

Correlating Disease Genes and Phenotypes

An NCBI Mini-Course

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

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

Outline:

In this exercise, we have the following goals:

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

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

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

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:

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

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

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

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

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

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

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

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

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

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

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

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

Summary:

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

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

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


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

PubMed All Databases BLAST OMIM Books TaxBrowser Structure

Search for **Go**

SITE MAP
 Alphabetical List
 Resource Guide

What does NCBI do? **Hot Spots**

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

Assembly Archive



Entrez, The Life Sciences Search Engine

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

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

Welcome to the Entrez cross-database search page

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

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

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

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


Entrez Gene

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

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

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

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

Sample Searches

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

NCBI Entrez Gene

Search Gene for hfe

Display Summary Show 20 Send to

All: 34 Current Only: 34 Genes Genomes: 30 SNP GeneView: 25

Items 1 - 20 of 34

1: **HFE**

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

NCBI Entrez Gene

Search Gene for

Display Full Report Show 20 Send to

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

1: **HFE hemochromatosis** [*Homo sapiens*]
 GeneID: 3077 updated 06-Jun-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 eleven 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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Genomic regions, transcripts, and products

Go to [reference sequence details](#)

NC_000006.10

Genomic context

chromosome: 6; Location: 6p21.3

See HFE in MapViewer

Entrez Gene Info

Feedback

Subscriptions

HIV-1 protein interactions ↑ ?

Protein Interaction

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

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

Interactions ↑ ?

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

General gene information ↑

Markers

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

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

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

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

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

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

General protein information

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

NCBI Reference Sequences (RefSeq)

Genomic

1. **NG_001335.1 Reference**
Range 71162..80773
Download [GenBank](#), [FASTA](#)

mRNA and Protein(s)

1. **NM_000410.3–NP_000401.1 hemochromatosis protein isoform 1 precursor**
Description Transcript Variant: This variant (1) encodes the longest isoform.
Source sequence(s) [AF115265](#), [AJ249337](#), [U91328](#)
Consensus CDS [CCDS4578.1](#)
Conserved Domains (2) [summary](#)

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.

Related Sequences

	Nucleotide	Protein
Genomic	AF184234.1	AAF01222.1
Genomic	AF204869.1	None
Genomic	AF331065.1	AAK16502.1
Genomic	AF525359.1	AAM82608.1
Genomic	AF525499.1	AAM91950.1
Genomic	CH471087.1	FAW55516.1
		FAW55517.1
		FAW55518.1
		FAW55519.1
		FAW55520.1
		FAW55521.1
		FAW55522.1
		FAW55523.1
		FAW55524.1
		FAW55525.1
		FAW55526.1
		FAW55527.1
Genomic	CS187189.1	CAJ42862.1
Genomic	U80914.1	AAD00449.1
Genomic	U91328.1	AAB82083.1
Genomic	Y09801.1	CAA70934.1
Genomic	Z92910.1	CAB07442.1
mRNA	AF079407.1	AAC62646.1
mRNA	AF079408.1	AAC62647.1
mRNA	AF079409.1	AAC62648.1
mRNA	AF109385.1	AAD52104.1
mRNA	AF115264.1	AAG29571.1
mRNA	AF115265.1	AAG29572.1
mRNA	AF144238.1	AAG29573.1
mRNA	AF144239.1	AAG29574.1
mRNA	AF144240.1	AAG29575.1

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Protein

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

Exon information:

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

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

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

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

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

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

Review

CCDS

Evidence Viewer

GDB

GeneTests for MIM: 235200

HGMD

HGNC

HPRD

KEGG

MGC

ModelMaker

UniGene

LinkOut

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

1: HFE hemochromatosis [*Homo sapiens*]

GeneID: 3077 updated 06-Jun-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 eleven alternatively spliced variants have been described for this gene. Additional variants have been found but their full-length nature has not been determined.

Genomic regions, transcripts, and products

Go to [reference sequence details](#)

NC_000006.10

[26195427] [26205438]

NM_133915.2 MP_620574.1 isoform 5 precursor
 NM_133915.2 MP_620571.1 isoform 2 precursor
 NM_133915.2 MP_620572.1 isoform 3 precursor
 NM_133915.2 MP_620573.1 isoform 4 precursor
 NM_133915.2 MP_620574.1 isoform 5 precursor
 NM_133915.2 MP_620575.1 isoform 6 precursor
 NM_133915.2 MP_620576.1 isoform 7 precursor
 NM_133915.2 MP_620577.1 isoform 8 precursor
 NM_133915.2 MP_620578.1 isoform 9 precursor
 NM_133915.2 MP_620579.1 isoform 10 precursor
 NM_133915.2 MP_620580.1 isoform 11 precursor
 NM_133915.2 MP_620581.1 isoform 12 precursor

■ - coding region ■ - untranslated region

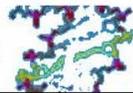
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- HGNC
- HPRD
- USCS



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

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

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

Search for: .0001 HEMOCHROMATOSIS [HFE, CYS282TYR] dbSNP

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[HEMOCHROMATOSIS, JUVENILE, DIGENIC, INCLUDED](#)
[ALZHEIMER DISEASE, SUSCEPTIBILITY TO, INCLUDED](#)

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

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

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

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

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Display: Allelic Variants Show: 20 Send to:

All: 1 OMIM dbSNP: 1 OMIM UniSTS: 1

+235200
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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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 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. Ceylan Bilik, MD; Dr. Vedat Kalkan, MD, PhD						

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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.

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

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

Left sidebar: [Summary](#), [Diagnosis](#), [Clinical Description](#), [Prevalence](#), [Differential Diagnosis](#), [Management](#), [Genetic Counseling](#), [Molecular Genetics](#), [Resources](#), [References](#), [Author Information](#), [Top of Page](#)

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region, complementation group from OMIM, protein name from Swiss-Prot.

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OMIM Entries for HFE-Associated Hereditary Hemochromatosis

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

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

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

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

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

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

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

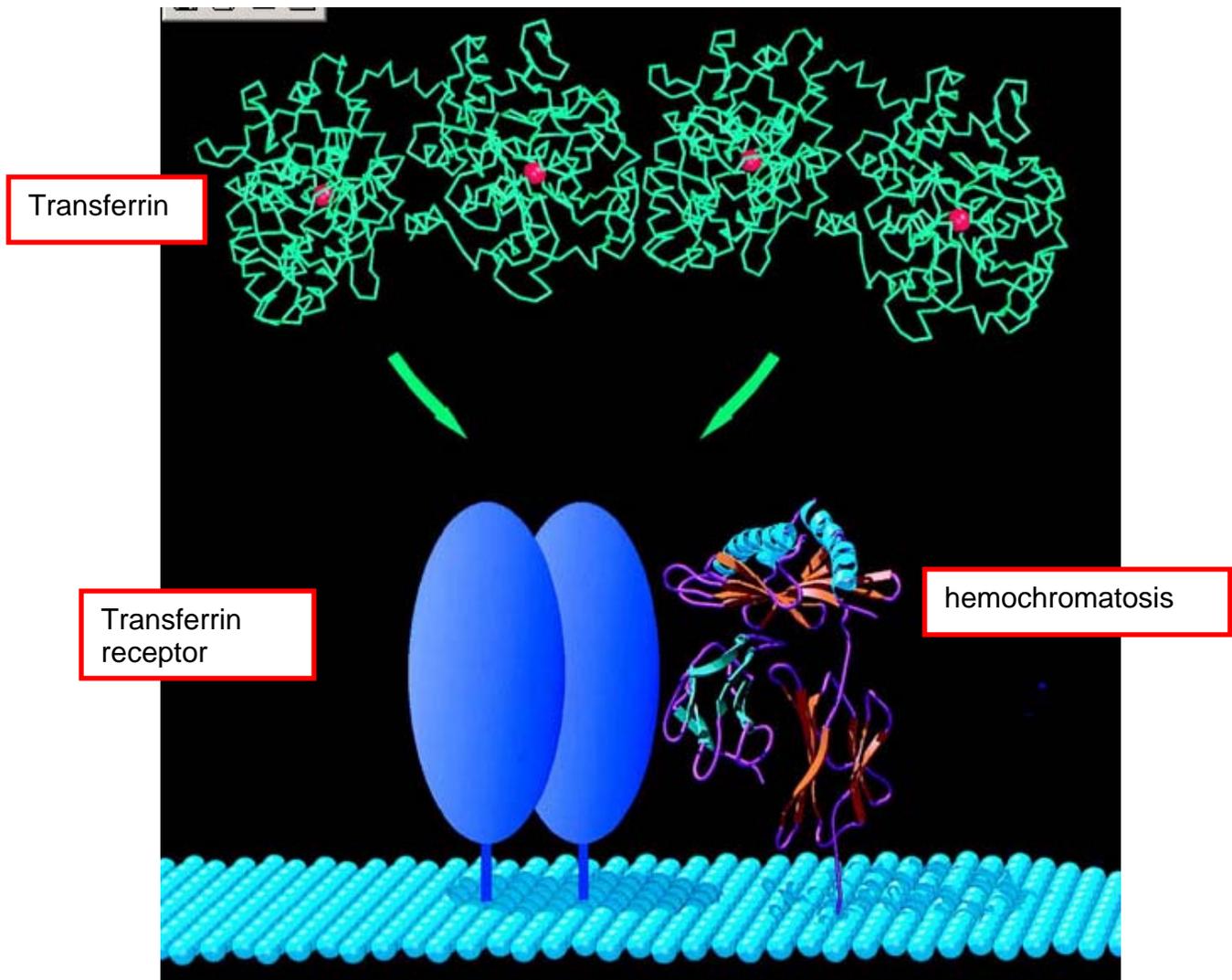
Abnormal gene product: The p.C282Y mutation destroys a key cysteine residue that is required for disulfide bonding with beta-2-microglobulin. As a result, the HFE protein does not mature properly and becomes trapped in the endoplasmic reticulum and Golgi apparatus, leading to decreased cell-surface expression.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

Resources

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

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

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+235200
HEMOCHROMATOSIS; HFE

Alternative titles; symbols

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

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

TEXT

DESCRIPTION

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

Links

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- OMIA
- Free in PMC
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- GeneView in dbSNP
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- Related Entries
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- Protein
- SNP
- Structure

Genomic regions, transcripts, and products

Go to [reference sequence details](#)

NC_000006.10

[26195427] 5' [26205038] 3'

NM_139885.2
 NM_139892.2
 NM_00410.3
 NM_139894.2
 NM_139895.2
 NM_139899.2
 NM_139907.2
 NM_139908.2
 NM_139910.2
 NM_139911.2
 NM_139906.2

NP_628574 isoform 5 precursor
 NP_628571 isoform 2 prccu
 NP_004401 isoform 1 prccu
 NP_628573 isoform 4 prccu
 NP_628572 isoform 3 prccu
 NP_628578 isoform 9 prccu
 NP_628576 isoform 7 prccu
 NP_628577 isoform 8 prccu
 NP_628579 isoform 10 prccu
 NP_628580 isoform 11 prccu
 NP_628575 isoform 6 prccu

■ - coding region ■ - untranslated region

Links

PROTEIN LINKS

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- GENEPT
- Blink
- Conserved Domains

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 ✓ SNP: GeneView
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 HGMD
 HSNL
 HPRD
 KEGG
 MGC
 ModelMaker
 UniGene
 LinkOut

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Genomic context

chromosome: 6; Location: 6p21.3

[26153618] [26216343]

HIST1H3C HIST1H1C HFE HIST1H4C HIST1H1T

See HFE in MapViews

NCBI

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

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

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

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

348 aa

SCORE	E	ACCESSION	GI	PROTEIN DESCRIPTION
Conserved Domain Database hits				
1870	31	AAC51823	1469790	HLA-H
1870	29	AAM09793	22854810	hereditary hemochromatosis [Pan troglodytes]
1870	31	CAB07442	1890180	HFE [Homo sapiens]
1870	31	AAB82083	2088551	hereditary hemochromatosis [Homo sapiens]
1870	31	CAA70934	2370111	HFE [Homo sapiens]
1870	31	Q30201	2497915	Hereditary hemochromatosis protein precursor (HLA-H)
1870	31	EAW55524	119575928	hemochromatosis, isoform CRA_1 [Homo sapiens]
1870	29	F60018	38502807	Hereditary hemochromatosis protein homolog precursor (HLA-H)
1870	31	AAI17204	109658506	Hemochromatosis (Homo sapiens)
1870	31	AAI17202	109658670	Hemochromatosis (Homo sapiens)
1870	29	NP_001144	57114069	hemochromatosis protein [Pan troglodytes]
1870	31	AAQ29572	11094315	hemochromatosis termination variant terE6; HFE [Homo sapiens]
1776	31	AAM74721	50960016	HFE protein [Homo sapiens]
1772	31	AAC62646	3695107	hemochromatosis splice variant dell4E4 [Homo sapiens]
1772	31	EAW55523	119575927	hemochromatosis, isoform CRA_h [Homo sapiens]
1772	31	NP_620575	21040347	hemochromatosis protein isoform 6 precursor [Homo sapiens]
1713	31	CAC67792	15485419	hemochromatosis protein [Homo sapiens]
1713	31	NP_620578	21040353	hemochromatosis protein isoform 9 precursor [Homo sapiens]
1713	31	EAW55521	119575925	hemochromatosis, isoform CRA_f [Homo sapiens]
1517	31	I462C	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	31	I464A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	I464D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	I464G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	I462A	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
1495	21	Q9GL42	24418418	Hereditary hemochromatosis protein homolog precursor
1495	21	AAQ23703	10945692	HFE protein [Diceros bicornis sumatrensis]
1495	21	Q9GK20	24418446	Hereditary hemochromatosis protein homolog precursor
1495	21	AAQ23701	10945688	HFE protein [Ceratotherium simum]
1492	21	Q9GL43	24418449	Hereditary hemochromatosis protein homolog precursor
1492	21	AAQ23702	10945690	HFE protein [Diceros bicornis]
1491	31	NP_620574	21040345	hemochromatosis protein isoform 5 precursor [Homo sapiens]
1491	31	EAW55527	119575931	hemochromatosis, isoform CRA_l [Homo sapiens]
1489	21	AAQ23704	10945694	HFE protein [Rhinoceros unicornis]
1489	21	Q9GL41	24418447	Hereditary hemochromatosis protein homolog precursor
1463	31	AAQ47091	28800982	hemochromatosis [Homo sapiens]
1412	21	AAQ39940	11692703	HFE [Diceros bicornis]
1303	22	NP_445753	25742631	hemochromatosis [Rattus norvegicus]

NCBI

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

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

348 aa

SCORE	E	ACCESSION	GI	PROTEIN DESCRIPTION
Conserved Domain Database hits				
1517	31	I462C	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	31	I464A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	I464D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	I464G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
1517	31	I462A	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
525	0	1B7IA	3891929	Chain A, The Crystal Structure Of H-2dd Mhc Class I In Complex With The Hiv-1 Derived Peptide P18-11
507	0	1S7RA	48425592	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	0	1S7RD	48425595	Chain D, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	0	1S7SA	48425598	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	0	1S7TA	48425601	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	0	1S7TD	48425604	Chain D, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
507	0	1S7TB	48425599	Chain A, Crystal Structures Of The Murine Class I Major Histocompatibility Complex H-2kb In Complex
502	0	1X84D	49258567	Chain D, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	0	1X7CR	49258567	Chain A, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	0	1X7VD	49258567	Chain D, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	0	2HN7A	119389933	Chain A, Hla-A1101 In Complex With Hbv Peptide Homologue
502	0	1X7QA	73535522	Chain A, Crystal Structure Of Hla-A1101 With Sars Nucleocapsid Peptide
502	0	1Q94A	49258564	Chain A, Structures Of Hla-A1101 In Complex With Immunodominant Nonamer And Decamer Hiv-1 Epitopes C
502	0	2BCKD	88192434	Chain D, Crystal Structure Of Hla-A2402 Complexed With A Telomerase Peptide
502	0	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](#)]

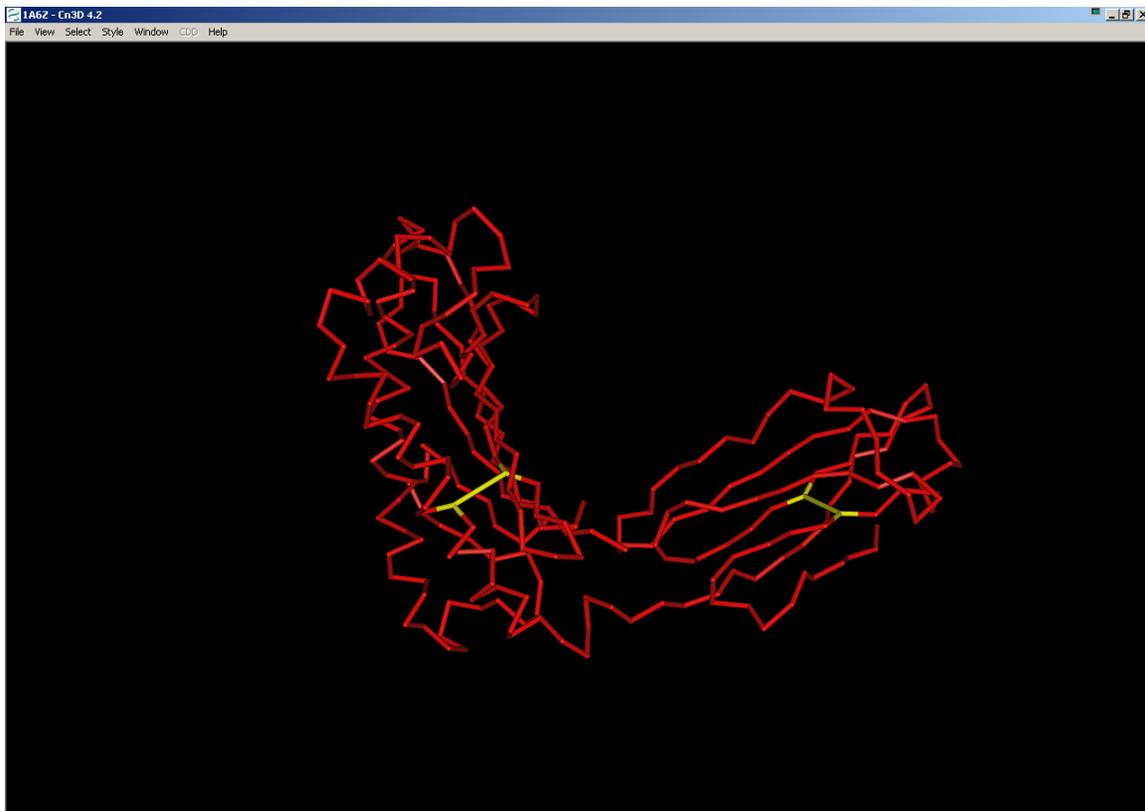
Structure: 1A6Z Chain C, Hfe (Human) Hemochromatosis Protein

Reference: [MMDDB] [PubMed]

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

		10	20	30	40	50	60	70	80
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1A6Z_C	1	RLLRSHSLHYLFMGASEQDLGSLFEALGYVDDQLFVFDHESRRVEPRTPWVSSRISSQMWLQLSQSLKGNWDMFTVDF	80						
		90	100	110	120	130	140	150	160
gi_4504377	103	WTIMENHNHKSESHTLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPDTLDWRAAEPRAWPTKLEWERHKIRARQNRAY	182						
1A6Z_C	81	WTIMENHNHKSESHTLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPDTLDWRAAEPRAWPTKLEWERHKIRARQNRAY	160						
		170	180	190	200	210	220	230	240
gi_4504377	183	LERDCPAQLQQLLELGRGVLDQQVPLVKVTHHVTSSVITLRCRALNYYPQNITMKWLKDKQPMDAKEFEPKDVLPNGDG	262						
1A6Z_C	161	LERDCPAQLQQLLELGRGVLDQQVPLVKVTHHVTSSVITLRCRALNYYPQNITMKWLKDKQPMDAKEFEPKDVLPNGDG	240						
		250	260	270					
gi_4504377	263	TYQGWITLAVPPGEEQRYTCQVEHPGLDQPLIVI	297						
1A6Z_C	241	TYQGWITLAVPPGEEQRYTCQVEHPGLDQPLIVI	275						



1A6Z - Sequence/Alignment Viewer

View Edit Mouse Mode Unaligned Justification Imports

1A6Z C	KDKQPMDAKEFEPKDVLPNGDGT YQGWI TLAVPPGEEQRYT QVEHPGLDQPLI VIW
gi 4504377	KDKQPMDAKEFEPKDVLPNGDGT YQGWI TLAVPPGEEQRYT QVEHPGLDQPLI VIW e p s p s g t l v i g v i s g i a v f v v i l f i g

gi 4504377, loc 282 Block 1, Row 2

Problem 2:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A. Information about the wild type protein

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

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

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

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

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

Summary:

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

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