H Blood Group System

Number of antigens 1

High prevalence	H

Terminology

ISBT symbol (number)	H (018)
CD number	CD173
Obsolete name	O
History	In 1948, Morgan and Watkins suggested changing the terms "anti-O" and "O substance" to "anti-H" and "H substance," as this would differentiate it as a heterogeneic, basic or primary substance common to the great majority of red cells irrespective of their ABO phenotype.

Expression

Soluble form	Saliva and all body fluids (in secretors) except CSF
Other blood cells	Lymphocytes (in secretors), platelets
Tissues	Broad tissue distribution (see ABO section)

Gene

Chromosome	19q13.33
Name	*H* (*FUT1*)
Organization	4 exons distributed over 8 kbp of gDNA
Product	2-α-fucosyltransferase (α2Fuc-T1; 2-α-L-fucosyltransferase 1; α1,2-fucosyltransferase 1) that adds α-L-fucose to precursor type 2 chains on RBCs and other cells

The homologous gene (*FUT2*; *Se*) encoding 2-α-L-fucosyltransferase 2 (α2Fuc-T2) is 35 kbp closer to the centromere also at 19q13.33. This transferase

The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00020-X

adds α-L-fucose to precursor type 1 chains in secretions (see below). It should be noted that the two enzymes prefer the precursor chains indicated, but some cross-reactivity may occur.

Database accession numbers

GenBank	NM_000148 (mRNA), M35531 (mRNA)
Entrez Gene ID	2523 *(FUT1)*

Molecular basis of H antigen expression on RBCs

Changes in *FUT1* can give rise to H-deficient phenotypes. Inactive alleles of *FUT1* fail to express an enzyme that can synthesize H epitopes on RBCs. People having these (*h*) alleles in the homozygous or compound heterozygous states have the H– (Bombay, O_h) or H+^{W} phenotype (often called Para-Bombay). In Bombay people, mutated *FUT1* and *FUT2* both fail to encode functional 2-α-fucosyltransferases, and these individuals lack ABH antigens on RBCs and in secretions.

There are two types of H+^{W} (Para-Bombay) people: (i) those who lack RBC ABH antigens produced on RBCs, but possess them in secretions (inactive *FUT1*-encoded enzyme and functional *FUT2*); and (ii) those who produce very few ABH antigens on RBCs, and may or may not possess them in secretions (altered but weakly active *FUT1*-encoded enzyme in combination with active or inactive *FUT2*-encoded enzyme). When H substance is expressed in secretions, it can be absorbed by the RBCs, which then can type weakly H+ (H+^{W}). If *A* or *B* are present at the *ABO* locus, the phenotype may be A+^{w} and/or B+^{w} but H– (sometimes referred to as A_h and B_h).

Another extremely rare and principally different reason for the H-deficient phenotype is homozygosity for inactivating mutations at *SLC35C1* (the GDP-fucose transporter gene), see "Disease association" below.

Molecular basis of H+ phenotype in RBCs

The reference allele, *FUT1*01* (Accession number M35531), encodes 2-α-fucosyltransferase that synthesizes H type 2 antigen on RBCs and other cells. Nucleotide differences, and amino acids affected, are given. H expression will be partially masked if a functional *A* or *B* allele is also inherited.

Allele encodes	Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
H+	*FUT1*02*	4	35C>T	Ala12Val	All, but may be more common in Asians

Molecular bases of weak H antigens

Homozygosity or compound heterozygosity leads to the H+^{W} (Para-Bombay) phenotype.
Differences from the *FUT1*01* reference allele (Accession number M35531) are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*FUT1*01W.01*	4	293C>T	Thr98Met	Chinese (Rare)
*FUT1*01W.02*	4	328G>A	Ala110Thr	Chinese (Rare)
*FUT1*01W.03*	4	349C>T	His117Tyr	Reunion (Rare)
*FUT1*01W.04*	4	442G>T	Asp148Tyr	Japanese (Rare)
*FUT1*01W.05*	4	460T>C	Tyr154His	Taiwanese (Rare)
*FUT1*01W.06*	4	460T>C; 1042G>A	Tyr154His; Glu348Lys	Japanese (Rare)
*FUT1*01W.07*	4	491T>A	Leu164His	North American (Rare)
*FUT1*01W.08*	4	522C>A	Phe174Leu	Chinese (Rare)
*FUT1*01W.09*	4	658C>T	Arg220Cys	Taiwanese (Rare)
*FUT1*01W.10*	4	659G>A	Arg220His	Taiwanese (Rare)
*FUT1*01W.11*	4	661C>T	Arg221Cys	Australian (Rare)
*FUT1*01W.12*	4	682A>G	Met228Val	Chinese (Rare)
*FUT1*01W.13*	4	689A>C	Gln230Pro	Portugese (Rare)
*FUT1*01W.14*	4	721T>C	Tyr241His	Japanese (Rare)
*FUT1*01W.15*	4	801G>C	Trp267Cys	Caucasian (Rare)
*FUT1*01W.16*	4	801G>T	Trp267Cys	Caucasian (Rare)
*FUT1*01W.17*	4	832G>A	Asp278Asn	(Rare)
*FUT1*01W.18*	4	904_906 insAAC	His302_Thr303 insAsn	Japanese (Rare)
*FUT1*01W.19*	4	917C>T	Thr306Ile	Brazilian (Rare)
*FUT1*01W.20*	4	990delG	330fs336 Stop	Japanese (Rare)
*FUT1*01W.21*	4	235G>C	Gly79Arg	Chinese (Rare)
*FUT1*02W.01*	4	269G>T	Gly90Val	(Rare)
*FUT1*02W.02*	4	371T>G	Phe124Cys	(Rare)

H expression will be further weakened in the presence of a functional *A* or *B* allele. Also, H expression may be weakly detectable on RBCs where *FUT1*01N* homozygosity occurs, due to the adsorption of soluble H antigen synthesized by *FUT2*.

Molecular bases of silencing of *FUT1*01*

Homozygosity or compound heterozygosity leads to an H– (Bombay, O_h) phenotype.
Differences from the *FUT1*01* reference allele (Accession number M35531) are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*FUT1*01N.01*	4	422G>A	Trp141Stop	Brazilian (Rare)
*FUT1*01N.02*	4	461A>G	Tyr154Cys	Caucasian (Rare)
*FUT1*01N.03*	4	462C>A	Tyr154Stop	Japanese (Rare)
*FUT1*01N.04*	4	513G>C	Trp171Cys	Caucasian (Rare)
*FUT1*01N.05*	4	538C>T	Gln180Stop	Israeli (Rare)
*FUT1*01N.06*	4	547_548delAG	182fs248Stop	Taiwanese, Chinese (Rare)
*FUT1*01N.07*	4	586C>T	Gln196Stop	Chinese (Rare)
*FUT1*01N.08*	4	695G>A	Trp232Stop	Japanese (Rare)
*FUT1*01N.09*	4	725T>G^	Leu242Arg	Indian (Several)
*FUT1*01N.10*	4	776T>A	Val259Glu	Caucasian (Rare)
*FUT1*01N.11*	4	785G>A; 786C>A	Ser262Lys	Caucasian (Rare)
*FUT1*01N.12*	4	826C>T	Gln276Stop	North American (Rare)
*FUT1*01N.13*	4	880_881delTT	294fs333Stop	Taiwanese, Chinese (Rare)
*FUT1*01N.14*	4	944C>T	Ala315Val	Caucasian (Rare)
*FUT1*01N.15*	4	948C>G	Tyr316Stop	North American (Rare)
*FUT1*01N.16*	4	980A>C	Asn327Thr	(Rare)
*FUT1*01N.17*	4	1047G>C	Trp349Cys	Caucasian (Rare)
*FUT1*01N.18*	4	684G>A	Met228Ile	Czech (Rare)
*FUT1*01N.19*	4	694T>C	Trp232Pro	Czech (Rare)

H expression may be weakly detectable on RBCs where *FUT1*01N* homozygosity occurs, due to the adsorption of soluble H antigen synthesized by *FUT2*.
^Travels with a complete deletion of *FUT2* (together, these alterations are the genetic basis of the originally-discovered Bombay phenotype).

Molecular basis of H expression in secretions

Gene name	*FUT2*
Number of exons	2
GenBank	NM_000511 (mRNA), U17894 (gene)
Entrez Gene ID	2524

Differences from the *FUT2*01* reference allele (Accession number U17894) are given.
The reference allele encodes a 2-α-fucosyltransferase that synthesizes H type 1 antigen present in secretions.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*FUT2*02*	2	4G>A	Ala2Thr	Mongolian (Rare)
*FUT2*03.01*	2	40A>G	Ile14Val	Xhosa (Rare)
*FUT2*03.02*	2	40A>G; 113C>T	Ile14Val; Ala38Val	Ghanian (Rare)
*FUT2*03.03*	2	40A>G; 481G>A	Ile14Val; Asp161Asn	Xhosa (Rare)
*FUT2*04*	2	379C>T	Arg127Cys	Xhosa (Rare)
*FUT2*05*	2	400G>A	Val134Ile	Samoan (Rare)
*FUT2*06*	2	481G>A	Asp161Asn	Xhosa (Rare)
*FUT2*07*	2	665G>A	Arg222His	Turkish (Rare)
*FUT2*08*	2	685G>A	Val229Met	(Rare)
*FUT2*09*	2	716G>A	Arg239Gln	Chinese (Rare)
*FUT2*10*	2	748_750insGTG	249_250insVal	Chinese (Rare)

Molecular bases of H+^{W} phenotype in secretions^

Differences from *FUT2*01* reference allele (Accession number U17894) are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*FUT2*01W.01*	2	278C>T	Ala93Val	Israeli (Rare)
*FUT2*01W.02*	2	385A>T	Ile129Phe	Asian, Polynesian, Taiwanese (Common)
*FUT2*01W.03*	2	853G>A	Ala285Thr	Chinese (Rare)

^associated with the Le(a+b+) phenotype.

Molecular bases of H– phenotype in secretions

Differences from the *FUT2*01* reference allele (Accession number U17894) are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*FUT2*01N.01*	2	244G>A; 385A>T	Ala82Thr; Ile129Phe	Mongolian (Rare)
*FUT2*01N.02*	2	428G>A^	Trp143Stop	Europeans, Africans, Iranians (Common)
*FUT2*01N.03*	2	569G>A	Arg190His	Turkish (Rare)
*FUT2*01N.04*	2	571C>T	Arg191Stop	Japanese, Filipino Polynesian, Taiwanese (Rare)
*FUT2*01N.05*	2	628C>T	Arg210Stop	Japanese (Rare)
*FUT2*01N.06*	2	658C>T	Arg220Stop	Chinese, Taiwanese (Rare)
*FUT2*01N.07*	2	664C>T	Arg222Cys	New Guinean (Rare)
*FUT2*01N.08*	2	685_686delGT	230fs234 Stop	Taiwanese (Rare)
*FUT2*01N.09*	2	688_690delGTC	Val230del	Filipino (Rare)
*FUT2*01N.10*	2	400G>A; 760G>A	Val134Ile; Asp254Asn	New Guinean (Rare)
*FUT2*01N.11*	2	778delC	259fs275Stop	South African (Rare)
*FUT2*01N.12*	2	849G>A	Trp283Stop	Filipino, Taiwanese (Rare)
*FUT2*01N.13*	2	868G>A	Gly290Arg	New Guinean (Rare)
*FUT2*01N.14*	2	950C>T	Pro317Leu	Mongolian (Rare)
*FUT2*0N.01*		gene deletion		Bangladeshi (Rare)
*FUT2*0N.02*		coding region deleted^^		Indian (Several)
*FUT2*0N.03*		fusion gene 1 between FUT2 and Sec1		Japanese (Rare)
*FUT*0N.04*		fusion gene 2 between FUT2 and Sec1		Mongolian (Rare)

^The most common allele associated with nonsecretor status, especially in the Western hemisphere. It carries multiple other SNPs not given here.
^^Travels with the *FUT1*01N.09*.

H-depleted RBC phenotypes may be due to changes in GDP-fucose transporter gene[1,2]

Changes in this gene (*SLC35C1*) result in the GDP-fucose transporter being ineffective, and as no fucose can be transported there is no fucosylation despite normal 2-α- or 3/4-α-fucosyltransferase histo-blood genes (*FUT1*, *FUT2* or *FUT3*; see also Chapter on Lewis). Thus, the RBCs have the Bombay, Le(a–b–) phenotype, and WBCs lack CD15/sialyl-Le^X. These changes give rise to the very rare leukocyte adhesion deficiency (LADII or CDGII). Differences from the *SLC35C1* (*FUCT1*) reference allele (Accession number NG_009875) are given.

Nucleotide change	Amino acid change	Ethnicity (prevalence)
439C>T	Arg147Lys	Turkish
923C>G	Thr308Arg	Arab
588delG	Ser195fs Stop	Brazilian

Amino acid sequence of α-2-L-fucosyltransferase 1 (from *FUT1*)

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MWLRSHRQLC  LAFLLVCVLS  VIFFLHIHQD  SFPHGLGLSI  LCPDRRLVTP   50
PVAIFCLPGT  AMGPNASSSC  PQHPASLSGT  WTVYPNGRFG  NQMGQYATLL  100
ALAQLNGRRA  FILPAMHAAL  APVFRITLPV  LAPEVDSRTP  WRELQLHDWM  150
SEEYADLRDP  FLKLSGFPCS  WTFFHHLREQ  IRREFTLHDH  LREEAQSVLG  200
QLRLGRTGDR  PRTFVGVHVR  RGDYLQVMPQ  RWKGVVGDSA  YLRQAMDWFR  250
ARHEAPVFVV  TSNGMEWCKE  NIDTSQGDVT  FAGDGQEATP  WKDFALLTQC  300
NHTIMTIGTF  GFWAAYLAGG  DTVYLANFTL  PDSEFLKIFK  PEAAFLPEWV  350
GINADLSPLW  TLAKP                                          365
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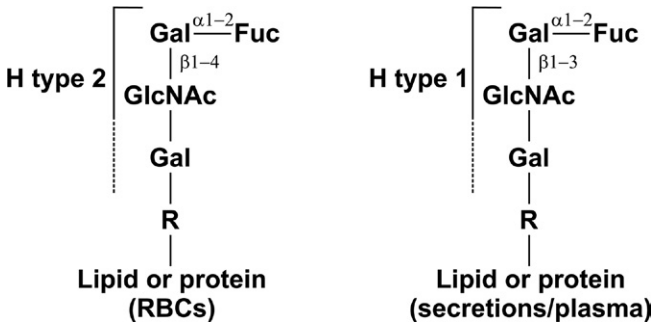
Carrier molecule[3,4]

H antigen is not the primary gene product. The *FUT1* product, the α-2-L-fucosyltransferase 1, attaches an α-L-fucose to the terminal galactose on type 2 carbohydrate precursor chains attached to proteins or lipids on cells. The immunodominant fucose constitutes the defining sugar of the H antigen, which is in turn the precursor of A and B antigens (see **ABO** blood group system).
In analogy, the *FUT2* product attaches α-L-fucose to the terminal galactose on type 1 carbohydrate precursor chains in secretions.



Function

Fucosylated glycans that are the products of *FUT1* and *FUT2* may serve as ligands in cell adhesion or as receptors for certain microorganisms.

Disease association

Weakened expression in acute leukemia and carcinomatous tissue cells.
Children with leukocyte adhesion deficiency (LADII; CDGII) have mental retardation and severe recurrent infections with a high white blood cell count, which is caused by an inability of leucocytes to adhere. Their RBCs are H–, and also lack A, B, Le^a, and Le^b antigens.

Phenotypes

Most RBCs have some H antigen: $O > A_2 > B > A_2B > A_1 > A_1B > H+^W$.
Null: O_h (Bombay)
Unusual: $H+^W$ (Para-Bombay)

Characteristics of phenotypes

Type	H antigen on RBCs	H antigen in secretion	Predicted genotype	Antibody
Common				
Secretor	Yes	Yes	*HH* or *Hh*; *SeSe* or *Sese*	Anti-HI
Non-secretor	Yes	No	*HH* or *Hh*; *sese*	Anti-HI
H-deficient				
Bombay	No	No	*hh*; *sese*	Anti-H
$H+^W$	Weak	No	(*H*); *sese*	Anti-H
$H+^W$	Weak	Yes	(*H*); *SeSe* or *Sese*	Anti-HI
H_m (dominant)^	Weak	Yes	*HH* or *Hh*; *SeSe* or *Sese*	None
LADII (CDGII)	No	No	Any genotype possible	Anti-H

^Molecular basis unknown.

For more alleles and details, see http://www.bioc.aecom.yu.edu/bgmut/index.htm.

References

[1] Hidalgo, A., et al., 2003. Insights into leukocyte adhesion deficiency type 2 from a novel mutation in the GDP-fucose transporter gene. Blood 101, 1705–1712.

[2] Lühn, K., et al., 2001. The gene defective in leukocyte adhesion deficiency II encodes a putative GDP-fucose transporter. Nat Genet 28, 69–72.
[3] Lowe, J.B., 1995. Biochemistry and biosynthesis of ABH and Lewis antigens: characterization of blood group-specific glycosyltransferases. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, pp. 75–115.
[4] Oriol, R., 1995. ABO, Hh, Lewis, and secretion: serology, genetics, and tissue distribution In: Cartron, J.-P. Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens, 1995. Plenum Press, New York, NY, pp. 37–73.

H Antigen

Terminology

ISBT symbol (number)	H1 (018001 or 18.1)
History	See H Blood Group System page.

Occurrence

All populations	99.9%

H-deficient people [Bombay (O_h) and H+^{W} (Para-Bombay)]: 1 in 8,000 in Taiwan; 2 in 300,000 in Japan; 1 in 10,000 in India; 1 per million in Europe.

Expression

Adult RBCs	In decreasing order: O>A_2>B>A_2B>A_1>A_1B>H+^{W}
Cord RBCs	Weak
Altered	Weak on H+^{W} (Para-Bombay)

Molecular basis associated with H antigen[1]

See System pages.

Effect of enzymes and chemicals on H antigen on intact RBCs

Ficin/Papain	Resistant (markedly enhanced)
Trypsin	Resistant (markedly enhanced)
α-Chymotrypsin	Resistant (markedly enhanced)
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-H

Immunoglobulin class	IgM more common than IgG
Optimal technique	RT or 4°C
Neutralization	Saliva, all body fluids except CSF (secretors)
Complement binding	Some

Clinical significance of alloanti-H in Bombay (O_h) and H+^{W} (Para-Bombay) people

Transfusion reaction	No to severe; immediate/delayed/hemolytic; anti-H made by people with the H+^{W} phenotype is often of lower titer and less significant
HDFN	Possible in O_h mothers, but no reports

Autoanti-H

Yes, usually cold reactive.

Comments

With the exception of Bombay (O_h) and Para-Bombay people (whose serum contains anti-A, -B and -H), anti-HI is more common than anti-H. Anti-HI is commonly found in the serum of pregnant group A_1 women, and can in fact be found in most people's plasma at +4°C. If reactive at higher temperatures, type-specific blood will be cross-match compatible.
For people with Bombay (O_h) and possibly also H+^{W} (Para-Bombay) phenotype, siblings of the patient should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

Reference

[1] Lowe, J.B., 1995. Biochemistry and biosynthesis of ABH and Lewis antigens: characterization of blood group-specific glycosyltransferases. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 75–115.