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Haptoglobin

Haptoglobin (abbreviated as **Hp**) is the protein that in humans is encoded by the *HP* gene.[5][6] In blood plasma, haptoglobin binds to *free* hemoglobin,[7] compared to hemopexin that binds to *free* heme,[8] released from erythrocytes with high affinity, and thereby inhibits its deleterious oxidative activity. The haptoglobin-hemoglobin complex will then be removed by the reticuloendothelial system (mostly the spleen).

In clinical settings, the haptoglobin assay is used to screen for and monitor intravascular hemolytic anemia. In intravascular hemolysis, free hemoglobin will be released into circulation and hence haptoglobin will bind the hemoglobin. This causes a decline in haptoglobin levels.

Contents

HP

Available structures

PDB	Ortholog search: PDBe (https://www.ebi.ac.uk/pdbe/searchResults.html?display=both&term=Q61646%20or%20P00738%20or%20J3KRH2) RCSB (https://www.rcsb.org/search?q=rcsb_polymer_entity_container_identifiers.reference_sequence_identifiers.database_name:UniProt%20AND%20rcsb_polymer_entity_container_identifiers.reference_sequence_identifiers.database_accession:Q61646,P00738,J3KRH2)

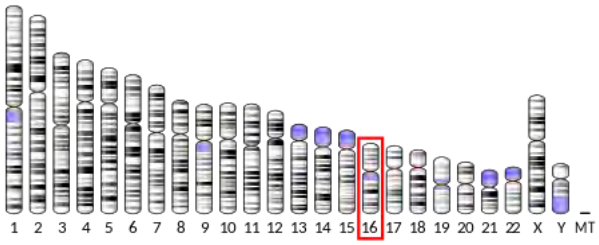
List of PDB id codes

4X0L (https://www.rcsb.org/structure/4X0L), 4WJG (https://www.rcsb.org/structure/4WJG), 5HU6 (https://www.rcsb.org/structure/5HU6)

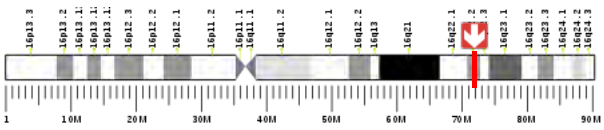
Identifiers

Aliases	HP (https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/5141), BP, HP2ALPHA2, HPA1S, haptoglobin
External IDs	OMIM: 140100 (https://omim.org/entry/140100) MGI: 96211 (http://www.informatics.jax.org/marker/MGI:96211) HomoloGene: 121756 (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=homologene&dopt=HomoloGene&list_uids=121756) GeneCards: HP (https://www.genecards.org/cgi-bin/carddisp.pl?gene=HP)

Gene location (Human)



Chr.	Chromosome 16 (human)[1]



Band	16q22.2	**Start**	72,054,505 bp[1]
		End	72,061,055 bp[1]

Function

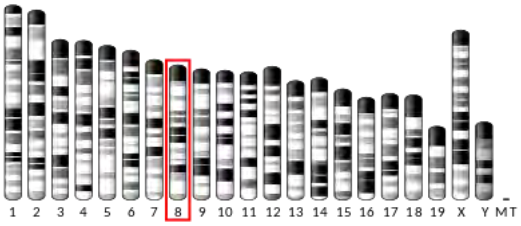
Hemoglobin that has been released into the blood plasma by damaged red blood cells has harmful effects. The *HP* gene encodes a preproprotein that is processed to yield both alpha and beta chains, which subsequently combines as a tetramer to produce haptoglobin. Haptoglobin functions to bind the free plasma hemoglobin, which allows degradative enzymes to gain access to the hemoglobin while at the same time preventing loss of iron through the kidneys and protecting the kidneys from damage by hemoglobin.[9]

The cellular receptor target of Hp is the monocyte/macrophage scavenger receptor, CD163.[7] Following Hb-Hp binding to CD163, cellular internalization of the complex leads to globin and heme metabolism, which is followed by adaptive changes in antioxidant and iron metabolism pathways and macrophage phenotype polarization.[7]

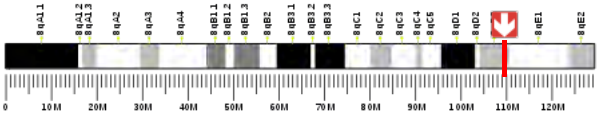
Differentiation with hemopexin

When hemoglobin is released from RBCs within the physiologic range of hemopexin, the potential deleterious effects of hemoglobin are prevented. However, during hyper-hemolytic conditions or with chronic hemolysis, hemoglobin is depleted and readily distributes to tissues where it might be exposed to oxidative conditions. In such conditions, heme can be released from ferric (Fe^{3+}-bound) hemoglobin. The free heme can then accelerate tissue damage by promoting peroxidative reactions

Gene location (Mouse)



Chr. Chromosome 8 (mouse)[2]



Band 8 D3|8 57.11 cM **Start** 109,575,128 bp[2]

End 109,579,172 bp[2]

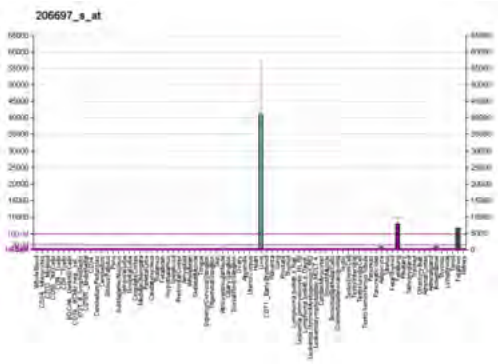
RNA expression pattern

Bgee (https://bgee.org/) **Top expressed in** (https://bgee.org/?page=gene&gene_id=ENSG00000257017)

- liver
- Right lobe of liver
- organ system
- pericardium
- parietal pleura
- visceral pleura
- bone marrow
- lymph node

More reference expression data (https://bgee.org/?page=gene&gene_id=ENSG00000257017)

BioGPS (http://biogps.org/)



More reference expression data (http://biogps.org/gene/3240/)

Gene ontology

Molecular function

- antioxidant activity (http://amigo.geneontology.org/amigo/term/GO:0016209)
- GO:0001948 protein binding (http://amigo.geneontology.org/amigo/term/GO:0005515,)

and activation of inflammatory cascades. Hemopexin (Hx) is another plasma glycoprotein, like hemoglobin, that is able to bind heme with high affinity. Hemopexin sequesters heme in an inert, non-toxic form and transports it to the liver for catabolism and excretion.[7]

Synthesis

Haptoglobin is produced mostly by hepatic cells but also by other tissues such as skin, lung and kidney. In addition, the haptoglobin gene is expressed in murine and human adipose tissue.[10]

Haptoglobin had been shown to be expressed in adipose tissue of cattle as well.[11]

Structure

Haptoglobin, in its simplest form, consists of two alpha and two beta chains, connected by disulfide bridges. The chains originate from a common precursor protein, which is proteolytically cleaved during protein synthesis.

Hp exists in two allelic forms in the human population, so-called *Hp1* and *Hp2*, the latter one having arisen due to the partial duplication of *Hp1* gene. Three genotypes of Hp, therefore, are found in humans: Hp1-1, Hp2-1, and Hp2-2. Hp of different genotypes have been shown to bind hemoglobin with different affinities, with Hp2-2 being the weakest binder.

In other species

Hp has been found in all mammals studied so far, some birds, e.g., cormorant and ostrich but also, in its

- hemoglobin binding (http://amigo.geneontology.org/amigo/term/GO:0030492)
- serine-type endopeptidase activity (http://amigo.geneontology.org/amigo/term/GO:0004252)

Cellular component

- extracellular region (http://amigo.geneontology.org/amigo/term/GO:0005576)
- endocytic vesicle lumen (http://amigo.geneontology.org/amigo/term/GO:0071682)
- extracellular exosome (http://amigo.geneontology.org/amigo/term/GO:0070062)
- blood microparticle (http://amigo.geneontology.org/amigo/term/GO:0072562)
- haptoglobin-hemoglobin complex (http://amigo.geneontology.org/amigo/term/GO:0031838)
- extracellular space (http://amigo.geneontology.org/amigo/term/GO:0005615)
- specific granule lumen (http://amigo.geneontology.org/amigo/term/GO:0035580)
- tertiary granule lumen (http://amigo.geneontology.org/amigo/term/GO:1904724)

Biological process

- cellular oxidant detoxification (http://amigo.geneontology.org/amigo/term/GO:0098869)
- defense response (http://amigo.geneontology.org/amigo/term/GO:0006952)
- positive regulation of cell death (http://amigo.geneontology.org/amigo/term/GO:0010942)
- acute-phase response (http://amigo.geneontology.org/amigo/term/GO:0006953)
- receptor-mediated endocytosis (http://amigo.geneontology.org/amigo/term/GO:0006898)
- defense response to bacterium (http://amigo.geneontology.org/amigo/term/GO:0042742)
- response to hydrogen peroxide (http://amigo.geneontology.org/amigo/term/GO:0042542)
- negative regulation of oxidoreductase activity (http://amigo.geneontology.org/amigo/term/GO:0051354)
- negative regulation of hydrogen peroxide catabolic process (http://amigo.geneontology.org/amigo/term/GO:2000296)

simpler form, in bony fish, e.g., zebrafish. Hp is absent in at least some amphibians (*Xenopus*) and neognathous birds (chicken and goose).

Clinical significance

Mutations in this gene or its regulatory regions cause ahaptoglobinemia or hypohaptoglobinemia. This gene has also been linked to diabetic nephropathy,[12] the incidence of coronary artery disease in type 1 diabetes,[13] Crohn's disease,[14] inflammatory disease behavior, primary sclerosing cholangitis, susceptibility to idiopathic Parkinson's disease,[15] and a reduced incidence of *Plasmodium falciparum* malaria.[16]

Since the reticuloendothelial system will remove the haptoglobin-hemoglobin complex from the body,[8] haptoglobin levels will be decreased in case of intravascular hemolysis or *severe* extravascular hemolysis. In the process of binding to free hemoglobin, haptoglobin sequesters the iron within hemoglobin, preventing iron-utilizing bacteria from benefiting from hemolysis. It is theorized that, because of this, haptoglobin has evolved into an acute-phase protein. HP has a protective influence on the hemolytic kidney.[17][18]

The different haptoglobin phenotypes differ in their antioxidant, scavenging, and immunomodulatory properties. This aspect of haptoglobin may gain importance in immune suppressed conditions (such as liver cirrhosis) and the various phenotypes may result in different susceptibility levels towards bacterial

- immune system process (http://amigo.geneontology.org/amigo/term/GO:0002376)
- neutrophil degranulation (http://amigo.geneontology.org/amigo/term/GO:0043312)
- acute inflammatory response (http://amigo.geneontology.org/amigo/term/GO:0002526)
- proteolysis (http://amigo.geneontology.org/amigo/term/GO:0006508)
- response to organic substance (http://amigo.geneontology.org/amigo/term/GO:0010033)

Sources:Amigo (http://amigo.geneontology.org/) / QuickGO (https://www.ebi.ac.uk/QuickGO/)

Orthologs

Species	Human	Mouse
Entrez	3240 (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=retrieve&dopt=default&list_uids=3240&rn=1)	15439 (https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=retrieve&dopt=default&list_uids=15439&rn=1)
Ensembl	ENSG00000257017 (http://www.ensembl.org/Homo_sapiens/geneview?gene=ENSG00000257017;db=core)	ENSMUSG00000031722 (http://www.ensembl.org/Mus_musculus/geneview?gene=ENSMUSG00000031722;db=core)
UniProt	P00738 (https://www.uniprot.org/uniprot/P00738)	Q61646 (https://www.uniprot.org/uniprot/Q61646)
RefSeq (mRNA)	NM_001126102 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NM_001126102) NM_005143 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NM_005143) NM_001318138 (http	NM_017370 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NM_017370) NM_001329965 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NM_001329965)

infections.[19]

Some studies associate certain haptoglobin phenotypes with the risk of developing schizophrenia.[20]

Test protocol

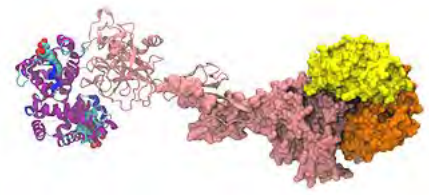
Measuring the level of haptoglobin in a patient's blood is ordered whenever a patient exhibits symptoms of anemia, such as pallor, fatigue, or shortness of breath, along with physical signs of hemolysis, such as jaundice or dark-colored urine. The test is also commonly ordered as a hemolytic anemia battery, which also includes a reticulocyte count and a peripheral blood smear. It can also be ordered along with a direct antiglobulin test when a patient is suspected of having a transfusion reaction or symptoms of autoimmune hemolytic anemia. Also, it may be ordered in conjunction with a bilirubin.

Interpretation

A decrease in haptoglobin can support a diagnosis of intravascular hemolytic anemia, especially when correlated with a decreased red blood cell count, hemoglobin, and hematocrit, and also an increased reticulocyte count.

If the reticulocyte count is increased, but the haptoglobin level is normal, this may indicate that cellular destruction is occurring in the spleen and liver, which may indicate an extravascular hemolytic anemia, drug-induced hemolysis, or a red cell dysplasia. The spleen and liver recognize an error in the red cells (either drug coating the red cell membrane or a dysfunctional red cell membrane), and destroy the cell. This type of destruction does not release hemoglobin into the peripheral blood, so the haptoglobin cannot bind to it. Thus, the haptoglobin will stay normal if the hemolysis is not severe. In severe extra-vascular hemolysis, haptoglobin levels can also be low, when large amount of hemoglobin in the reticuloendothelial system leads to transfer of free hemoglobin into plasma.[21]

	s://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NM_001318138)	
RefSeq (protein)	NP_001119574 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NP_001119574) NP_001305067 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NP_001305067) NP_005134 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NP_005134)	NP_001316894 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NP_001316894) NP_059066 (https://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NP_059066)
Location (UCSC)	Chr 16: 72.05 – 72.06 Mb (https://genome.ucsc.edu/cgi-bin/hgTracks?org=Human&db=hg38&position=chr16:72054505-72061055)	Chr 8: 109.58 – 109.58 Mb (https://genome.ucsc.edu/cgi-bin/hgTracks?org=Mouse&db=mm0&position=chr8:109575128-109579172)
PubMed search	[3]	[4]
Wikidata		
View/Edit Human		View/Edit Mouse



A model of α,β-hemoglobin/haptoglobin hexamer complex. There are 2 α,β-hemoglobin dimers depicted: one space filling model (yellow/orange), and one ribbon model (purple/blue). Each is bound by a haptoglobin molecule (both haptoglobin molecules are shown in pink, with one as a space filling model and one as a ribbon model).

If there are symptoms of anemia but both the reticulocyte count and the haptoglobin level are normal, the anemia is most likely not due to hemolysis, but instead some other error in cellular production, such as aplastic anemia.

Haptoglobin levels that are decreased but do not accompany signs of anemia may indicate liver damage, as the liver is not producing enough haptoglobin to begin with.

As haptoglobin is indeed an acute-phase protein, any inflammatory process (infection, extreme stress, burns, major crush injury, allergy, etc.) may increase the levels of plasma haptoglobin.

See also

- Hemopexin
- Haptoglobin-related protein

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External links

- Haptoglobins (https://meshb.nlm.nih.gov/record/ui?name=Haptoglobins) at the US National Library of Medicine Medical Subject Headings (MeSH)
- Overview of all the structural information available in the PDB for UniProt: *P00738 (https://www.ebi.ac.uk/pdbe/pdbe-kb/proteins/P00738)* (Haptoglobin) at the PDBe-KB.
