

Correlating Disease Genes to 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>

Instructor:

Dr. Medha Bhagwat, NCBI

Problem 1

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

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3. Learning more about the hemochromatosis disease and its genetic testing (using OMIM and Gene Tests)
4. Elucidating the biochemical and structural basis for the function of the wild type and the mutant protein, if possible (using CDD).

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

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

What is the location and orientation of the HFE gene on the human genome? List the genes adjacent to it. How many alternatively spliced products have been annotated for the HFE gene when the RefSeq mRNA entries were reviewed? 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 "Geneview in dbSNP" 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.

Summary:

1. The HFE gene is located on chromosome 6 and has at least 11 alternatively spliced products.
2. Currently, there are 8 non-synonymous SNPs annotated on the protein NP_000401.
3. The Cys282Tyr mutant is associated with the hemochromatosis disease and the site of mutation is used in hemochromatosis genetic testing.
4. The HFE protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin whereas the Cys282Tyr mutant fails to regulate this interaction leading to iron overload. The conserved cysteine 282 in the immunoglobulin constant region domain in the HFE protein is involved in formation of a disulphide bridge. Its mutation to tyrosine will alter the folding of the protein.

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

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Search for

SITE MAP
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What does NCBI do? **Hot Spots**

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

  **Entrez, The Life Sciences Search Engine**

HOME SEARCH SITE MAP PubMed 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

Entrez PubMed Nucleotide Protein Genome Structure PMC Taxonomy Books OMIM

Search Gene for hfe Go Clear current records only

Limits Preview/Index History Clipboard Details

- Enter one or more search terms.
- More information about available fields is available [here](#).
- Consider use of the limits and preview/index functions.
- Remember, boolean operators (AND, OR, NOT) must be in uppercase.

Entrez
SITE MAP
Entrez Help

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Search Gene for hfe Go Clear current records only

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1: [HFE](#) MGC cDNA clone, [Links](#)
hemochromatosis [*Homo sapiens*]
Other Aliases: HGNC:4886, HFE1, HH, HLA-H
Other Designations: hemochromatosis protein; hereditary haemochromatosis protein
Chromosome: 6; **Location:** 6p21.3
GeneID: 3077

2: [Hfe](#) [Links](#)
hemochromatosis [*Mus musculus*]
Other Aliases: MGI:109191, MR2
Chromosome: 13; **Location:** 13 15.0 cM
GeneID: 15216

Entrez
SITE MAP
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FTP site

Related sites
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OMIM

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Search for current records only

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

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; 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.

Transcripts and products

[RefSeq below](#)

■ - coding region ■ - untranslated region

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Genomic context See HFE in MapViewer

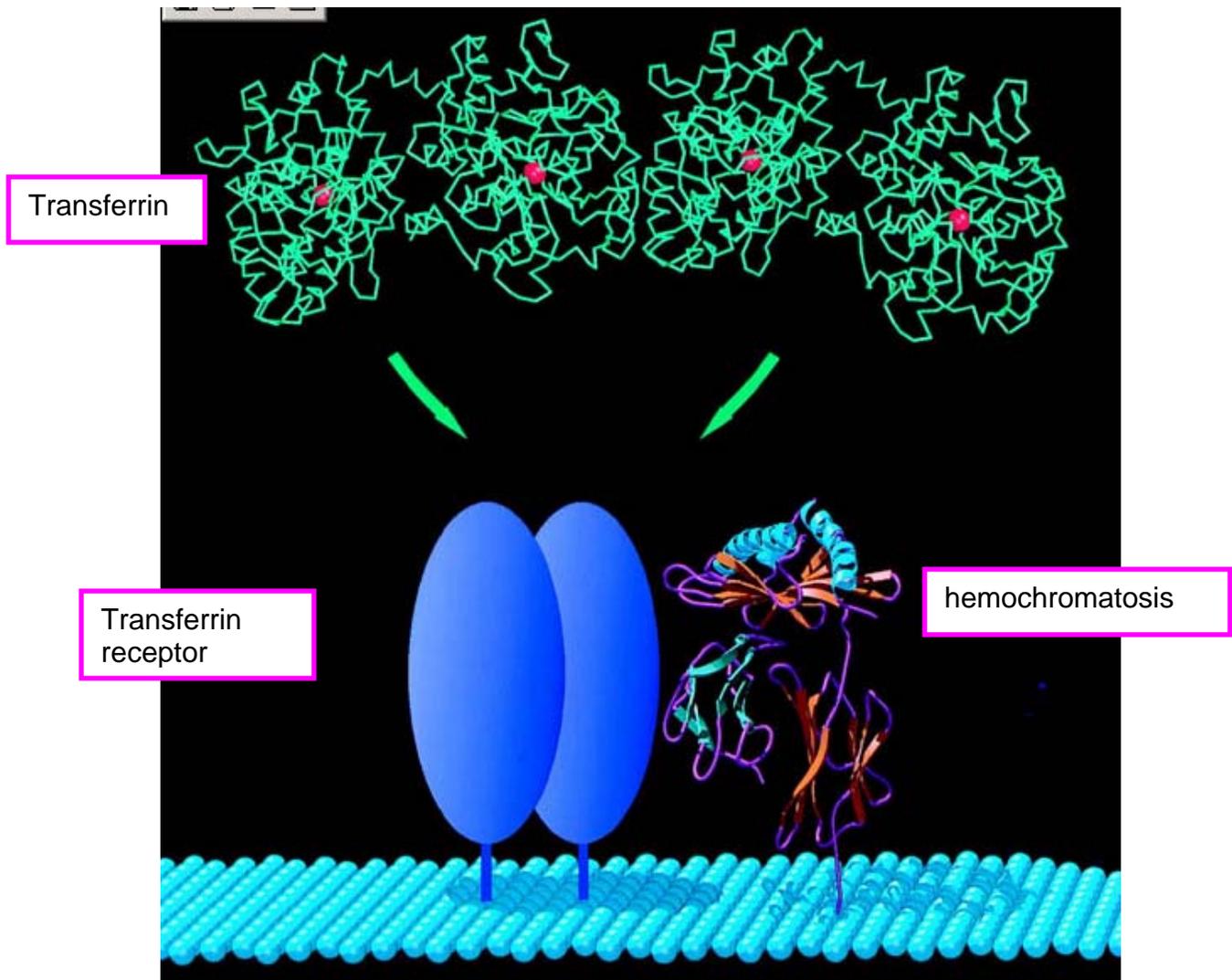
chromosome: 6; Location: 6p21.3

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



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.

General gene information

GeneOntology
 Provided by [GOA](#)

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

Process

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

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](#)

Markers (Sequence Tagged Sites/STS)
[STS-U60319](#) (e-PCR)
 Alternate name RH75899
 Alternate name sts-U60319
[PMC19311P1](#) (e-PCR)
[PMC196491P2](#) (e-PCR)
 Alternate name PMC23476P1
[HFE_3382](#) (e-PCR)

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 |

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1: Brief
 ASN.1
 XML

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 Gene
 GENSAT Links

Gene description: hemochromatosis
 RefSeq status: Reviewed
 Organism: *Homo sapiens*
 Lineage: *Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae; Homo*
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 OMIA
 OMIM
 Full text in PMC
 Probe
 Protein
 PubMed
 PubMed (GeneRIF)

| | mRNA | bp | exons | Protein | aa | exons |
|----------------|---------------------------|------|-------|---------------------------|-----|-------|
| LocusLink | NM_000410 | 2717 | 7 | NP_000401 | 349 | 6 |
| Map Viewer | NM_139004 | 1922 | 5 | NP_620573 | 257 | 5 |
| OMIM | NM_139009 | 1280 | 6 | NP_620578 | 326 | 6 |
| RefSeq | NM_139007 | 1085 | 5 | NP_620576 | 261 | 5 |
| UniGene | NM_139010 | 809 | 4 | NP_620579 | 169 | 4 |
| Feedback | NM_139011 | 533 | 3 | NP_620580 | 77 | 3 |
| Help Desk | NM_139005 | 1140 | 5 | NP_620574 | 277 | 5 |
| Corrections | NM_139003 | 804 | 5 | NP_620572 | 243 | 5 |
| About GeneRIFs | NM_139006 | 1045 | 6 | NP_620575 | 335 | 6 |
| Subscriptions | NM_139008 | 781 | 5 | NP_620577 | 247 | 5 |
| RefSeq | NM_139002 | 726 | 4 | NP_620571 | 162 | 4 |
| Gene | | | | | | |
| Map Viewer | | | | | | |

Exon information:
[NM_000410](#) length: 2717 bp, number of exons: 7
[NP_000401](#) 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 | | | | |

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Official Symbol: HFE and Name: hemochromatosis provided by [HUGO Gene Nomenclature Committee](#)
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 RefSeq status: Reviewed
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Transcripts and products ? ↑

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Legend: ■ - coding region ■ - untranslated region

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- LinkOut

NCBI **Single Nucleotide Polymorphism**

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

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SNP linked to Gene (geneID:3077)

dbSNP BUILD 124

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SNP are linked from gene **HFE** via the following methods:

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

Send all rs# to Batch Query all rs# to file.

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 Submission **EA**
 Specifications
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 Sample Individual

RELATED SITES
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Gene Model (mRNA alignment) information from genome sequence

Total gene model (contig mRNA transcript): 22

| mna | transcript | protein | mna 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 |
| 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 |
| NM_139009 | plus strand | NP_620578 | forward | NT_007592 | reference | view |
| NM_139009 | plus strand | NP_620578 | forward | NW_922984 | Celera | view |
| NM_139010 | plus strand | NP_620579 | forward | NT_007592 | reference | view |
| NM_139010 | plus strand | NP_620579 | forward | NW_922984 | Celera | view |
| NM_139011 | plus strand | NP_620580 | forward | NT_007592 | reference | view |
| NM_139011 | plus strand | NP_620580 | forward | NW_922984 | Celera | view |

in gene region cSNP has frequency double hit haplotype tagged

Working Group
 Whole Genome
 Association
 dbMHC

in gene region cSNP has frequency double hit haplotype tagged

gene model (contig mRNA transcript): reference [NT_007592](#) [NM_000410](#) [NP_000401](#) forward plus strand 8, coding

| Region | Contig position | dbSNP rs# | 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 |
| | | | | | | | contig reference | T | Met [M] | 2 | 35 |
| | 16949430 | rs1799945 | 0.139 | | Yes | | nonsynonymous | G | Asp [D] | 1 | 63 |
| | | | | | | | contig reference | C | His [H] | 1 | 63 |
| | 16949436 | rs1800730 | N.D. | | Yes | | nonsynonymous | T | Cys [C] | 1 | 65 |
| | | | | | | | contig reference | A | Ser [S] | 1 | 65 |
| | 16949520 | rs28934597 | N.D. | | Yes | Yes | nonsynonymous | C | Arg [R] | 1 | 93 |
| | | | | | | | contig reference | G | Gly [G] | 1 | 93 |
| | 16949557 | rs28934596 | N.D. | | Yes | Yes | nonsynonymous | C | Thr [T] | 2 | 105 |
| | | | | | | | contig reference | T | Ile [I] | 2 | 105 |
| exon_4 | 16949833 | rs28934595 | N.D. | | Yes | Yes | nonsynonymous | C | His [H] | 3 | 127 |
| | | | | | | | contig reference | A | Gln [Q] | 3 | 127 |
| exon_5 | 16951197 | rs4986950 | 0.005 | | Yes | | nonsynonymous | T | Ile [I] | 2 | 217 |
| | | | | | | | contig reference | C | Thr [T] | 2 | 217 |
| | | | | | | | 16951392 | rs1800562 | 0.043 | | 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

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+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
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+235200 [GeneTests, Links](#)

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]

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



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

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

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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 Altıok, MD, PhD | | | | ● | | | |
| Alberta Children's Hospital Molecular Diagnostic Laboratory Calgary, Alberta, Canada Peter Bridge, PhD, FCCMG, FACMG; Jillian Parboosingh, PhD, FCCMG | | | | ● | | | |

| | | | | | |
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| Home Page | About GeneTests | | Laboratory Directory | Clinic Directory | Educational Materials |
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Search Result for OMIM# 235200

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

Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —Ed.

Molecular Genetics of HFE-Associated Hereditary Hemochromatosis

| Gene Symbol | Chromosomal Locus | Protein Name |
|-------------|-------------------|------------------------------------|
| HFE | 6p21.3 | Hereditary hemochromatosis protein |

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

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 | 119309 | HFE | 119309 | HFE |

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

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

| | | | | | |
|---------------------------|---------------------------------|--|--------------------------------------|----------------------------------|---------------------------------------|
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|---------------------------|---------------------------------|--|--------------------------------------|----------------------------------|---------------------------------------|

[\[Printable Copy\]](#)

HFE-Associated Hereditary Hemochromatosis

[Summary](#)
[Diagnosis](#)
[Clinical Description](#)
[Prevalence](#)
[Differential Diagnosis](#)
[Management](#)
[Genetic Counseling](#)
[Molecular Genetics](#)
[Resources](#)
[References](#)
[Author Information](#)
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(Returns to top)

[Title Index](#)

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.

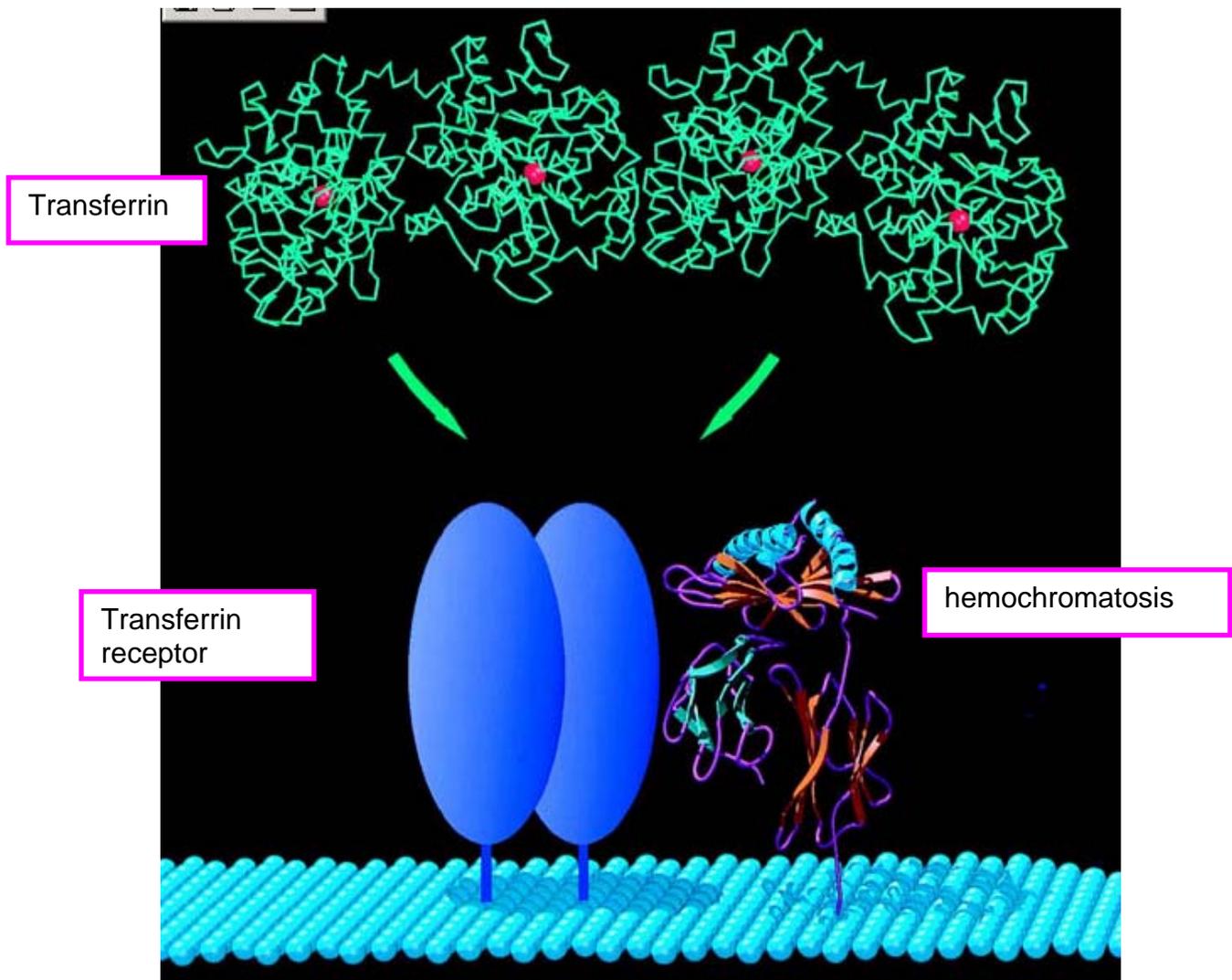
Normal gene product: A cell-surface [protein](#) of 321 amino acids with sequence similarity to HLA Class I molecules. The normal [protein](#) forms a heterodimer with beta-2-microglobulin, and this interaction is necessary for normal presentation on the cell surface. The normal [protein](#) binds to 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](#)].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. —Ed.

- CDC: Iron Overload and Hemochromatosis, Frequently Asked Questions**
www.cdc.gov/nccddphp/dnps/hemochromatosis/faq.htm
- National Digestive Diseases Information Clearinghouse (NDDIC)**
[Hemochromatosis](#)
- National Human Genome Research Institute**
[Learning About Hereditary Hemochromatosis](#)
- National Library of Medicine Genetics Home Reference**
[Hemochromatosis](#)



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 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]

GeneTests Links

- Books
- Gene
- GEO Profiles
- HomoloGene
- OMIA
- Free in PMC
- PubMed (calculated)
- PubMed (cited)
- Gene Genotype
- GeneView in dbSNP
- UniGene
- Related Entries
- Nucleotide
- Protein
- SNP
- Structure
- UniSTS
- LinkOut

View List

Clinical Synopsis
Gene map

have been found but their full length nature has not been determined.

Transcripts and products

RefSeq below

NC_000006

[26195427] 5' [26205938] 3'

NM_000410 NP_000401 isoform 1 precursor

NM_139004 NP_620573 isoform 4 prec

NM_139009 NP_620576 isoform 9 prec

NM_139007 NP_620576 isoform 7 prec

NM_139010 NP_620579 isoform 10 prec

NM_139011 NP_620580 isoform 11 prec

NM_139005 NP_620574 isoform 5 prec

NM_139003 NP_620572 isoform 3 prec

NM_139006 NP_620575 isoform 6 prec

NM_139008 NP_620577 isoform 8 prec

NM_139002 NP_620571 isoform 2 prec

■ - coding region ■ - untranslated region

Links

- PROTEIN LINKS
- FASTA
- GENEPT
- BLink
- Conserved Domains

PubMed
PubMed (GeneRIF)
SNP
SNP: Genotype
SNP: GeneView
Taxonomy
UniSTS
AceView
Ensembl
Evidence Viewer
GDB
GeneTests for MIM: 235200
HGMD
HGNC
KEGG
MOC
ModelMaker
UCSC
UniGene
LinkOut

Query: gi|4504377 hemochromatosis protein isoform 1 precursor [Homo sapiens]
 Matching gi: [57114069](#), [38502807](#), [29709343](#), [22854810](#), [20250786](#), [15115850](#), [14100030](#), [11094315](#), [2497915](#), [2370111](#), [2088551469790](#)

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

200 BLAST hits to 23 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]

348 aa

| SCORE | P | ACCESSION | GI | PROTEIN DESCRIPTION |
|--|----|---------------------------|--------------------------|--------------------------------------|
| Conserved Domain Database hits | | | | |
| 1870 | 28 | NP_001... | 57114069 | hemochromatosis protein [Pan troglod |
| 1870 | 28 | P60018 | 38502807 | Hereditary hemochromatosis protein |
| 1870 | 28 | AAN09793 | 22854810 | hereditary hemochromatosis [Pan tro |
| 1870 | 30 | AAG29572 | 11094315 | hemochromatosis termination variant |
| 1870 | 30 | Q30201 | 2497915 | Hereditary hemochromatosis protein |
| 1870 | 30 | CAA70934 | 2370111 | HFE [Homo sapiens] |
| 1870 | 30 | AAB82083 | 2088551 | hereditary hemochromatosis [Homo sa |
| 1870 | 30 | CAB07442 | 1890180 | HFE [Homo sapiens] |

Query: gi|4504377 hemochromatosis protein isoform 1 precursor [Homo sapiens]
 Matching gi: [57114069](#), [38502807](#), [29709343](#), [22854810](#), [20250786](#), [15115850](#), [14100030](#), [11094315](#), [2497915](#), [2370111](#), [2088551469790](#)

[Get Cn3D Now!](#)

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

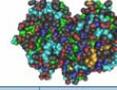
200 BLAST hits to 4 unique species Sort by taxonomy proximity

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

Keep only [] Cut-Off 100 [Select] [Reset]

348 aa

| SCORE | P | ACCESSION | GI | PROTEIN DESCRIPTION |
|--|---|-----------------------|--------------------------|--------------------------------------|
| Conserved Domain Database hits | | | | |
| 1517 | • | 1DE4G | 6980500 | Chain G, Hemochromatosis Protein Hfe |
| 1517 | • | 1DE4D | 6980497 | Chain D, Hemochromatosis Protein Hfe |
| 1517 | • | 1DE4A | 6980494 | Chain A, Hemochromatosis Protein Hfe |
| 1517 | • | 1A62C | 4699712 | Chain C, Hfe (Human) Hemochromatosis |
| 1517 | • | 1A62A | 4699710 | Chain A, Hfe (Human) Hemochromatosis |
| 525 | • | 1BIIA | 3891929 | Chain A, The Crystal Structure Of H- |
| 507 | • | 1S7TD | 48425604 | Chain D, Crystal Structures Of The M |
| 507 | • | 1S7TA | 48425601 | Chain A, Crystal Structures Of The M |
| 507 | • | 1S7SA | 48425598 | Chain A, Crystal Structures Of The M |

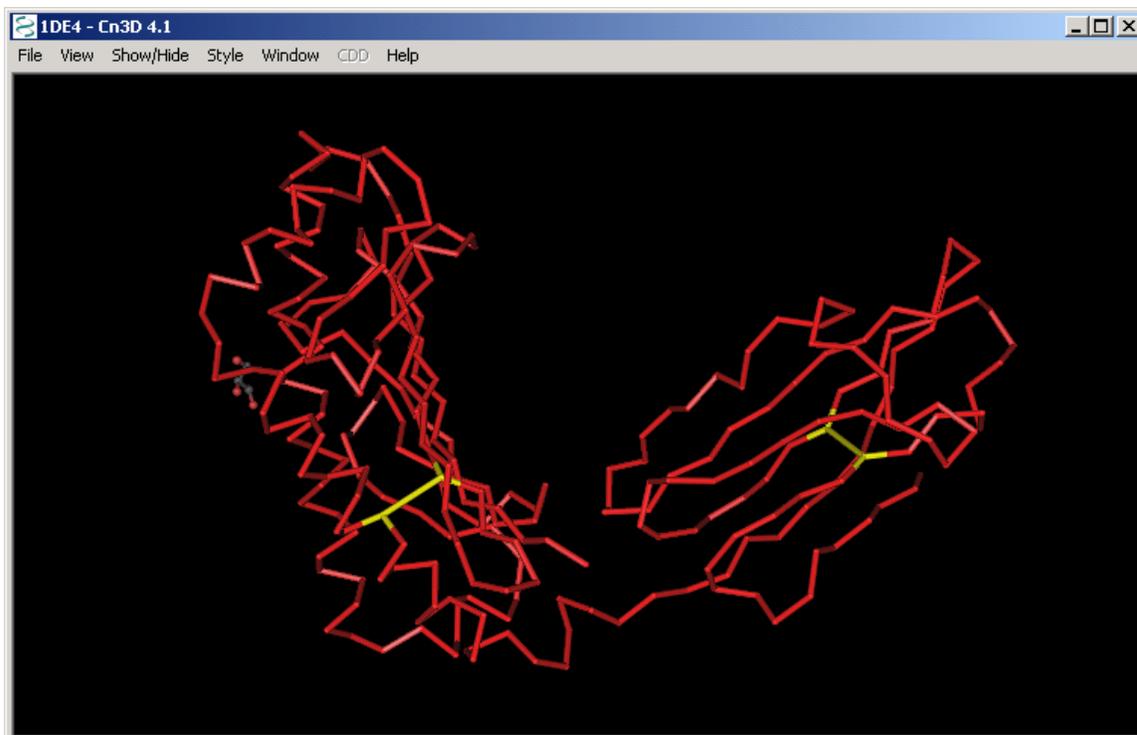


Query: hemochromatosis protein isoform 1 precursor [Homo sapiens]
 [gi: 4504377]
Structure: 1DE4 Chain G, Hemochromatosis Protein Hfe Complexed With Transferrin Receptor
Reference: [MMDB] [PubMed]

[Get 3D Structure data](#) to: (To display structure, download [Cn3D](#))

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

| | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
|------------|-----|---|-----|-----|-----|-----|-----|-----|
| gi_4504377 | 23 | RLLRSHSLHYLFGASEQDLGLSLFEALGYVDDQLFVFDHESRRVEPRTPWSSRISSQHWLQLSQSLKRGWDHMF | 102 | | | | | |
| 1DE4 G | 1 | RLLRSHSLHYLFGASEQDLGLSLFEALGYVDDQLFVFDHESRRVEPRTPWSSRISSQHWLQLSQSLKRGWDHMF | 80 | | | | | |
| | 90 | 100 | 110 | 120 | 130 | 140 | 150 | 160 |
| gi_4504377 | 103 | WTIMENHNHSHKESHTLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPTLDWRAAEPRAWPTKLEWERHKIRARQNRAY | 182 | | | | | |
| 1DE4 G | 81 | WTIMENHNHSHKESHTLQVILGCEMQEDNSTEGYWKYGYDGDHLEFCPTLDWRAAEPRAWPTKLEWERHKIRARQNRAY | 160 | | | | | |
| | 170 | 180 | 190 | 200 | 210 | 220 | 230 | 240 |
| gi_4504377 | 183 | LERDCPAQLQQLLELGRGVLDDQVPLVKVTHHVTSSVTLRCRALNYYPQNTMKWLKDKOPMDAKEFEPKDVLPNGDG | 262 | | | | | |
| 1DE4 G | 161 | LERDCPAQLQQLLELGRGVLDDQVPLVKVTHHVTSSVTLRCRALNYYPQNTMKWLKDKOPMDAKEFEPKDVLPNGDG | 240 | | | | | |
| | 250 | 260 | 270 | | | | | |
| gi_4504377 | 263 | TYQGWITLAVPPGEEQRYTCQVEHPGLDQPLIVIM | 297 | | | | | |
| 1DE4 G | 241 | TYQGWITLAVPPGEEQRYTCQVEHPGLDQPLIVIM | 275 | | | | | |

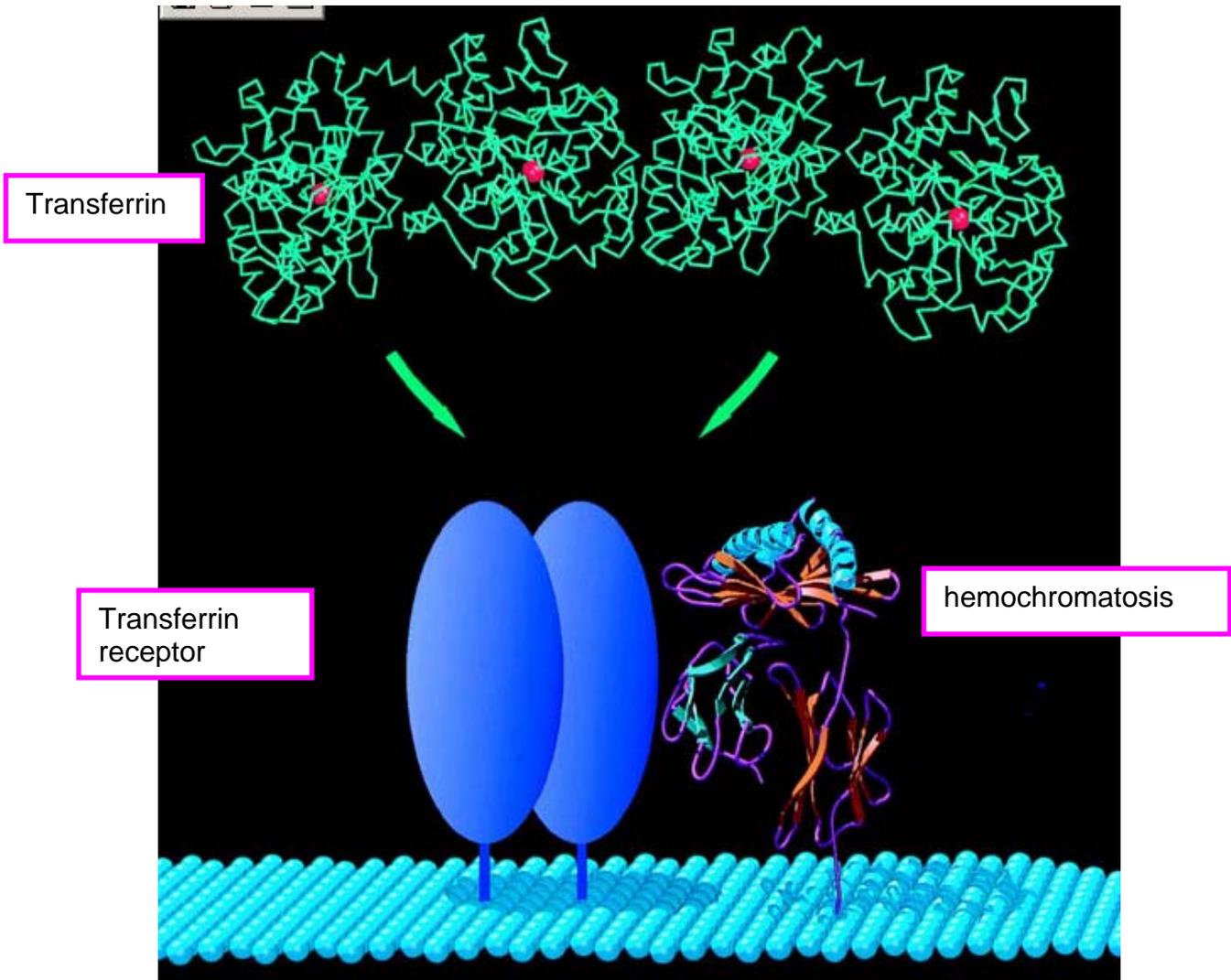


IDE4 - Sequence/Alignment Viewer

View Edit Mouse Mode Unaligned Justification Imports

| | |
|------------|--|
| IDE4 G | TSSVTTLCRALNYYPQNI TMKWLKDKQPMDAKE FEPKDVLPNGDGT YQGWITLAVPPGEEQRYT CQVEHPGLDQPLIWIW~ |
| gi 4504377 | TSSVTTLCRALNYYPQNI TMKWLKDKQPMDAKE FEPKDVLPNGDGT YQGWITLAVPPGEEQRYT CQVEHPGLDQPLIWIW e p |

gi 4504377, loc 282 Block 1, Row 2



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

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 "Geneview in dbSNP" 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 first on the NP_000509 protein link and then on Blink. Click on the 3D structures button. The output contains a list of similar proteins with 3D structures known. Find the entry, for example 1DXTD, representing the structure of deoxyhemoglobin. Click on the blue dot next to 1DXTD to get the sequence alignment of the query protein to the D chain of 1DXT. 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 Primary Citation). 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 unclick 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 and 3 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.