

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)

Problem 1

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

Outline:

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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 for

SITE MAP
Alphabetical List
Resource Guide

▶ **What does NCBI do?**

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 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

News: New "has cds" property added. [News archives...](#)

Sample Searches

Find genes by... Search text

free text [human muscular dystrophy](#)

partial name and multiple species [transporter\[title\] AND \("Drosophila melanogaster"\[organ\] OR "Mus musculus"\[organ\]\)](#)

chromosome and symbol [\(\[1\[chr\] OR 2\[chr\]\].AND_adh*\[sym\]\)](#)

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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: 27 Current Only: 27 Genes Genomes: 27 SNP GeneView: 22

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

2: [Hfe](#) Official Symbol: Hfe and Name: hemochromatosis [*Mus musculus*]
 Other Aliases: RP23-480B19.9, MGC151121, MGC151123, MR2

NCBI Entrez Gene

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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: 5 Send to:

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

1: [HFE hemochromatosis](#) [*Homo sapiens*]
 GeneID: 3077 updated 06-Nov-2006

Summary

Official Symbol	HFE	provided by HGNC
Official Full Name	hemochromatosis	provided by HGNC
Primary source	HGNC:4886	
See related	HPRD:01993 ; MIM:235200	
Gene type	protein coding	
RefSeq status	Reviewed	
Organism	Homo sapiens	
Lineage	<i>Eukaryota</i> ; <i>Metazoa</i> ; <i>Chordata</i> ; <i>Craniata</i> ; <i>Vertebrata</i> ; <i>Euteleostomi</i> ; <i>Mammalia</i> ; <i>Eutheria</i> ; <i>Euarchontoglires</i> ; <i>Primates</i> ; <i>Haplorrhini</i> ; <i>Catarrhini</i> ; <i>Hominidae</i> ; <i>Homo</i>	

Entrez Gene Home

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Genomic context ↑ ? [Chromosome LinkOut](#)

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

Bibliography ↑ ?

Related Articles in PubMed

[PubMed](#) links

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

1. the homozygous Cys282Tyr missense mutation and high levels of serum ferritin. It is important to recognise the symptoms of iron overloading at an early stage because hereditary haemochromatosis needs to be treated immediately.
2. Apical distribution of HFE-beta2-microglobulin is associated with inhibition of apical iron uptake in intestinal epithelia cells.
3. determined race-specific frequencies of the HFE mutations, C282Y and H63D
4. Glucose intolerance may be important risk factor for the development of hepatic fibrosis in subjects with the C282Y/H63D HFE genotype.

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

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

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)

RefSeqs maintained independently of Annotated Genomes
These reference sequences exist independently of genome builds. [Explain](#)

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	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.
Location:223-298	
Blast Score:169	

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 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

NCBI Entrez Gene

Search: Gene for [Go] [Clear]

Display: Full Report (All: 1) Summary

1: [Gene Table](#)

Primary source: [HGNC:4886](#)

See related: [HPRD:01993](#); [MIM:235200](#)

Gene type: protein coding

RefSeq status: Reviewed

Organism: [Homo sapiens](#)

Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia;

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Links

- Order cDNA clone

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		Coding EXON		INTRON	
coords	length	coords	length	coords	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		

[SNP GeneView](#)
[Taxonomy](#)
[UniSTS](#)
[AceView](#)
[CCDS](#)
[Evidence Viewer](#)
[GDB](#)
[GeneTests for MIM: 235200](#)
[HGMD](#)
[HGNC](#)
[HPRD](#)
[KEGG](#)
[MGC](#)
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[UniGene](#)
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All: 1 | [Current Only: 1](#) | [Genes Genomes: 1](#) | [SNP GeneView: 1](#)

1: HFE hemochromatosis [*Homo sapiens*]
 GeneID: 3077 updated 06-Nov-2006 [Entrez Gene Home](#)
RefSeq status: Reviewed [Explain](#)
 total gene size: 9612 bp

Genomic regions, transcripts, and products [?](#)

Go to [reference sequence details](#)

NC_000006.10

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

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[PubMed \(GeneRIF\)](#)
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[SNP: Genotyp](#)
[SNP: GeneView](#)
[Taxonomy](#)
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[CCDS](#)
[Evidence Viewer](#)

NCBI Single Nucleotide Polymorphism

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

Search Entrez for

SNP linked to Gene (geneID:3077)

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

[Contig Annotation](#) [GenBank\(mrna\) Mapping](#)

Send 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	snp 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

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SNP SUBMISSION
 How to Submit

Region	position	pos	cluster id	zygosity	Validation	3D	OMIM	Function	allele	residue	pos	acid pos
exon_2	16949347	325	rs2242956	N.D.		Yes		nonsynonymous	C	Thr [T]	2	35
				N.D.		Yes		contig reference	T	Met [M]	2	35
	16949430	408	rs1799945	0.139		Yes		nonsynonymous	G	Asp [D]	1	63
				0.139		Yes		contig reference	C	His [H]	1	63
	16949436	414	rs1800730	N.D.		Yes		nonsynonymous	T	Cys [C]	1	65
				N.D.		Yes		contig reference	A	Ser [S]	1	65
	16949520	498	rs28934597	N.D.		Yes		nonsynonymous	C	Arg [R]	1	93
				N.D.		Yes	Yes	contig reference	G	Gly [G]	1	93
	16949557	535	rs28934596	N.D.		Yes		nonsynonymous	C	Thr [T]	2	105
				N.D.		Yes	Yes	contig reference	T	Ile [I]	2	105
exon_3	16949833	602	rs28934595	N.D.		Yes		nonsynonymous	C	His [H]	3	127
				N.D.		Yes	Yes	contig reference	A	Gln [Q]	3	127
exon_4	16951197	871	rs4986950	0.005		Yes		nonsynonymous	T	Ile [I]	2	217
				0.005		Yes		contig reference	C	Thr [T]	2	217
	16951392	1066	rs1800562	0.043		Yes		nonsynonymous	A	Tyr [Y]	2	282
				0.043		Yes	Yes	contig reference	G	Cys [C]	2	282

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

[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
 Entrez Gene
 Nomenclature
 RefSeq
 GenBank

PORPHYRIA VARIEGATA, INCLUDED
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 16.3% 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

[MIM +235200](#)
 Description
 Clinical Features
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 Genotype/Phenotype
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 Entrez Gene
 Nomenclature
 RefSeq
 GenBank

OMIM
 Online Mendelian Inheritance in Man
 Johns Hopkins University

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

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

Search Result for OMIM# 235200

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

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HFE-Associated Hereditary Hemochromatosis

Select all clinical laboratories

Laboratories offering clinical testing:	Analysis of the entire coding region: Sequence analysis	Sequence analysis of select exons	Analysis of the entire coding region: Mutation scanning	Targeted mutation analysis	Prenatal diagnosis	Preimplantation genetic diagnosis	Clinical confirmations of mutations identified in a research lab	Carrier testing
ARUP Laboratories, Inc. ARUP Laboratories 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 Altioek, 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;								

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Search Result for OMIM# 235200

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

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HFE-Associated Hereditary Hemochromatosis

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[Management](#)
[Genetic Counseling](#)
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HFE-Associated Hereditary Hemochromatosis

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Robin L Bennett, MS
Arno G Motulsky, MD

[About the Authors](#)

Initial Posting: 3 April 2000 **Last Revision:** 13 July 2005

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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 40 and 60 years of age and

Click on [defined terms](#); definition displays here.

HFE-Associated Hereditary Hemochromatosis

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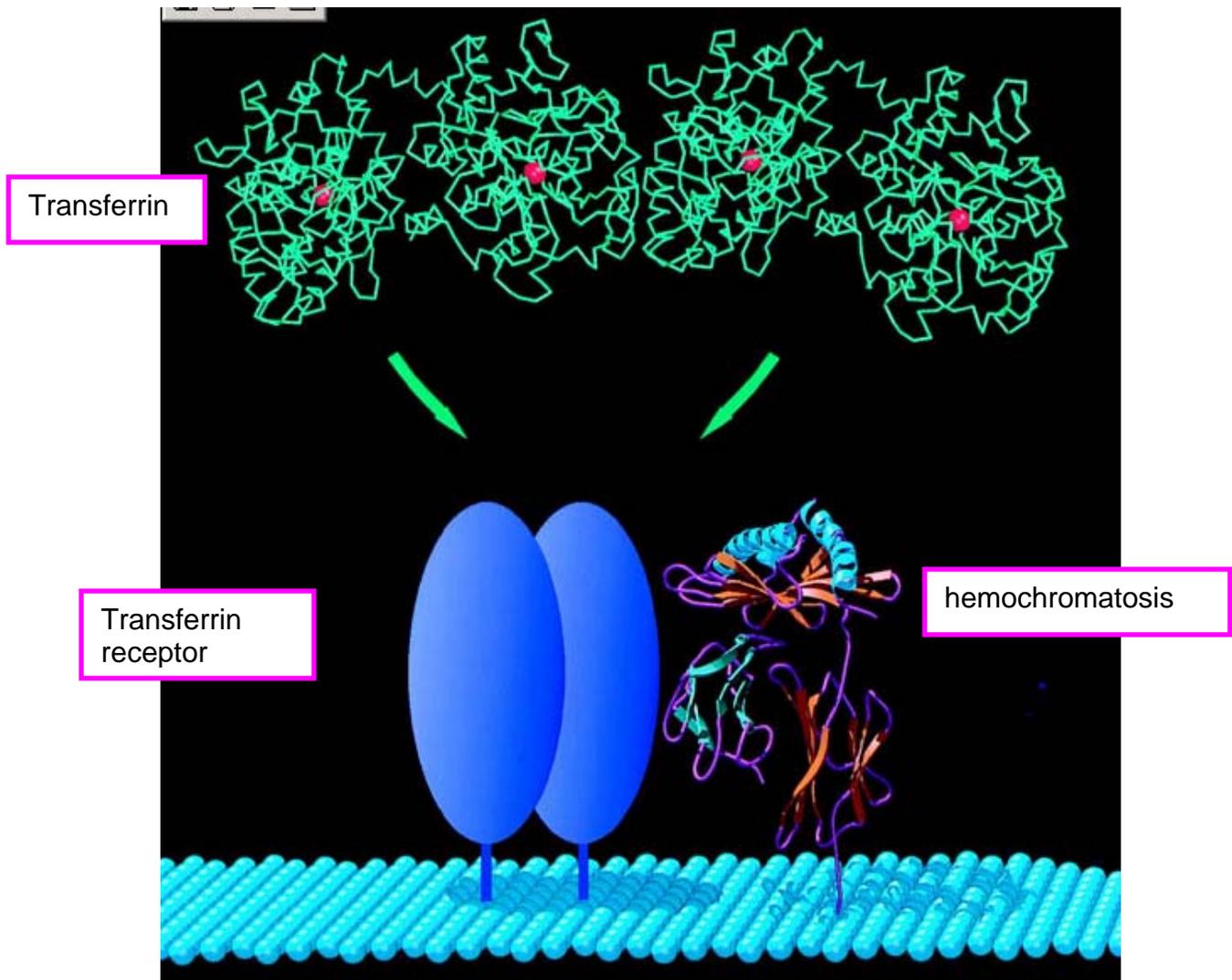
Normal allelic variants: A serine at position 65 to cysteine (S65C) has been identified. The effect of this **mutation** is unclear.

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](#)].



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.

Entrez

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Limits Preview/Index History Clipboard Details

Display Detailed Show 20 Send to

All: 1 OMIM dbSNP: 1 OMIM UniSTS: 1

1: **+235200**

HEMOCHROMATOSIS; HFE

Alternative titles; symbols

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

TABLE OF CONTENTS

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Links

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- GeneView in dbSNP
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- Protein
- SNP
- Structure
- UniSTS
- LinkOut

Genomic regions, transcripts, and products

Go to [reference sequence details](#)

NC_000006.10

[26195427] 5' [26205938] 3'

NM_139005.2
 NM_139002.2
 NM_009418.3
 NM_139004.2
 NM_139003.2
 NM_139009.6
 NM_139007.6
 NM_139007.5
 NM_139008.2
 NM_139011.2
 NM_139011.2
 NM_139006.2

NP_628574.1 isoform 5 precursor
 NP_628571.1 isoform 2 precursor
 NP_081481.1 isoform 1 precursor
 CC034576.1
 NP_628573.1 isoform
 NP_628572.1 isoform
 NP_628576.1 isoform
 NP_628576.1 isoform
 NP_628577.1 isoform
 NP_628579.1 isoform
 NP_628580.1 isoform
 NP_628575.1 isoform

FASTA
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protein link
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 SNP
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 HPRD
 KEGG
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 ModelMaker
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Genomic context

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

[26153616] [26216343]

HIST1H3C HIST1H3C HFE HIST1H4C HIST1H1T

Bibliography

Related Articles in PubMed

NCBI

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

Query: gi4504377 hemochromatosis protein isoform 1 precursor [Homo sapiens]
Matching gi: 112088318, 112053064, 109658670, 109658506, 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 G! list Run BLAST

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
Conserved Domain Database hits				
1870	31	AAI17202	109658670	Hemochromatosis [Homo sapiens]
1870	31	AAI17204	109658506	Hemochromatosis [Homo sapiens]
1870	29	NP_001...	57114069	hemochromatosis protein [Pan troglodytes]
1870	29	P60018	38502807	Hereditary hemochromatosis protein homolog precursor (HLA-H)
1870	29	AAN09793	22854810	hereditary hemochromatosis [Pan troglodytes]
1870	31	AAG29572	11094315	hemochromatosis termination variant terE6; HFE [Homo sapiens]
1870	31	Q30201	2497915	Hereditary hemochromatosis protein precursor (HLA-H)
1870	31	CAA70934	2370111	HFE [Homo sapiens]
1870	31	AAB82083	2088551	hereditary hemochromatosis [Homo sapiens]

NCBI

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

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Matching gi: 112088318, 112053064, 109658670, 109658506, 83323630, 80748852, 57114069, 38502807, 29709343, 22854810, 20250786, 15115850, 14100030, 11094315, 2497915, 2370111, 2088551, 1890180, 1469790

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200 BLAST hits to 4 unique species Sort by taxonomy proximity

0 Archaea 0 Bacteria 200 Metazoa 0 Fungi 0 Plants 0 Viruses 0 Other Eukaryotae

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

348 aa

SCORE	P	ACCESSION	GI	PROTEIN DESCRIPTION
Conserved Domain Database hits				
1517	•	1DE4G	6980500	Chain G, Hemochromatosis Protein Hfe Complexed With Transferrin Recep
1517	•	1DE4D	6980497	Chain D, Hemochromatosis Protein Hfe Complexed With Transferrin Recep
1517	•	1DE4A	6980494	Chain A, Hemochromatosis Protein Hfe Complexed With Transferrin Recep
1517	•	1A62C	4699712	Chain C, Hfe (Human) Hemochromatosis Protein
1517	•	1A62A	4699710	Chain A, Hfe (Human) Hemochromatosis Protein
525	•	1B1IA	3891929	Chain A, The Crystal Structure Of H-2dd Mhc Class I In Complex With T
507	•	1S7TD	48425604	Chain D, Crystal Structures Of The Murine Class I Major Histocompatik
507	•	1S7TA	48425601	Chain A, Crystal Structures Of The Murine Class I Major Histocompatik
507	•	1S7SA	48425598	Chain A, Crystal Structures Of The Murine Class I Major Histocompatik
507	•	1S7RD	48425595	Chain D, Crystal Structures Of The Murine Class I Major Histocompatik
507	•	1S7RA	48425592	Chain A, Crystal Structures Of The Murine Class I Major Histocompatik
507	•	1S7QA	48425589	Chain A, Crystal Structures Of The Murine Class I Major Histocompatik

NCBI **Related Structures**

HOME SEARCH SITE MAP PubMed Blast Entrez Structure Help

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

Structure: 1DE4 Chain G, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor

Reference: [MMDB] [PubMed]

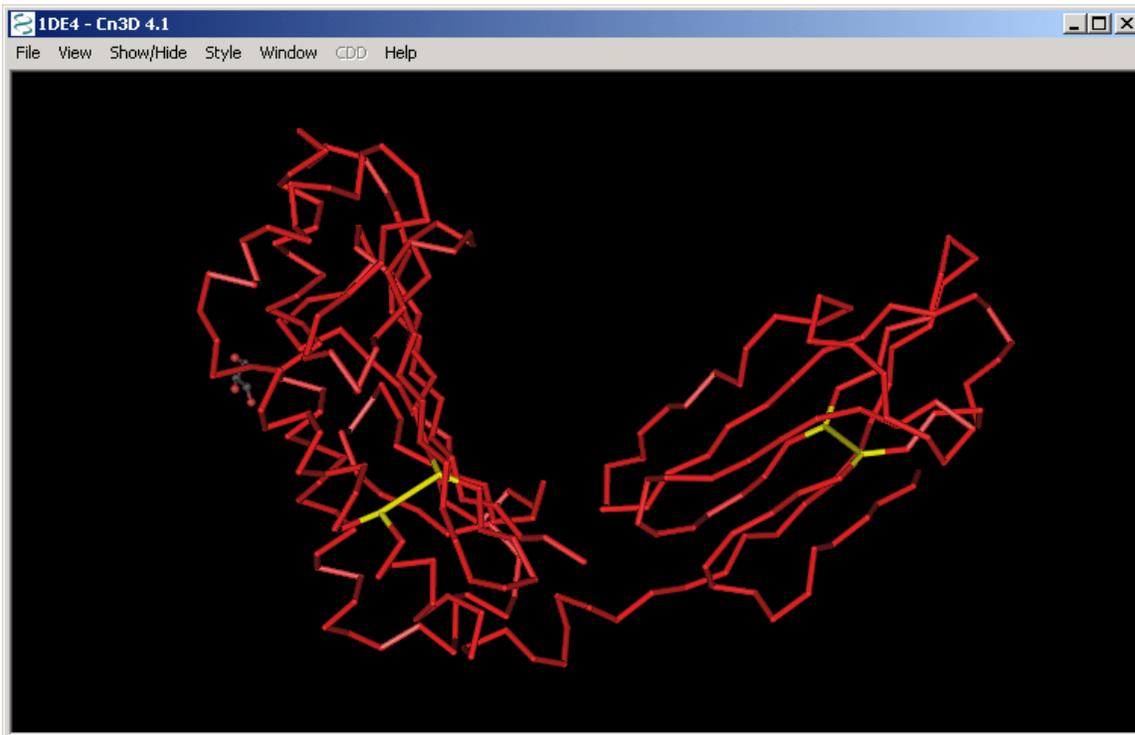
Get 3D Structure data to: View in Cn3D (To display structure, download Cn3D)

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

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1DE4_G	1	RLLRSHSLHYLFGASEQDLGSLFEALGYVDDQLFVFDHESRRVEPRTPVWSSRISSQHWLQSQSLRGWDHMF	80						

		90	100	110	120	130	140	150	160
gi_4504377	103	WTIMENHNHNSKESHTLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPTLDWRAAEPRANPTKLEWERHKIRARQ	182						
1DE4_G	81	WTIMENHNHNSKESHTLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPTLDWRAAEPRANPTKLEWERHKIRARQ	160						

		170	180	190	200	210	220	230	240
	********



1DE4 - Sequence/Alignment Viewer

View Edit Mouse Mode Unaligned Justification Imports

1DE4_G	TSSVTTLRICALNYYYPQNI	TMKWLKDKQPMDAKE	FEPKDVLPNGDGT	YQGWITLAVPPGEEQRYT	QVEHPGLDQPLIVIW
gi_4504377	TSSVTTLRICALNYYYPQNI	TMKWLKDKQPMDAKE	FEPKDVLPNGDGT	YQGWITLAVPPGEEQRYT	QVEHPGLDQPLIVIW

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.