Mini Courses NCBI Resources one course at a time

Correlating Disease Genes and Phenotypes

An NCBI Mini-Course

This mini-course focuses on the correlation of a disease gene to the phenotype. It demonstrates how NCBI resources such as 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:

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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 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.

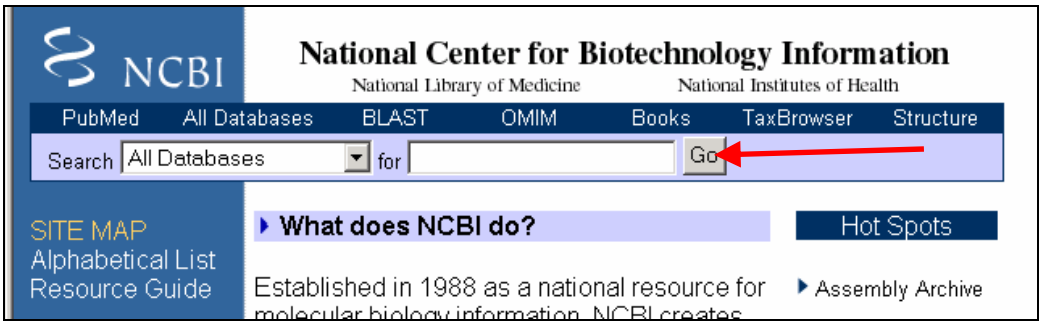
You can now easily explain why the C282Y mutant has an altered function.

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 cystenie 282 in the immunoglobulin constant region domain of the HFE protein is involved in formation of a disulphide bridge. Its mutation to tyrosine will alter the folding of the protein.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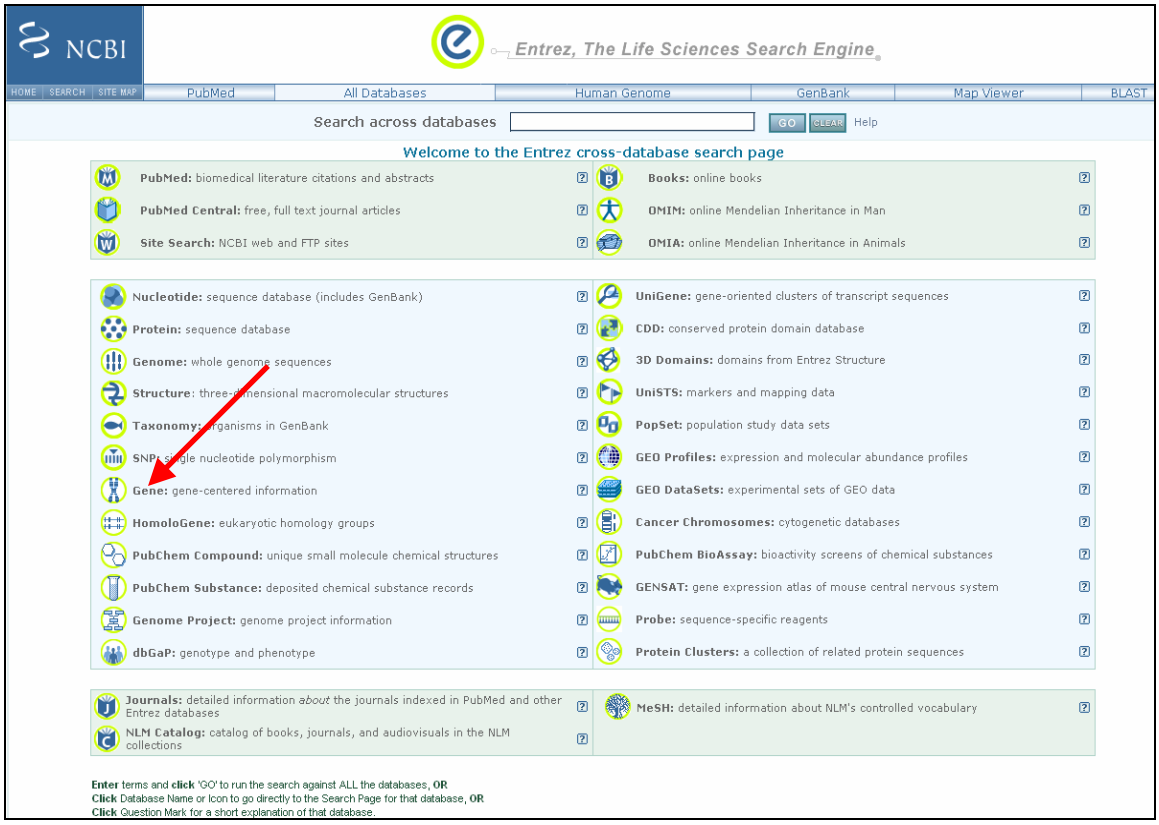
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PubMed Central: free, full text journal articles
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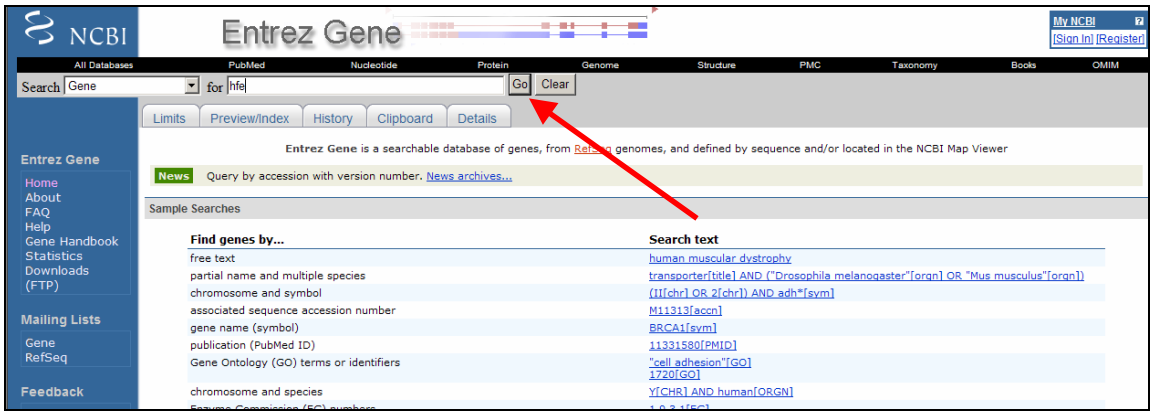
Site Search: NCBI web and FTP sites
OMIA: online Mendelian Inheritance in Animals
Nucleotide: sequence database (includes GenBank)
UniGene: gene-oriented clusters of transcript sequences
Protein: sequence database
CDD: conserved protein domain database
Genome: whole genome sequences
3D Domains: domains from Entrez Structure
Structure: three-dimensional macromolecular structures
UniSTS: markers and mapping data
Taxonomy: organisms in GenBank
PopSet: population study data sets
SNPs: 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.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Query by accession with version number. News archives...
Sample Searches
Find genes by...
Search text
free text
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publication (PubMed ID)
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Gene Ontology (GO) terms or identifiers
"cell adhesion"[GO]
1720[GO]
chromosome and species
Y[CHR] AND human[ORGN]

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- Downloads (FTP)

Mailing Lists
- Gene
- RefSeq

1: HFE

Order cDNA clone, Links

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

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

1: HFE hemochromatosis [*Homo sapiens*]

GeneID: 3077 updated 19-Apr-2007

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	*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.

Entrez Gene Home

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Links Explain
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- OMIA
- OMIM
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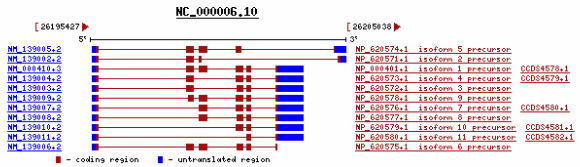
Genomic regions, transcripts, and products

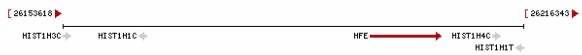
Go to reference sequence details



Genomic context

chromosome: 6; Location: 6p21.3

See HFE in MapViewer



Probe
Protein
PubMed
PubMed (GeneRIF)
SNP
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

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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

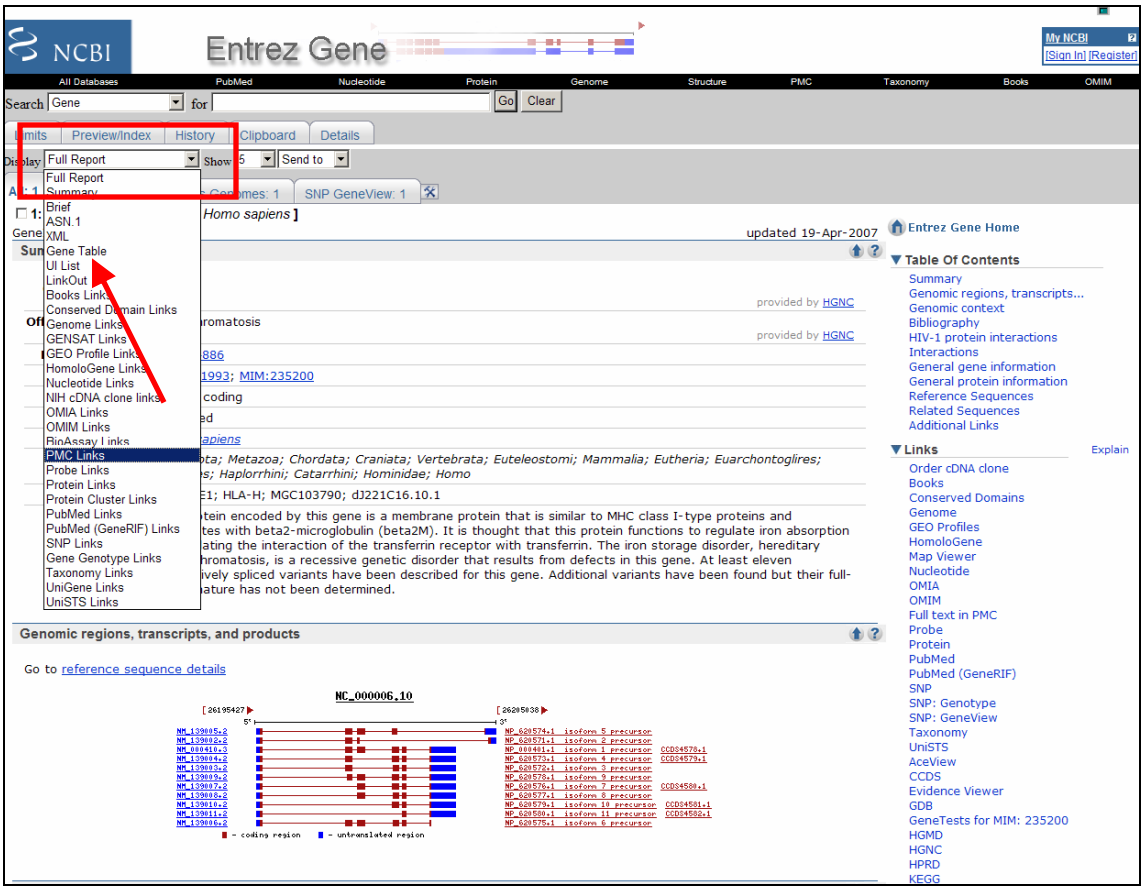
cd00098 Location:223-298 Blast Score:169	IGc; Immunoglobulin domain constant region subfamily; members of the IGc subfamily are components of immunoglobulins, T-cell receptors, CD1 cell surface glycoproteins, secretory glycoproteins A/C, and Major Histocompatibility Complex (MHC) class I/II molecules
pfam00129 Location:27-202 Blast Score:314	MHC_I; Class I Histocompatibility antigen, domains alpha 1 and 2

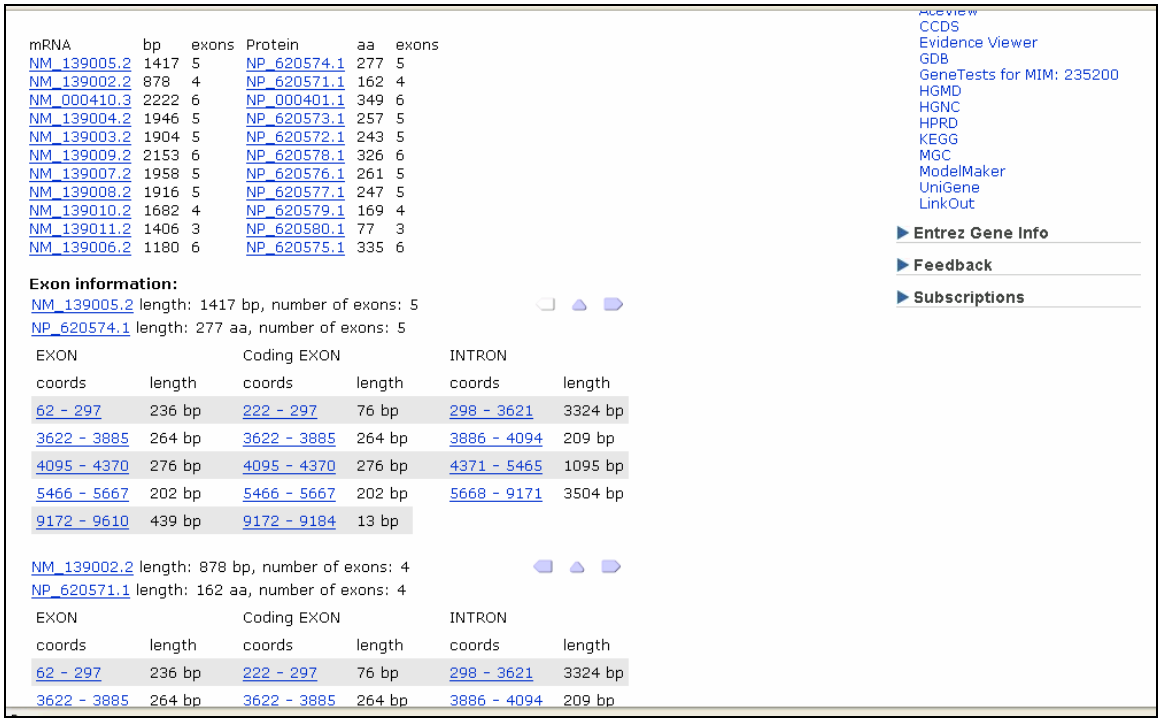
2. NM_139002.2→NP_620571.1 **hemochromatosis protein isoform 2 precursor**

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	EAW55516.1
		EAW55517.1
		EAW55518.1
		EAW55519.1
		EAW55520.1
		EAW55521.1
		EAW55522.1
		EAW55523.1
		EAW55524.1
		EAW55525.1
		EAW55526.1
		EAW55527.1
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





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		

NM_139002.2 length: 878 bp, number of exons: 4

NP_620571.1 length: 162 aa, number of exons: 4

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

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

1: **HFE hemochromatosis [** *Homo sapiens* **]**

GeneID: 3077
RefSeq status: Reviewed
total gene size: 9612 bp

updated 19-Apr-2007

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

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
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:

NCBI **Single Nucleotide Polymorphism**

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

Search for SNP on NCBI Reference Assembly

Search Entrez SNP for Go

BUILD 127

Have a question about dbSNP? Try searching the SNP FAQ Archive!

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

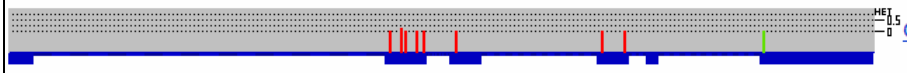
Send rs# on all gene models to Batch Query | Download all rs# to file. | Gene Genotype Report

Gene Model (mRNA alignment) information from genome sequence

Total gene model (contig mRNA transcript): 22

mrna	transcript	protein	mrna orientation	Contig	Contig Label	List SNP
NM_000410	plus strand	NP_000401	forward	NT_007592	reference	<- currently shown
NM_000410	plus strand	NP_000401	forward	NW_922984	Celera	View snp on GeneModel
NM_139002	plus strand	NP_620571	forward	NT_007592	reference	View snp on GeneModel
NM_139002	plus strand	NP_620571	forward	NW_922984	Celera	View snp on GeneModel
NM_139003	plus strand	NP_620572	forward	NT_007592	reference	View snp on GeneModel
NM_139003	plus strand	NP_620572	forward	NW_922984	Celera	View snp on GeneModel
NM_139004	plus strand	NP_620573	forward	NT_007592	reference	View snp on GeneModel
NM_139004	plus strand	NP_620573	forward	NW_922984	Celera	View snp on GeneModel
NM_139005	plus strand	NP_620574	forward	NT_007592	reference	View snp on GeneModel
NM_139005	plus strand	NP_620574	forward	NW_922984	Celera	View snp on GeneModel
NM_139006	plus strand	NP_620575	forward	NT_007592	reference	View snp on GeneModel
NM_139006	plus strand	NP_620575	forward	NW_922984	Celera	View snp on GeneModel
NM_139007	plus strand	NP_620576	forward	NT_007592	reference	View snp on GeneModel
NM_139007	plus strand	NP_620576	forward	NW_922984	Celera	View snp on GeneModel
NM_139008	plus strand	NP_620577	forward	NT_007592	reference	View snp on GeneModel
NM_139008	plus strand	NP_620577	forward	NW_922984	Celera	View snp on GeneModel

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



Color Legend

Region	Contig position	mRNA pos	dbSNP rs# cluster id	Hetero-zygosity	Validation	3D	OMIM	Function	dbSNP allele	Protein residue	Codon pos	Amino acid pos
exon_1	16945920	161						start codon				1
exon_2	16949347	264	rs2242956	N.D.		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	rs35201683	0.053				synonymous	T	Tyr [Y]	3	342
				0.053				contig reference	C	Tyr [Y]	3	342

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.0001 HEMOCHROMATOSIS [HFE, CYS282TYR] dbSNP

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 16.5% 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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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

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ARUP Laboratories Molecular Genetics Laboratory Salt Lake City, UT Elaine Lyon, PhD; Rong Mao, MD; Edward R Ashwood, MD; Marzia Pasquali, PhD; Pinar Bayrak-Toydemir, MD, PhD				•			•
Acibadem Healthcare Group Acibadem Genetic Diagnostic Center Istanbul, Turkey Ender Altiok, MD, PhD				•			•
Alberta Children's Hospital Molecular Diagnostic Laboratory Calgary, Alberta, Canada Peter Bridge, PhD, FCCMG, FACMG; Jillian Parboosingh, PhD, FCCMG				•			
Baylor College of Medicine Medical Genetics Laboratories Houston, TX Christine M Eng, MD, FACMG; William E O'Brien, PhD; Lee-Jun Wong, PhD; Sau W. Cheung, PhD				•			
BioLab spol. s.r.o. Molecular Biology Laboratory Klatovy, Czech Republic Frantisek Musil, MUDr				•			
BloodCenter of Wisconsin Molecular Diagnostics Laboratory Milwaukee, WI Daniel B Bellissimo, PhD				•			
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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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GeneReviews
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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

HFE-Associated Hereditary Hemochromatosis

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OMIM Entries for HFE-Associated Hereditary Hemochromatosis

235200	HEMOCHROMATOSIS; HFE

Genomic Databases for HFE-Associated Hereditary Hemochromatosis

Gene Symbol	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
HFE	235200	HFE	*HFE*	119309	*HFE*

For a description of the genomic databases listed, click here.

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

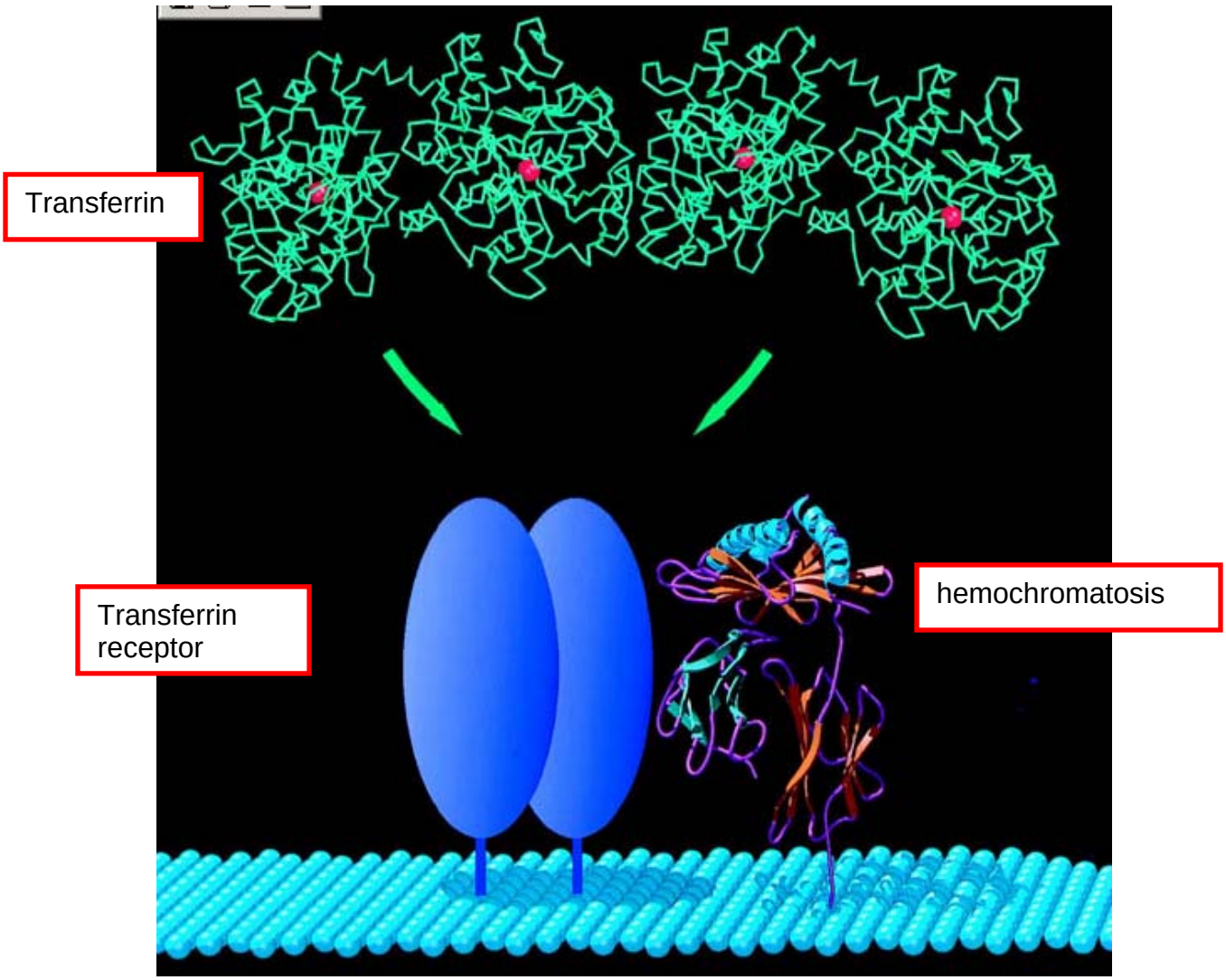
Pathologic allelic variants: At least 28 distinct mutations have been reported, most being missense or nonsense mutations. Two missense mutations account for the vast majority of disease-causing alleles in the population:

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

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

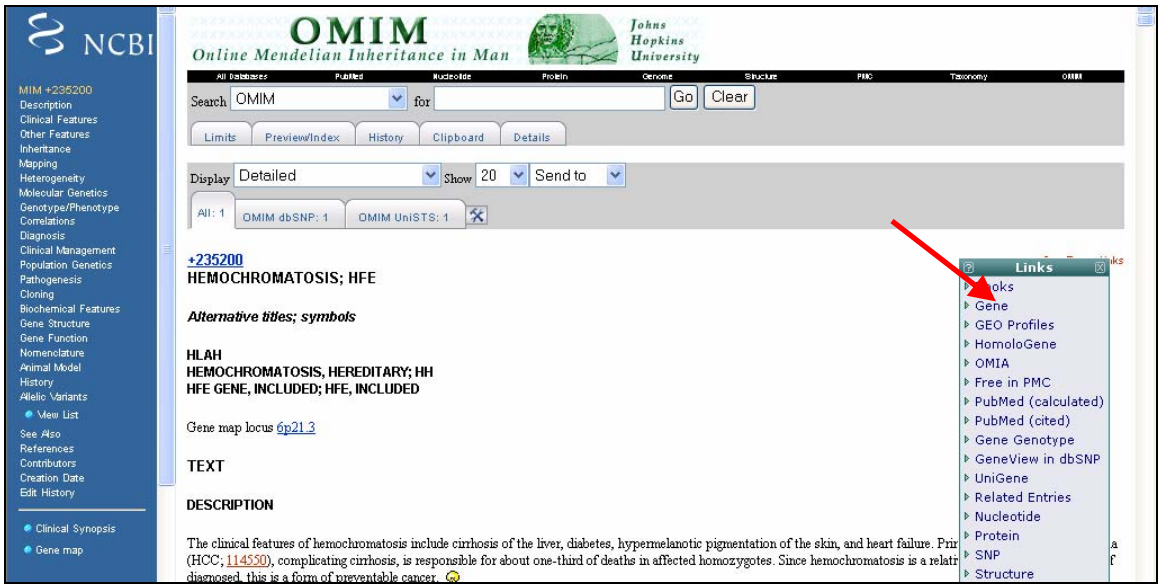
Abnormal gene product: The p.C282Y mutation destroys a key cysteine residue that is required for disulfide bonding with beta-2-microglobulin. As a result, the HFE protein does not mature properly and becomes trapped in the endoplasmic reticulum and Golgi apparatus, leading to decreased cell-surface expression.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

Resources



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

The hemochromatosis protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin.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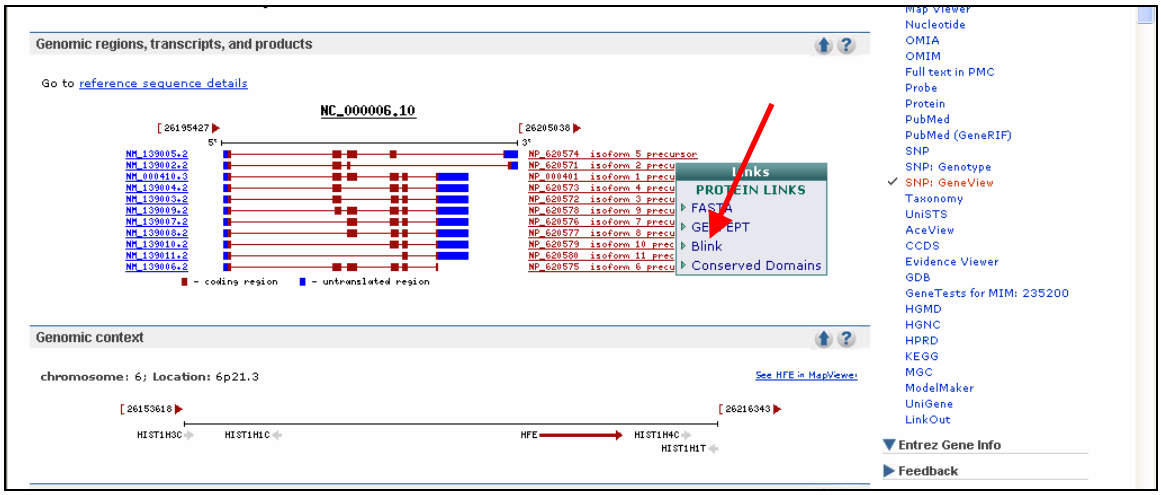
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PubMed (GeneRIF)
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SNP: Genotype
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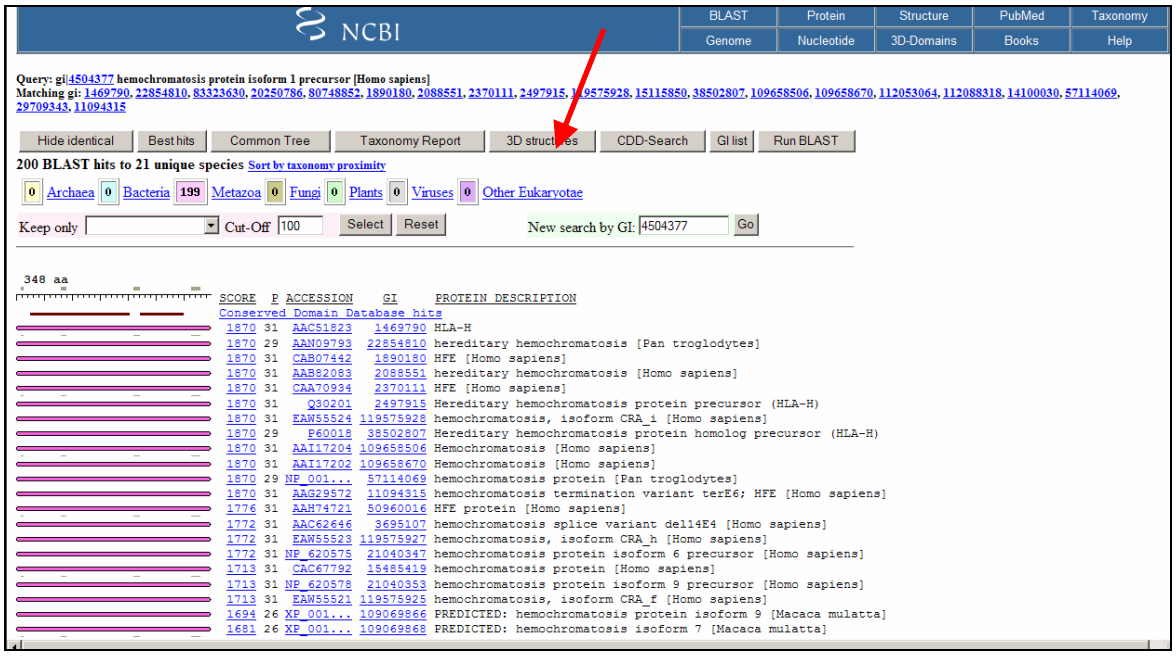
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Taxonomy Report
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CDD-Search
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Cut-Off 100
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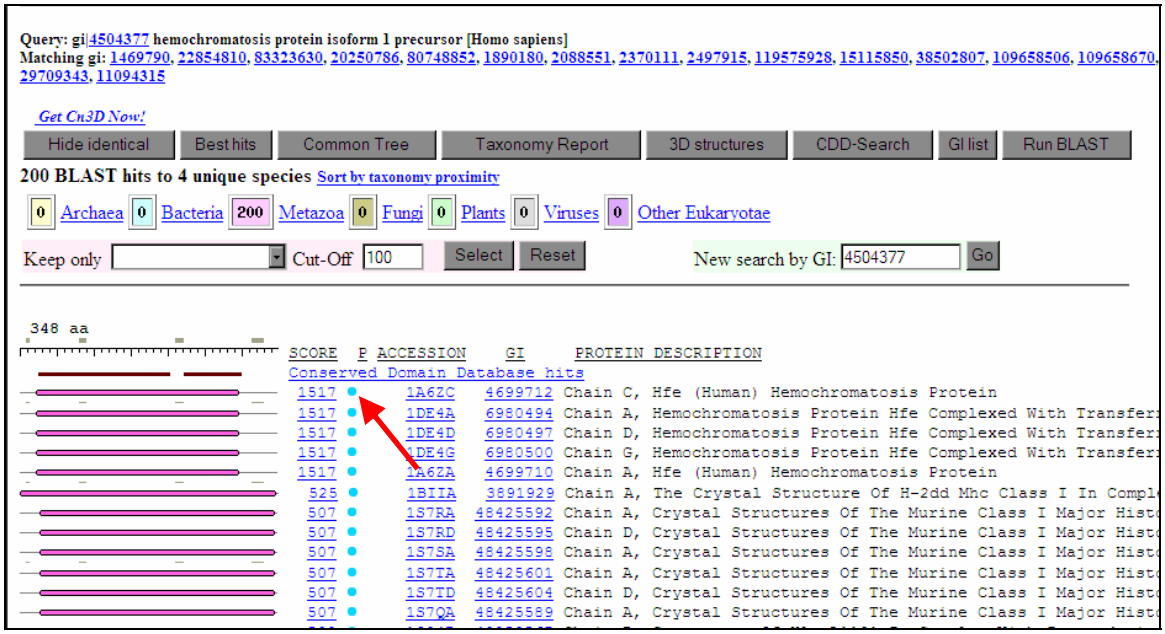
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Cut-Off 100
Select
Reset
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Go
348 aa
SCORE P ACCESSION GI PROTEIN DESCRIPTION
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1517 1DE4D 6980497 Chain D, Hemochromatosis Protein Hfe Complexed With Transfer
1517 1DE4G 6980500 Chain G, Hemochromatosis Protein Hfe Complexed With Transfer
1517 1A6ZA 4699710 Chain A, Hfe (Human) Hemochromatosis Protein
525 1BIIA 3891929 Chain A, The Crystal Structure Of H-2dd Mhc Class I In Compl
507 1S7RA 48425592 Chain A, Crystal Structures Of The Murine Class I Major Hist
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507 1S7TD 48425604 Chain D, Crystal Structures Of The Murine Class I Major Hist
507 1S7QA 48425589 Chain A, Crystal Structures Of The Murine Class I Major Hist

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

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

Reference: [MMDB] [PubMed]

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

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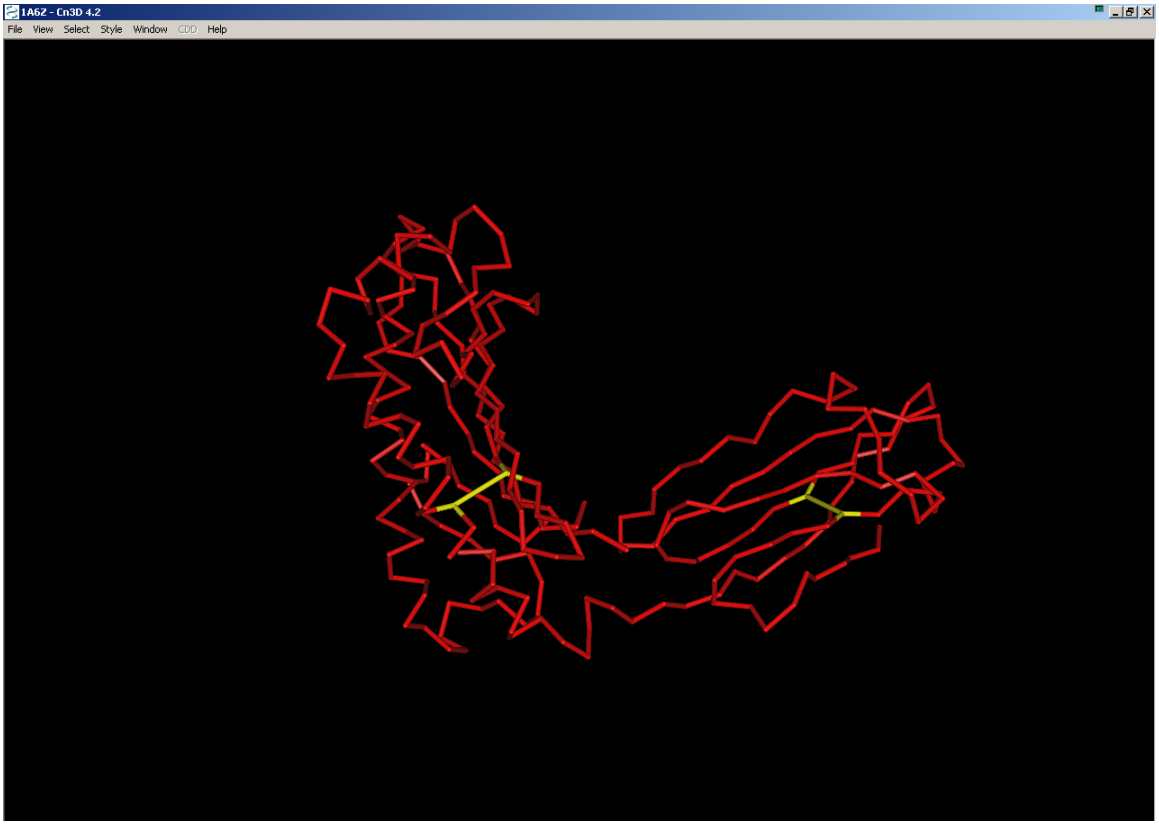

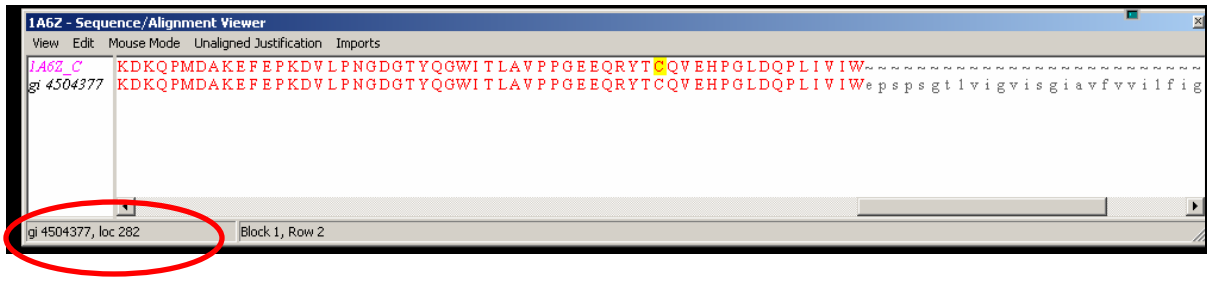
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Problem 2:
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Mutations in the HBB gene are associated with sickle cell anemia. A laboratory working on sickle cell anemia wants to elucidate the biochemical and structural basis for the function of 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 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.