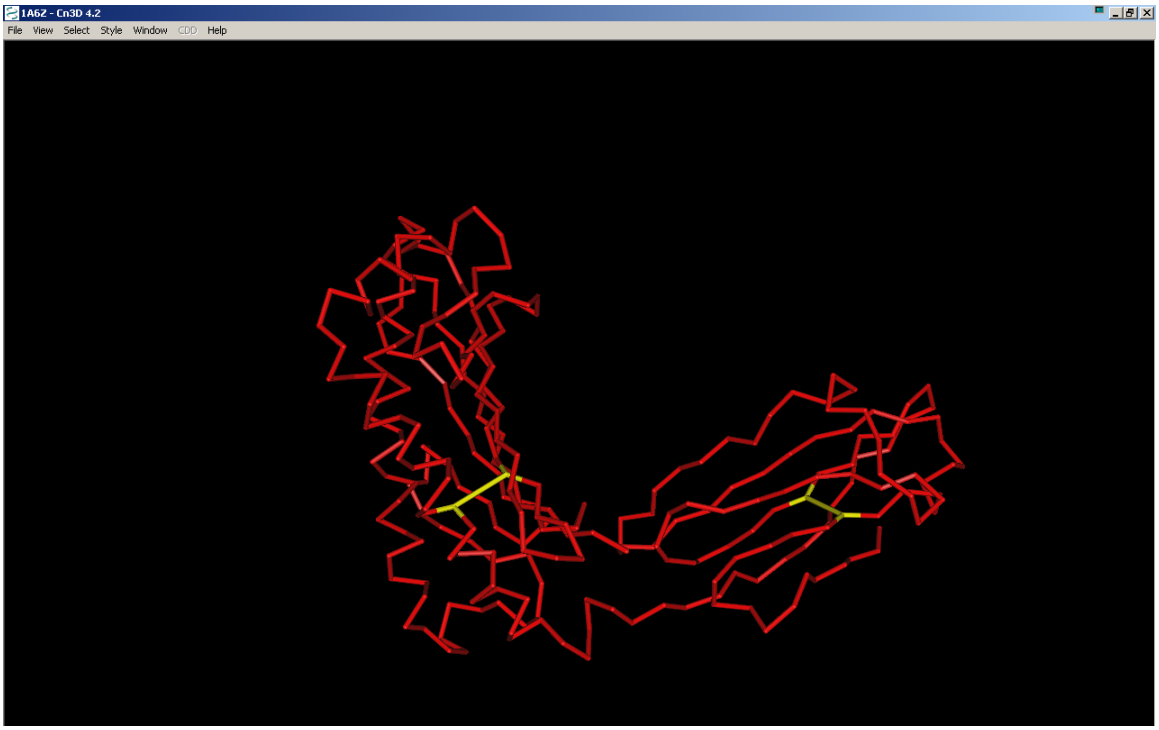
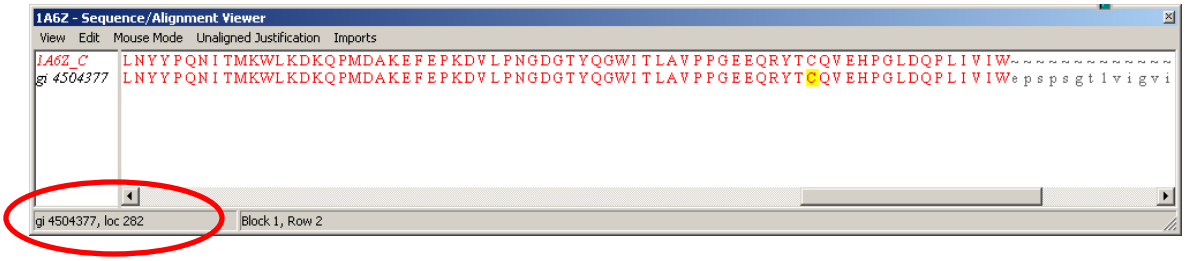

1A6Z - Cn3D 4.2
File View Select Style Window CDD Help


1A6Z - Sequence/Alignment Viewer
View Edit Mouse Mode Unaligned Justification Imports
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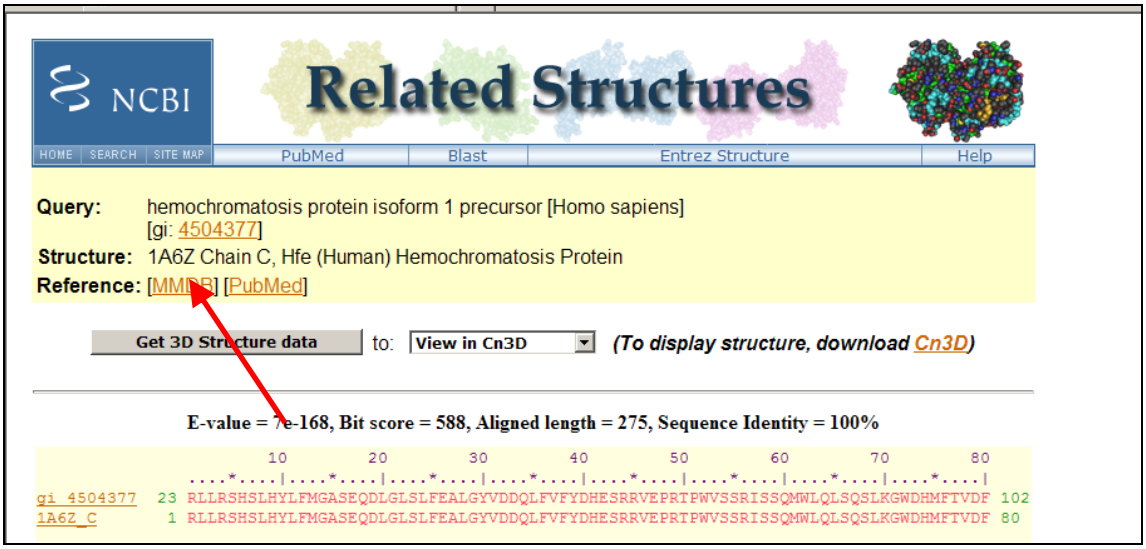
gi 4504377, loc 282
Block 1, Row 2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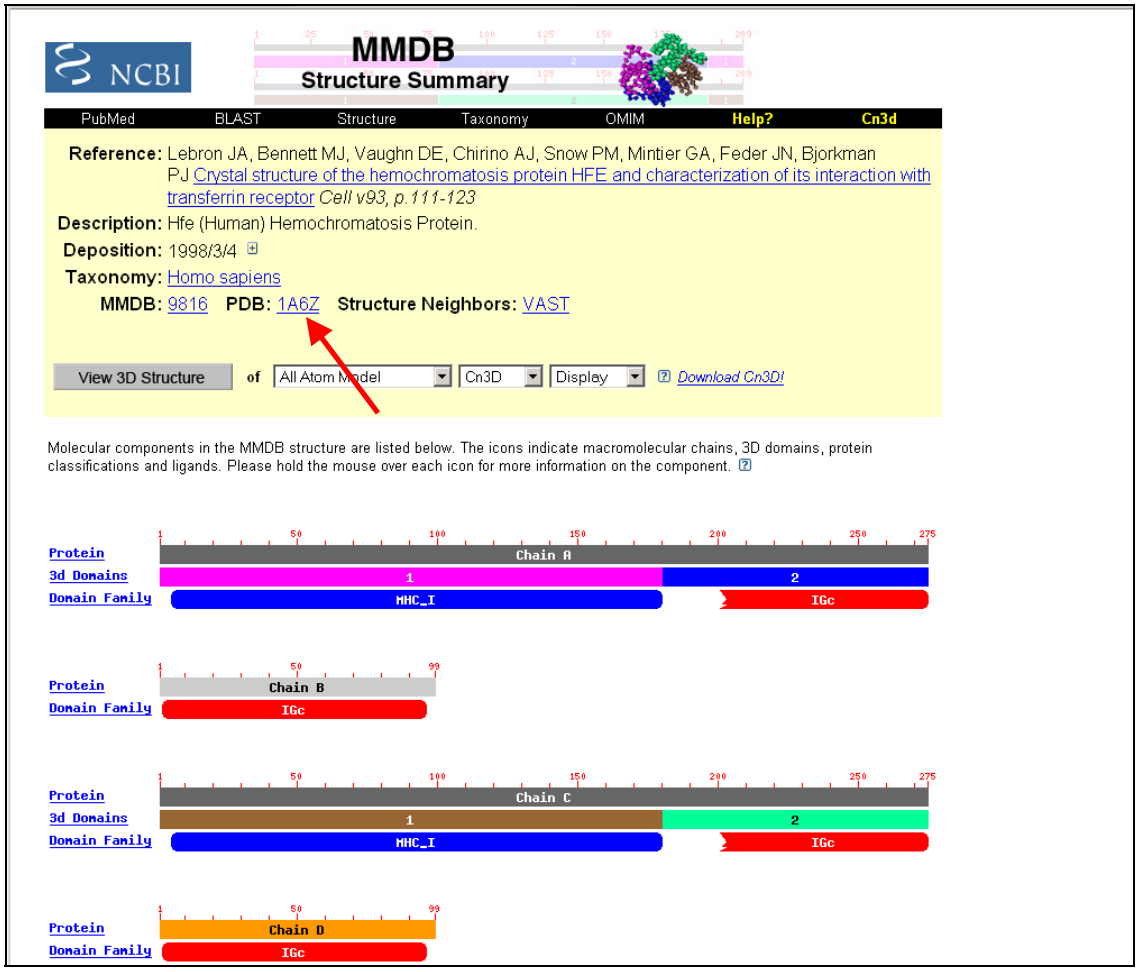
Related Structures
HOME SEARCH SITE MAP
PubMed
Blast
Entrez Structure
Help
Query: hemochromatosis protein isoform 1 precursor [Homo sapiens]
[gi: 4504377]
Structure: 1A6Z Chain C, Hfe (Human) Hemochromatosis Protein
Reference: [MMDB] [PubMed]
Get 3D Structure data
to:
View in Cn3D
(To display structure, download Cn3D)
E-value = 7e-168, Bit score = 588, Aligned length = 275, Sequence Identity = 100%
gi 4504377 23 RLLRSHSLHYLFMGASEQDLGLSLFEALGYVDDQLFVFYDHESRRVEPRTPWVSSRISSQMWLQLSQSLKGWDHMFTVDF 102
1A6Z_C 1 RLLRSHSLHYLFMGASEQDLGLSLFEALGYVDDQLFVFYDHESRRVEPRTPWVSSRISSQMWLQLSQSLKGWDHMFTVDF 80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Structure Summary
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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
3d Domains
Domain Family
Chain A
1
2
MHC_I
IGc
Protein
Domain Family
Chain B
IGc
Protein
3d Domains
Domain Family
Chain C
1
2
MHC_I
IGc
Protein
Domain Family
Chain D
IGc

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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] 2.60; R-Value 0.233 (obs.); R-Free 0.277; Space Group $P\ 2_1\ 2_1\ 2_1$
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: Chines hamster ovary cells (cho), cricetulus griseus Polymer: 2 Scientific Name: Homo sapiens Name: Human Human

Images and Visualization
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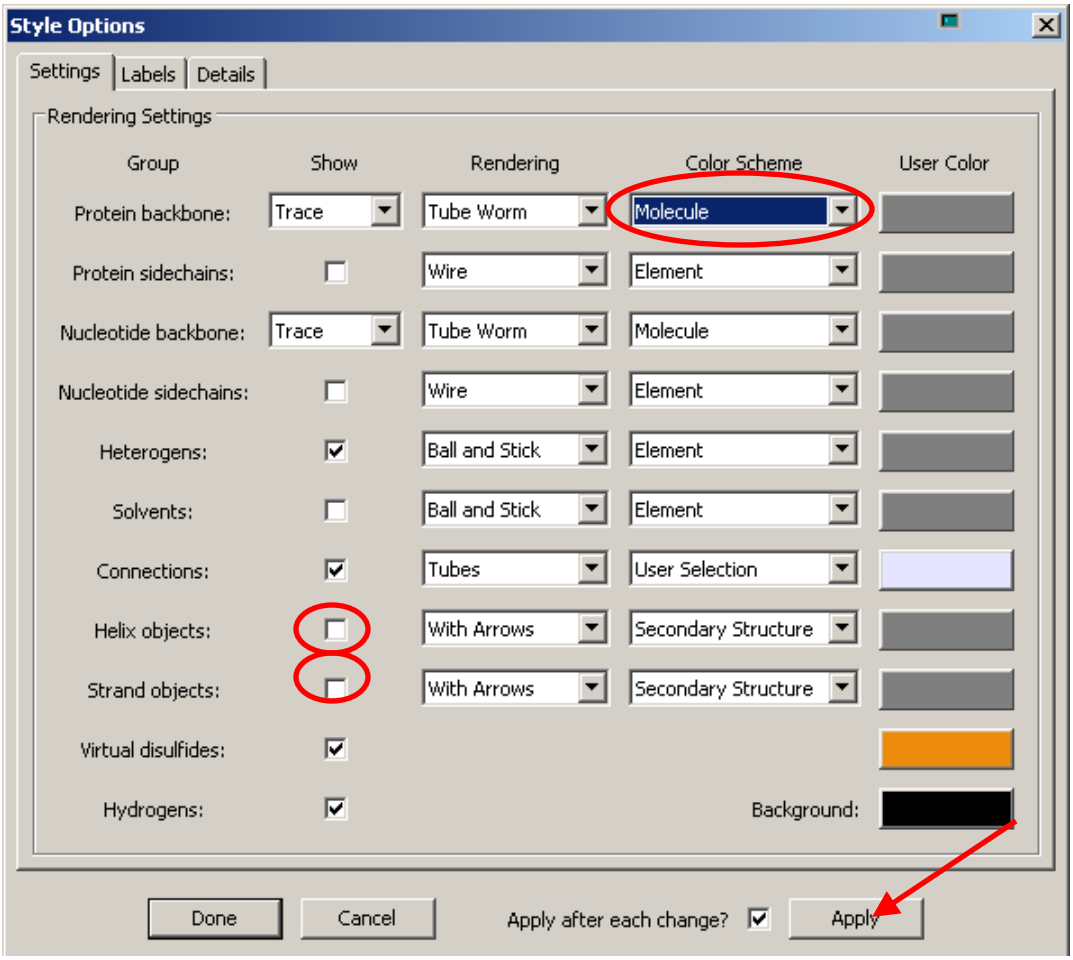
Reference: Lebron JA, Bennett MJ, Vaughn DE, Chirino AJ, Snow PM, Mintier GA, Feder JN, Bjorkman PJ Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor *Cell v93, p.111-123*
Description: Hfe (Human) Hemochromatosis Protein.
Deposition: 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 — Sequence A
3d Domains — 1, 2
Domain Family — MHC_I, IGc

1A6Z - Cn3D 4.2
File View Select Style Window CDD Help

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 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 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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Nucleotide backbone:
Trace
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Molecule
Nucleotide sidechains:
Wire
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Heterogens:
Ball and Stick
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Solvents:
Ball and Stick
Element
Connections:
Tubes
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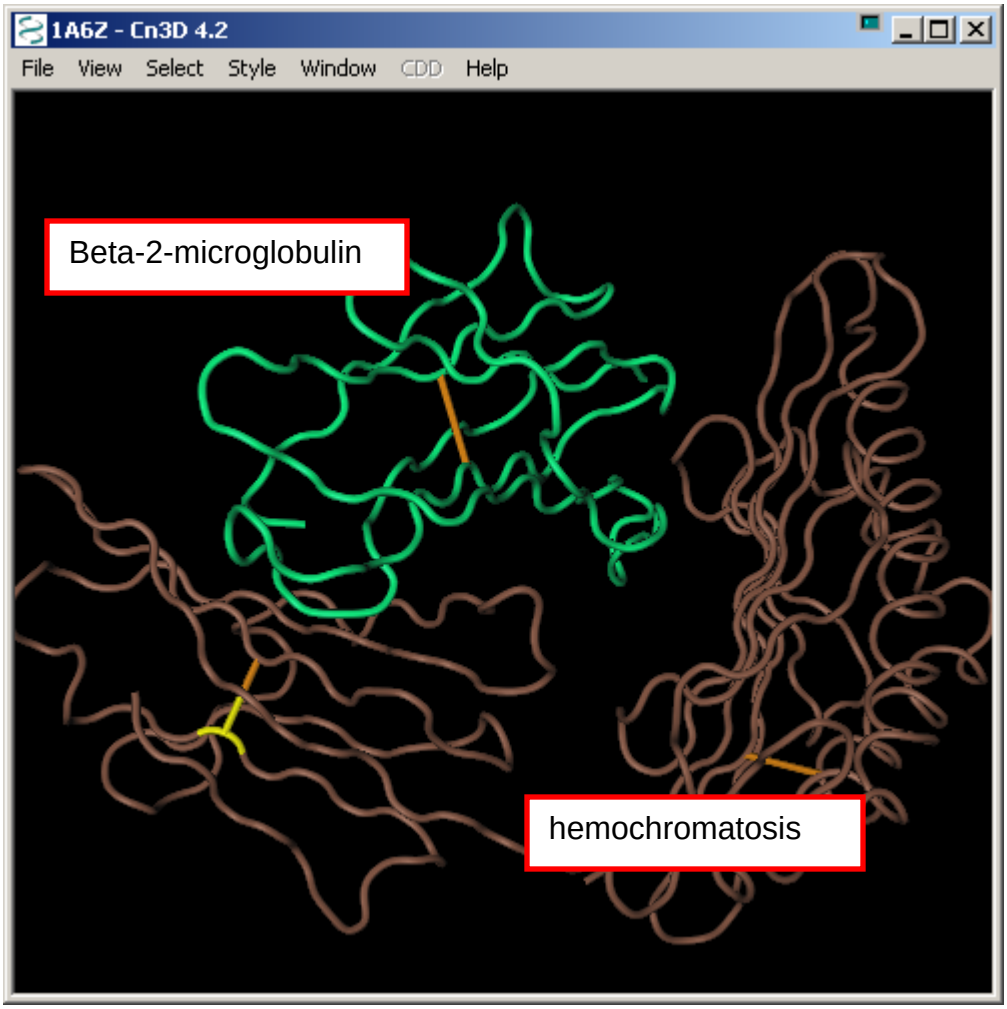
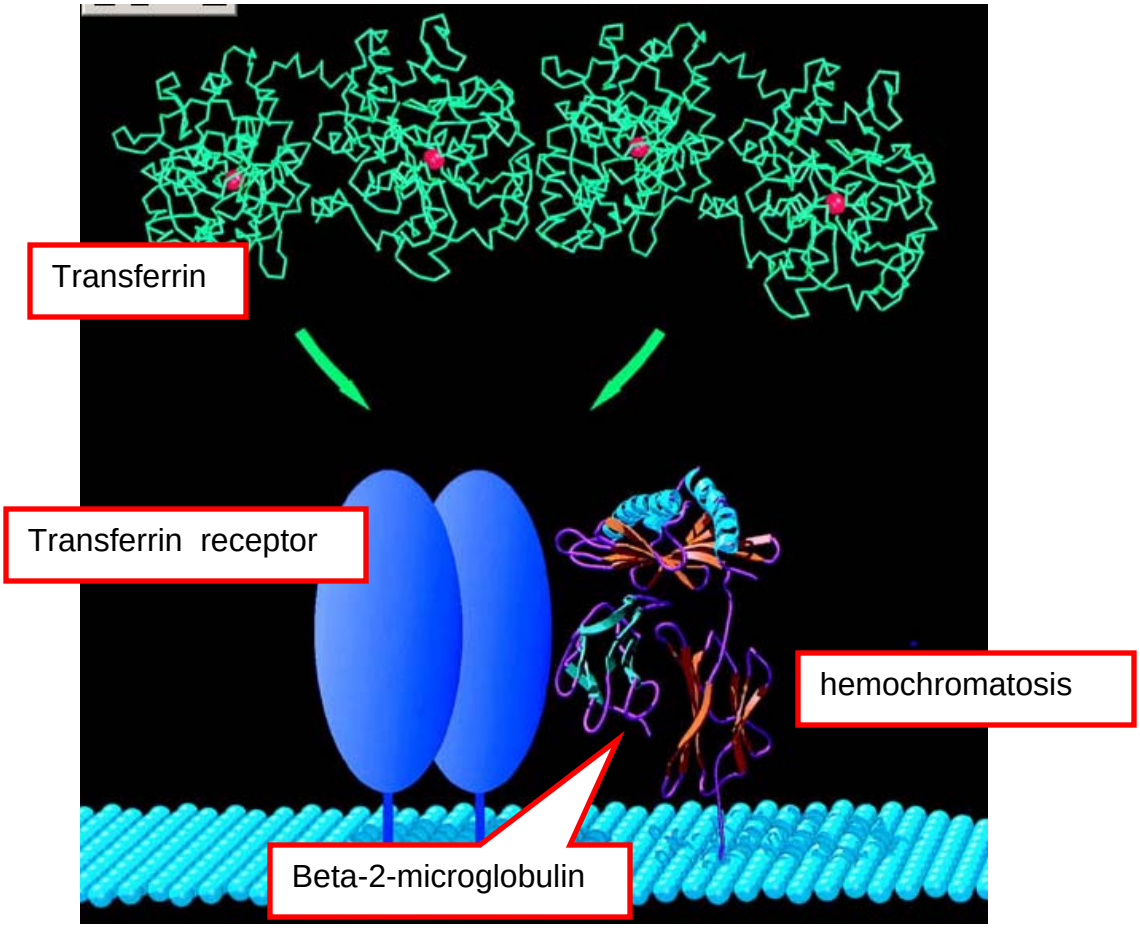
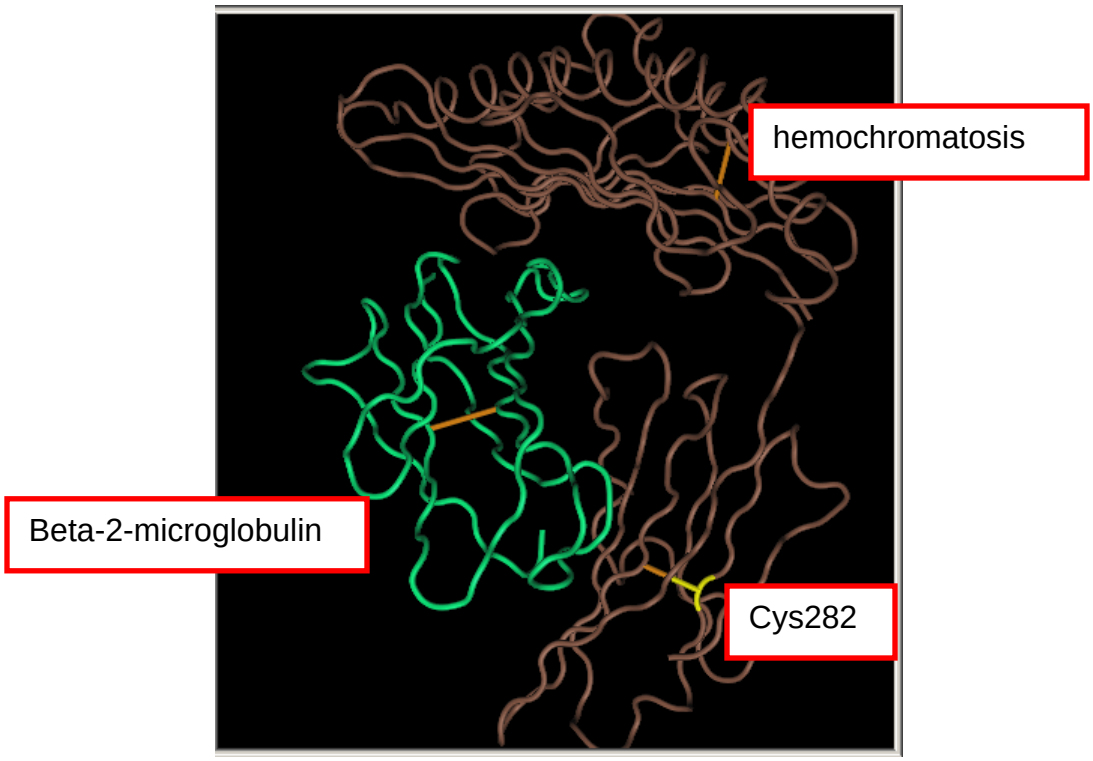


The interaction of hemochromatosis protein with beta-2-microglobulin allows cell surface presentation of the complex. Once on cell surface, the hemochromatosis protein regulates iron absorption by regulating the interaction of the transferrin receptor with transferrin.


Transferrin
Transferrin receptor
hemochromatosis
Beta-2-microglobulin


hemochromatosis
Beta-2-microglobulin
Cys282

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? 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” 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 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 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 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.