

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 the NCBI resources such as the literature, expression and structure information can help 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)

Instructors: Steve Pechous (pechous@ncbi.nlm.nih.gov)

Wayne Matten (matten@ncbi.nlm.nih.gov)

Problem 1

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

Outline:

In this exercise, we have the following goals:

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

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

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

What is the location and orientation of the HFE gene on the human genome? List the genes adjacent to it. How many alternatively spliced products have been annotated for the HFE gene when the RefSeq mRNA entries were reviewed? 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 first protein, NP_000401. 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, 1DE4G, represents the G chain of the hemochromatosis protein (complexed with transferrin receptor). Click on the blue dot next to 1DE4G to get the sequence alignment of the query protein to the G chain of 1DE4. Click on the "View 3D Structure" button. This downloads the structure of G chain of 1DE4 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 third 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 where as the Cys282Tyr mutant fails to regulate this interaction leading to iron overload. The conserved cysteine 282 in the immunoglobulin constant region domain in the HFE protein is involved in formation of a disulphide bridge. Its mutation to tyrosine will alter the folding of the protein.

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

PubMed All Databases BLAST OMIM Books TaxBrowser Structure

Search All Databases for Go

SITE MAP
Alphabetical List
Resource Guide

▶ **What does NCBI do?** Hot Spots

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

NCBI Entrez, The Life Sciences Search Engine

HOME SEARCH SITE MAP PubMed Entrez Human Genome GenBank Map Viewer BLAST

Search across databases GO CLEAR Help

Welcome to the new 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
Nucleotide: sequence database (GenBank)	Site Search: NCBI web and FTP sites
Protein: sequence database	UniGene: gene-oriented clusters of transcript sequences
Genome: whole genome sequences	CDD: conserved protein domain database
Structure: three-dimensional macromolecular structures	3D Domains: domains from Entrez Structure
Taxonomy: organisms in GenBank	UniSTS: markers and mapping data
SNP: single nucleotide polymorphism	PopSet: population study data sets
Gene: gene-centered information	GEO Profiles: expression and molecular abundance profiles
HomoloGene: eukaryotic homology groups	GEO DataSets: experimental sets of GEO data
PubChem Compound: small molecule chemical structures	Cancer Chromosomes: cytogenetic databases
PubChem Substance: chemical substances screened for bioactivity	PubChem BioAssay: bioactivity screens of chemical substances
Genome Project: genome project information	GENSAT: gene expression atlas of mouse central nervous system
Journals: detailed information about the journals indexed in PubMed and other Entrez databases	MeSH: detailed information about NLM's controlled vocabulary
NLM Catalog: catalog of books, journals, and audiovisuals in the NLM collections	

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

NCBI Entrez Gene

My NCBI [Sign In] [Register]

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

Search Gene for hfe Go Clear

Limits Preview/Index History Clipboard Details

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

Sample Searches

Find genes by... Search text

free text human muscular dystrophy

NCBI Entrez Gene

My NCBI [Sign In] [Register]

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

Search Gene for hfe Go Clear Save Search

Limits Preview/Index History Clipboard Details

Display Summary Show 20 Send to

All: 26 Current Only: 26 Genes Genomes: 26 SNP GeneView: 24

Items 1 - 20 of 26 Page 1 of 2 Next

1: [HFE](#) MGC 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
GeneID: 3077

2: [Hfe](#) Links
Official Symbol: Hfe and **Name:** hemochromatosis [*Mus musculus*]


Entrez Gene

[My NCBI](#)
[\[Sign In\]](#) [\[Register\]](#)

All Databases: PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

Search: Gene for

Limits: Preview/Index History Clipboard Details

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 Primary source: [HGNC:4886](#) updated 01-Mar-2006

[Entrez Gene Home](#)

Summary

Official Symbol: HFE and Name: hemochromatosis provided by [HUGO Gene Nomenclature Committee](#)
 See related: [HPRD:01993](#), [MIM:235200](#)
 Gene type: protein coding
 Gene name: HFE
 Gene description: hemochromatosis
 RefSeq status: Reviewed
 Organism: [Homo sapiens](#)
 Lineage: *Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae; Homo*
 Gene aliases: 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

[RefSeq below](#)

NC_000006.9
 [26195427] 5' [26205036] 3'

Legend: ■ - coding region ■ - untranslated region

NM_000410.2	NP_000401 isoform 1 precursor	CCDS4578.1
NM_139004.1	NP_620573 isoform 4 precursor	CCDS4579.1
NM_139009.1	NP_620578 isoform 9 precursor	
NM_139017.1	NP_620576 isoform 7 precursor	CCDS4580.1
NM_139019.1	NP_620579 isoform 10 precursor	CCDS4581.1
NM_139011.1	NP_620580 isoform 11 precursor	CCDS4582.1
NM_139005.1	NP_620574 isoform 5 precursor	
NM_139003.1	NP_620572 isoform 3 precursor	
NM_139006.1	NP_620575 isoform 6 precursor	
NM_139008.1	NP_620577 isoform 8 precursor	
NM_139002.1	NP_620571 isoform 2 precursor	

[Entrez Gene Info](#)
[Feedback](#)

Genomic context [See HFE in MapViewer](#)

chromosome: 6; Location: 6p21.3

[26153618] HIST1HC HIST1HC HFE HIST1HC HIST1MT [26216343]

Bibliography Gene References into Function (GeneRIF):

[PubMed links](#)

GeneRIFs:

- HFE C282Y mutation significantly increases the risk of venous leg ulceration in primary cardiovascular diseases by almost 7 times. [PubMed](#)
- multiple sclerosis patients carrying the mutant C282Y allele exhibited earlier onset of disease symptom relative to other genotypes, but it warrants further study in a larger series of MS patients. [PubMed](#)
- HFE gene mutation considered in patients with chronic viral hepatitis in taiwan. [PubMed](#)
- Additional risk of hereditary hemochromatosis given by class I HLA antigens may be secondary to the HFE gene linkage disequilibrium with certain class I alleles or to the existence of other neighboring genetic pathogenetic factors in our [PubMed](#)

[Entrez Gene Info](#)
[Feedback](#)
[Subscriptions](#)

General gene information ? ↑

Markers

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

PMC19311P1(e-PCR) (Links: [UniSTS:271747](#))

PMC19649IP2(e-PCR) (Links: [UniSTS:271810](#))
 Alternate name: PMC23476P1

HFE_3382(e-PCR) (Links: [UniSTS:462240](#))

GeneOntology

Provided by [GOA](#)

Function	Evidence
MHC class I receptor activity	IEA
iron ion binding	IEA

Process

antigen presentation	IEA
antigen presentation, endogenous antigen	IEA
antigen processing, endogenous antigen via MHC class I	IEA
ion transport	IEA
iron ion homeostasis	TAS PubMed
iron ion transport	TAS PubMed
protein complex assembly	TAS PubMed
receptor mediated endocytosis	TAS PubMed

Component

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

Homology:

Mouse, Rat

[Map Viewer](#)

Phenotypes

Hemochromatosis [MIM: 235200](#)

Porphyria variegata [MIM: 176200](#)

General protein information ? ↑

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

NCBI Reference Sequences (RefSeq) ? ↑

Reference [NG_001335](#)

mRNA Sequence [NM_000410](#)

Transcriptional Variant
 Transcript Variant: This variant (1) encodes the longest isoform.

Source Sequence [U60319](#)

Product [NP_000401](#) hemochromatosis protein isoform 1 precursor

Consensus CDS (CCDS) [CCDS4578.1](#)

Conserved Domains (2) [summary](#)

[pfam00129: MHC I, Class I Histocompatibility antigen, domains alpha 1 and 2](#)
 Location: 27 - 202 Blast Score: 314

[cd00098: IGC; Immunoglobulin domain constant region subfamily](#)
 Location: 223 - 298 Blast Score: 169

Related Sequences

Nucleotide	Protein
Genomic AF184234	AAF01222
Genomic AF331065	AAK16502
Genomic AF525359	AAM82608
Genomic AF525499	AAM91950
Genomic U80914	AAD00449
Genomic U91328	AAB82083
Genomic Y09801	CAA70934
Genomic Z92910	CAB07442
mRNA AF079407	AAC62646
mRNA AF079408	AAC62647
mRNA AF079409	AAC62648

NCBI Entrez Gene

My NCBI [Sign In] [Register]

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

Search Gene for [] Go Clear

Limits Preview/Index History Clipboard Details

Display Full Report Show 20 Send to

All: Full Report Summary Brief ASN.1 XML GeneID Summ Official See rel

Genomes: 1 SNP GeneView: 1

[Homo sapiens]
C.4886 updated 01-Mar-2006

Entrez Gene Home Table Of Contents

Summary Genomic regions, transcripts... Genomic context Bibliography Interactions General gene information

emochromatosis provided by HUGO Gene Nomenclature Committee 5200

mRNA bp exons Protein aa exons

NM_000410.2	2717	7	NP_000401.1	349	6
NM_139004.1	1922	5	NP_620573.1	257	5
NM_139009.1	1280	6	NP_620578.1	326	6
NM_139007.1	1085	5	NP_620576.1	261	5
NM_139010.1	809	4	NP_620579.1	169	4
NM_139011.1	533	3	NP_620580.1	77	3
NM_139005.1	1140	5	NP_620574.1	277	5
NM_139003.1	804	5	NP_620572.1	243	5
NM_139006.1	1045	6	NP_620575.1	335	6
NM_139008.1	781	5	NP_620577.1	247	5
NM_139002.1	726	4	NP_620571.1	162	4

Exon information:
[NM_000410.2](#) length: 2717 bp, number of exons: 7
[NP_000401.1](#) length: 349 aa, number of exons: 6

EXON		Coding EXON		INTRON	
coords	length	coords	length	coords	length
1 - 297	297 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 - 5741	276 bp	5466 - 5741	276 bp	5742 - 5899	158 bp
5900 - 6013	114 bp	5900 - 6013	114 bp	6014 - 6966	953 bp
6967 - 8022	1056 bp	6967 - 7007	41 bp	8023 - 9176	1154 bp
9177 - 9610	434 bp				

LinkOut: Entrez Gene Info, Feedback, Subscriptions

NCBI Entrez Gene

My NCBI [Sign In] [Register]

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

Search Gene for [] Go Clear [] current records only

Limits Preview/Index History Clipboard Details

Display Gene Table Show 20 Send to []

All: 1 Genes Genomes: 1 SNP GeneView: 1

1: HFE hemochromatosis [*Homo sapiens*]
 GeneID: 3077 Locus tag: [HGNC:4886](#); [MIM: 235200](#) updated 10-Sep-2005

Entrez Gene Home

Table Of Contents

Summary

Transcripts and products

Genomic context

Bibliography

General gene information

General protein information

Reference Sequences

Related Sequences

Additional Links

Links

Books

Conserved Domains

GEO Profiles

HomoloGene

Map Viewer

Nucleotide

OMIA

OMIM

Full text in PMC

Probe

Protein

PubMed

PubMed (GeneRIF)

SNP

SNP: Genotype

SNP: GeneView

Taxonomy

UniSTS

AcView

Ensembl

Evidence Viewer

GDB

GeneTests for MIM: 235200

HGMD

HGNC

KEGG

MGC

ModelMaker

UCSC

UniGene

LinkOut

Summary

Official Symbol: HFE and **Name:** hemochromatosis provided by [HUGO Gene Nomenclature Committee](#)

Gene type: protein coding

Gene name: HFE

Gene description: hemochromatosis

RefSeq status: Reviewed

Organism: [Homo sapiens](#)

Lineage: *Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Homimidae; Homo*

Gene aliases: 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.

Transcripts and products

[RefSeq below](#)

NC_000006

[26195427] 5' [26205038] 3'

NM_000410 isoform 1 precursor
 NM_139004 isoform 4 precursor
 NM_139003 isoform 9 precursor
 NM_139007 isoform 7 precursor
 NM_139010 isoform 10 precursor
 NM_139011 isoform 11 precursor
 NM_139005 isoform 5 precursor
 NM_139002 isoform 3 precursor
 NM_139006 isoform 6 precursor
 NM_139008 isoform 8 precursor
 NM_139002 isoform 2 precursor
 NP_000401 isoform 1 precursor
 NP_620573 isoform 4 precursor
 NP_620572 isoform 9 precursor
 NP_620576 isoform 7 precursor
 NP_620579 isoform 10 precursor
 NP_620580 isoform 11 precursor
 NP_620574 isoform 5 precursor
 NP_620572 isoform 3 precursor
 NP_620575 isoform 6 precursor
 NP_620577 isoform 8 precursor
 NP_620571 isoform 2 precursor

■ - coding region ■ - untranslated region

NCBI Single Nucleotide Polymorphism

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

Search Entrez SNP for [] Go

BUILD 126 SNP linked to Gene (geneID:3077)

SNP are linked from gene [HFE](#) via the following methods:

[Contig Annotation](#) [GeneBank\(ncrna\) Mapping](#)

Send [] all rs# 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	sup list
NM_000410	plus strand	NP_000401	forward	NT_007592	reference	currently shown
NM_000410	plus strand	NP_000401	forward	NW_922984	Celera	view
NM_139002	plus strand	NP_620571	forward	NT_007592	reference	view
NM_139002	plus strand	NP_620571	forward	NW_922984	Celera	view
NM_139003	plus strand	NP_620572	forward	NT_007592	reference	view
NM_139003	plus strand	NP_620572	forward	NW_922984	Celera	view
NM_139004	plus strand	NP_620573	forward	NT_007592	reference	view
NM_139004	plus strand	NP_620573	forward	NW_922984	Celera	view
NM_139005	plus strand	NP_620574	forward	NT_007592	reference	view
NM_139005	plus strand	NP_620574	forward	NW_922984	Celera	view
NM_139006	plus strand	NP_620575	forward	NT_007592	reference	view
NM_139006	plus strand	NP_620575	forward	NW_922984	Celera	view
NM_139007	plus strand	NP_620576	forward	NT_007592	reference	view
NM_139007	plus strand	NP_620576	forward	NW_922984	Celera	view
NM_139008	plus strand	NP_620577	forward	NT_007592	reference	view
NM_139008	plus strand	NP_620577	forward	NW_922984	Celera	view

GENERAL

Contact Us

dbSNP Homepage

SNP Science Primer

Announcements

dbSNP Summary

FTP Download

Build History

SNP SUBMISSION

How to Submit

Handle Request

DOCUMENTATION

Build Release Note

Search FAQ Archive

updated 2006

dbSNP Handbook

Overview

RefSNP Summary Info

Database Schema

Database Dictionary

Database Changes

Genotype Schema

Data Formats

Heterozygosity

Computation

SEARCH

Entrez SNP

EUtile API

Blast SNP

Batch Query

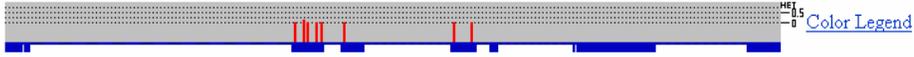
By Submitter

New Batches

NM_139011 plus strand NP_620580 forward NW_922984 Celera [view](#)

in gene region cSNP has frequency double hit haplotype tagged

gene model	Contig Label	Contig	mna	protein	mna orientation	transcript	snp count
(contig mRNA transcript):	reference	NT_007592 NM_000410 NP_000401			forward	plus strand 8, coding	



Region	Contig position	dbSNP rs# cluster id	Heterozygosity	Validation	3D	OMIM	Function	dbSNP allele	Protein residue	Codon position	Amino acid position
exon_3	16949347	rs2242956	N.D.		Yes		nonsynonymous	C	Thr [T]	2	35
			N.D.		Yes		contig reference	T	Met [M]	2	35
	16949430	rs1799945	0.139		Yes		nonsynonymous	G	Asp [D]	1	63
			0.139		Yes		contig reference	C	His [H]	1	63
	16949436	rs1800730	N.D.		Yes		nonsynonymous	T	Cys [C]	1	65
			N.D.		Yes		contig reference	A	Ser [S]	1	65
	16949520	rs28934597	N.D.		Yes		nonsynonymous	C	Arg [R]	1	93
			N.D.		Yes	Yes	contig reference	G	Gly [G]	1	93
	16949557	rs28934596	N.D.		Yes		nonsynonymous	C	Thr [T]	2	105
			N.D.		Yes	Yes	contig reference	T	Ile [I]	2	105
exon_4	16949833	rs28934595	N.D.		Yes		nonsynonymous	C	His [H]	3	127
			N.D.		Yes	Yes	contig reference	A	Gln [Q]	3	127
exon_5	16951197	rs4986950	0.005		Yes		nonsynonymous	T	Ile [I]	2	217
			0.005		Yes		contig reference	C	Thr [T]	2	217
	16951392	rs1800562	0.043		Yes		nonsynonymous	A	Tyr [Y]	2	282
			0.043		Yes	Yes	contig reference	G	Cys [C]	2	282

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

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM

Search OMIM for Go Clear

Limits Preview/Index History Clipboard Details

Display Detailed Show: 20 Send to Text

[+235200](#) GeneTests, Links

HEMOCHROMATOSIS; HFE

Alternative titles; symbols

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

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

TEXT

DESCRIPTION

MIM +235200
Description
Clinical Features
Other Features
Inheritance
Mapping
Heterogeneity
Molecular Genetics
Genotype/Phenotype
Correlations
Diagnosis
Clinical Management
Population Genetics
Pathogenesis
Cloning
Biochemical Features
Gene Structure
Gene Function
Nomenclature
Animal Model
History
Allelic Variants
• View List
See Also
References

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

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM

Search OMIM for Go Clear

Limits Preview/Index History Clipboard Details

Display Allelic Variants Show: 20 Send to

All: 1

[+235200](#) GeneTests, Links

HEMOCHROMATOSIS; HFE

ALLELIC VARIANTS
(selected examples)

- [0001 HEMOCHROMATOSIS](#) [HFE, CYS282TYR]
- [0002 HEMOCHROMATOSIS](#) [HFE, HIS63ASP]
- [0003 HEMOCHROMATOSIS](#) [HFE, SER65CYS]
- [0004 HFE INTRONIC POLYMORPHISM](#) [HFE, 5569G-A]
- [0005 HFE POLYMORPHISM](#) [HFE, VAL53MET]
- [0006 HFE POLYMORPHISM](#) [HFE, VAL59MET]
- [0007 PORPHYRIA VARIEGATA](#) [HFE, GLN127HIS]
- [0008 HEMOCHROMATOSIS](#) [HFE, ARG330MET]
- [0009 HEMOCHROMATOSIS](#) [HFE, ILE105THR]
- [0010 HEMOCHROMATOSIS](#) [HFE, GLY93ARG]
- [0011 HEMOCHROMATOSIS](#) [HFE, GLN283PRO]

Entrez Gene Copyright © 1966-2006 Johns Hopkins University

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

Home Page	About GeneTests	Reviews	Laboratory Directory	Clinic Directory	Educational Materials
---------------------------	---------------------------------	-------------------------	--------------------------------------	----------------------------------	---------------------------------------

Funded by the National Institutes of Health



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

Search Result for OMIM# 235200

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

Home Page	About GeneTests	Reviews	Laboratory Directory	Clinic Directory	Educational Materials
---------------------------	---------------------------------	-------------------------	--------------------------------------	----------------------------------	---------------------------------------

Funded by the National Institutes of Health



HFE- Associated Hereditary Hemochromatosis

Select all clinical laboratories

Laboratories offering clinical testing:	Sequencing of entire coding region	Sequencing of select exons	Mutation scanning	Targeted mutation analysis	Prenatal diagnosis	Preimplantation diagnosis	Clinical confirmation of mutations identified in a research lab
ARUP Laboratories, Inc. ARUP Laboratories Salt Lake City, UT				●			
Elaine Lyon, PhD; Rong Mao, MD; Edward R Ashwood, MD; Marzia Pasquali, 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							

Home Page	About GeneTests	GENEReviews	Laboratory Directory	Clinic Directory	Educational Materials
---------------------------	---------------------------------	-----------------------------	--------------------------------------	----------------------------------	---------------------------------------

Funded by the National Institutes of Health



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

Search Result for OMIM# 235200

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

Home Page	About GeneTests	GENEReviews	Laboratory Directory	Clinic Directory	Educational Materials
---------------------------	---------------------------------	-----------------------------	--------------------------------------	----------------------------------	---------------------------------------

[\[Printable Copy\]](#)

HFE-Associated Hereditary Hemochromatosis

utilizing the paramagnetic properties of iron; however, at this point MK1 technology remains experimental [[Clark & St Pierre 2000](#)].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work; listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. Clinicians must communicate directly with the laboratories to verify information. —ED.

Gene. All individuals **affected** with HFE-HHC have **mutations** in the **HFE gene**.

Molecular genetic testing: Clinical uses

- Confirmatory **diagnostic testing**
- **Predictive testing** for at-risk relatives
- **Carrier testing** (for the identification of heterozygotes)
- **Prenatal diagnosis**

Molecular genetic testing: Clinical methods

Summary
Diagnosis
Clinical Description
Differential Diagnosis
Management
Genetic Counseling
Molecular Genetics
Resources
References
Author Information
Top of Page

Disable Glossary
(Returns to top)

Title Index

Summary
Diagnosis
Clinical Description
Prevalence
Differential Diagnosis
Management
Genetic Counseling
Molecular Genetics
Resources
References
Author Information
Top of Page

Normal allelic variants: A serine at position 65 to cysteine (S65C) has been identified. The effect of this **mutation** is unclear.

Pathologic allelic variants: Two **missense mutations** have been identified, a cysteine at position 282 to tyrosine (C282Y); histidine at position 63 to aspartate (H63D).

- Cys282Tyr (synonyms: C282Y; **nucleotide** 845G>A) This **missense mutation** removes a highly conserved cysteine residue that normally forms an intramolecular disulfide bond, and thereby prevents the **protein** from being expressed on the cell surface.
- His63Asp (synonyms: H63D; **nucleotide** 187C>G) This **missense mutation** may impair interaction of the **HFE**-encoded **protein** with the transferrin receptor on the cell surface.

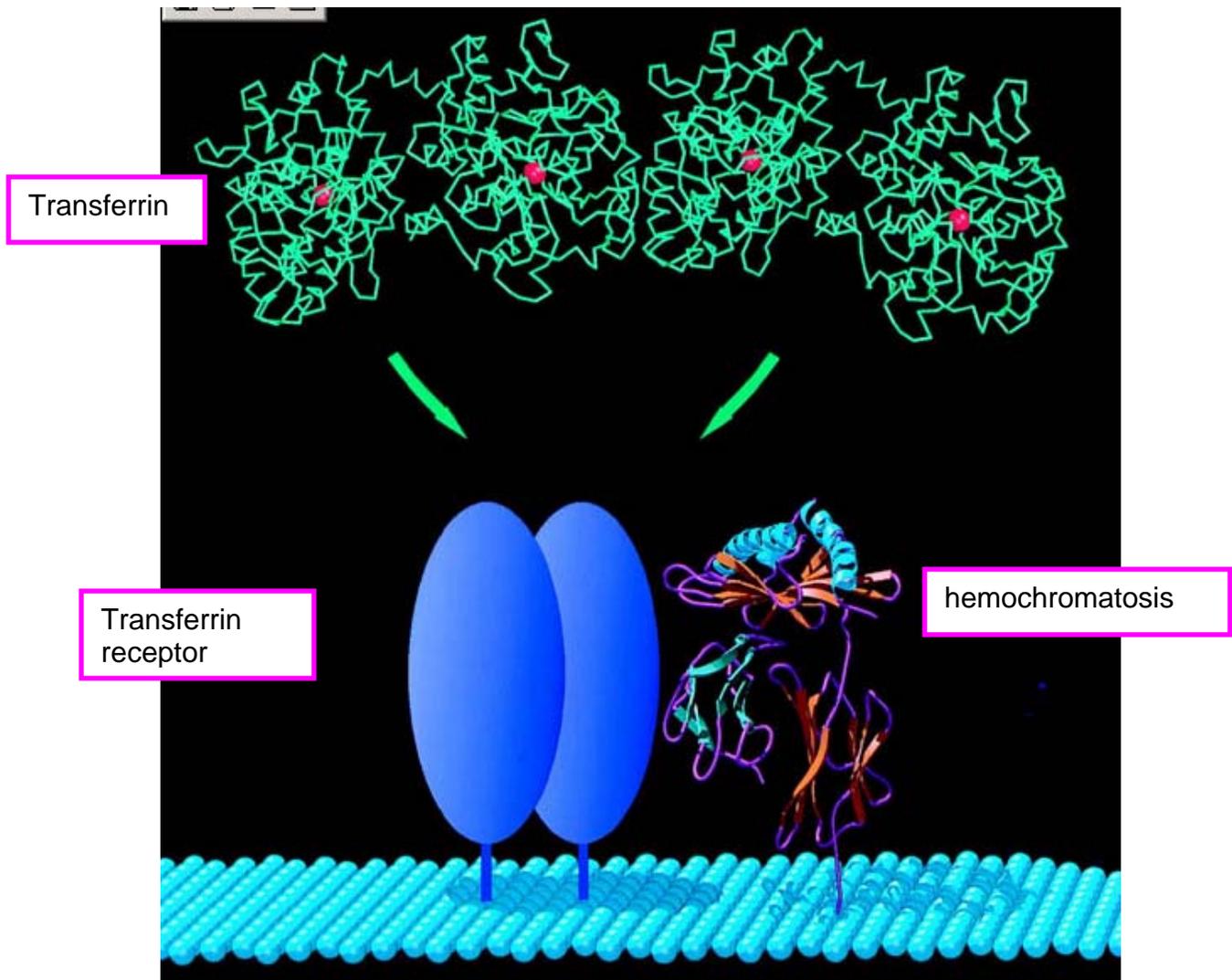
Normal gene product: A cell-surface **protein** of 321 amino acids with sequence similarity to HLA Class I molecules. The normal **protein** forms a heterodimer with beta-2-microglobulin, and this interaction is necessary for normal presentation on the cell surface. The normal **protein** binds to the transferrin receptor, and may act by modulating its affinity for transferrin.

Abnormal gene product: An impaired cell-surface **protein** is apparently formed. This **protein** does not migrate to the cell surface and does not bind transferrin (bound to diferric iron). Therefore, lack of internalization of transferrin into the small bowel absorptive cell may lead to compensatory increase in iron absorption [[Bacon et al 1999](#)].

Printable Copy
(Disable glossary before printing)

Disable Glossary
(Returns to top)

Title Index



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.

NCBI OMIM Online Mendelian Inheritance in Man Johns Hopkins University

All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM

Search OMIM for Go Clear

Limits Preview/Index History Clipboard Details

Display Allelic Variants Show 20 Send to

All: 1

+235200
HEMOCHROMATOSIS; HFE

ALLELIC VARIANTS
(selected examples)

- ◆ [0001 HEMOCHROMATOSIS \[HFE, CYS282TYR\]](#)

Links

- Books
- Gene
- GEO Profiles
- HomoloGene
- OMIA
- Free in PMC
- PubMed (calculated)

length nature has not been determined.

Genomic regions, transcripts, and products

RefSeq below

NC_000006.9

[26195427] [26205038]

5' 3'

NM_000410.3
NM_139004.1
NM_139009.1
NM_139007.1
NM_139010.1
NM_139011.1
NM_139005.1
NM_139003.1
NM_139006.1
NM_139008.1
NM_139002.1

NP_000401 isoform 1 precursor CCDS4578.1
NP_620573.1
NP_620578.1
NP_620576.1
NP_620579.1
NP_620580.1
NP_620574.1
NP_620572.1
NP_620575.1
NP_620577.1
NP_620571.1

Links

- PROTEIN LINKS
- FASTA
- GENEPT
- Blink
- Conserved Domains

■ - coding region ■ - untranslated region

SNP: Genotype
SNP: GeneView
Taxonomy
UniSTS
AceView
CCDS
Evidence Viewer
GDB
GeneTests for MIM: 235200
HGMD
HGNC
HPRD
KEGG
MGC
ModelMaker
UniGene
LinkOut

Entrez Gene Info
Feedback

NCBI

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

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

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

200 BLAST hits to 24 unique species Sort by taxonomy proximity

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

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

348 aa

SCORE	P	ACCESSION	GI	PROTEIN DESCRIPTION
<u>Conserved Domain Database hits</u>				
1870	28	NP_001...	57114069	hemochromatosis protein [Pan troglodytes]
1870	28	P60018	38502807	Hereditary hemochromatosis protein homolog precursor
1870	28	AAN09793	22854810	hereditary hemochromatosis [Pan troglodytes]
1870	30	AAG29572	11094315	hemochromatosis termination variant terE6; HFE [Homo sapiens]
1870	30	Q30201	2497915	Hereditary hemochromatosis protein precursor (HLA-H)
1870	30	CAA70934	2370111	HFE [Homo sapiens]
1870	30	AAB82083	2088551	hereditary hemochromatosis [Homo sapiens]
1870	30	CAB07442	1890180	HFE [Homo sapiens]
1870	30	AAC51823	1469790	HLA-H
1776	30	AAH74721	50960016	HFE protein [Homo sapiens]
1772	30	NP_620575	21040347	hemochromatosis protein isoform 6 precursor [Homo sapiens]
1772	30	AAC62646	3695107	hemochromatosis splice variant dell14E4 [Homo sapiens]
1713	30	NP_620578	21040353	hemochromatosis protein isoform 9 precursor [Homo sapiens]
1713	30	CAC67792	15485419	hemochromatosis protein [Homo sapiens]
1517	30	1DE4G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Tr
1517	30	1DE4D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Tr
1517	30	1DE4A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Tr
1517	30	1A62C	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	30	1A62A	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
1495	21	Q9GKZ0	24418446	Hereditary hemochromatosis protein homolog precursor

NCBI

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

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

Get Ca3D Now!

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

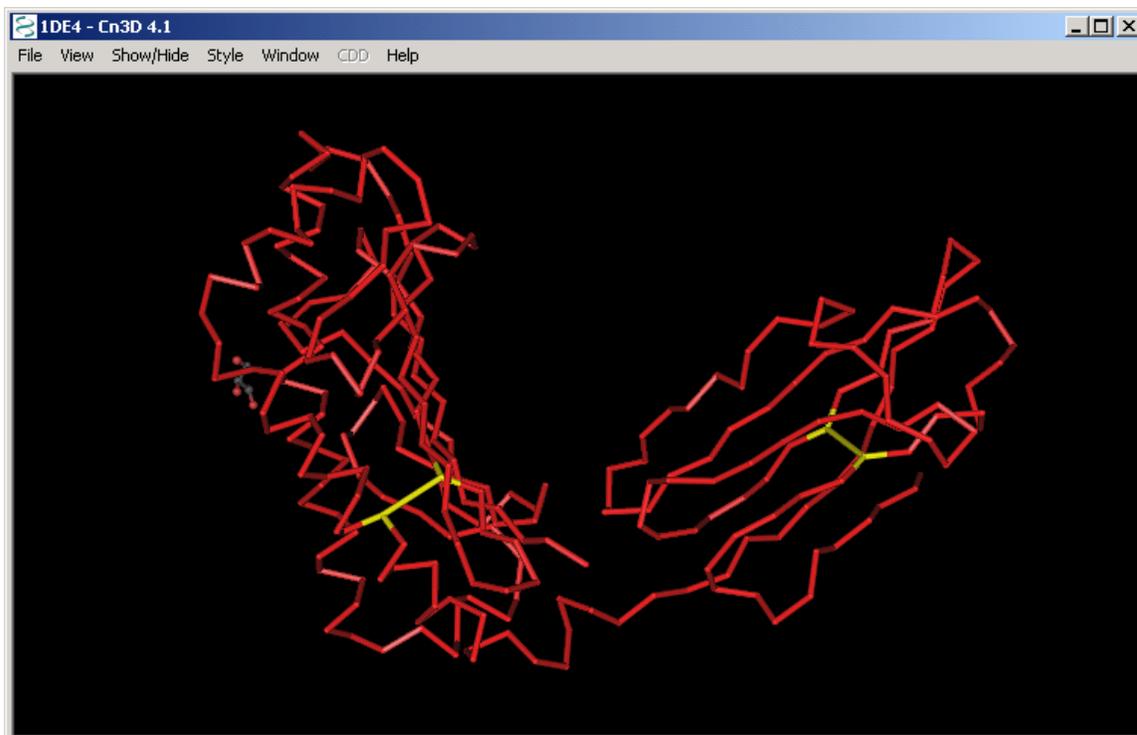
200 BLAST hits to 3 unique species Sort by taxonomy proximity

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
<u>Conserved Domain Database hits</u>				
1517	●	1DE4G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Tr
1517	●	1DE4D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Tr
1517	●	1DE4A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Tr
1517	●	1A62C	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	●	1A62A	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
525	●	1BIIA	3891929	Chain A. The Crvstal Structure Of H-2dd Mhc Class I In



IDE4 - Sequence/Alignment Viewer

View Edit Mouse Mode Unaligned Justification Imports

IDE4 G	TSSVTTLCRALNYYPNITMKWLKDKQPMDAKEFEPKDVLPNGDGTYYQWITLAVPPGEEQRYTCQVEHPGLDQPLIVIWIW~
gi 4504377	TSSVTTLCRALNYYPNITMKWLKDKQPMDAKEFEPKDVLPNGDGTYYQWITLAVPPGEEQRYTCQVEHPGLDQPLIVIWIWep

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 non-synonymous 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 7 non-synonymous 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.