Review

The H blood group system

E.A. Scharberg, C. Olsen, and P. Bugert

The H blood group system, ISBT symbol H (018), consists of a single antigen (H) defined by a terminal fucose residue found on red blood cells and in secretions formed by the action of α-1,2-fucosyltransferases 1 (α2FucT1) and 2 (α2FucT2), respectively. Mutant alleles of the corresponding *FUT1* and *FUT2* genes result in either a H– phenotype (Bombay phenotype, O_h) or a weak H phenotype (para-Bombay, $H+^w$). In addition, the *FUT2* gene is the molecular basis of the secretor (Se) status, and homozygosity or compound heterozygosity for null alleles is associated with the nonsecretor (se) status. H– individuals have natural anti-H (mostly IgM), which can cause severe hemolytic transfusion reactions with intravascular hemolysis. ***Immunohematology* 2016;32:112–118.**

Key Words: H antigen, Bombay phenotype, O_h, *FUT1, FUT2*

The H blood group system was discovered by Bhende et al.[1] in the early 1950s, when three individuals with a new unusual blood type were encountered in the city of Bombay (Mumbai) in India. The red blood cells (RBCs) of all three individuals typed as blood group O, but their serum samples were found to contain anti-A, anti-A1, anti-B, and anti-H and to agglutinate RBCs of all "ordinary" ABO groups.[1] Their samples were serologically compatible only with the RBCs of one another and contained the first examples of potent human anti-H in individuals with RBCs that, based on tests with anti-A and anti-B, appeared to be homozygous for a "new" allelomorph at the A1 A2 B O locus.[1] The phenotype was called Bombay phenotype. Further test results showed that the RBCs of these individuals did not react with human or animal anti-H sera. After the cloning and characterization of the *FUT1* gene[2] in 1990 and proving that the gene was the molecular basis of the Bombay phenotype[3] in 1994, the H blood group system was established.

This unusual blood group system has only one antigen (H). Complete lack of H is commonly known as the Bombay or O_h phenotype, and weak expression of H is referred to as the para-Bombay phenotype. The lack of H results in production of the corresponding naturally occurring antibodies, anti-A, anti-B, and anti-H.[4,5]

Biochemistry

The H antigen is a terminal fucose residue in an α-1,2-linkage on precursor carbohydrate chains of two different types (Fig. 1). The H antigen on the type 1 precursor is predominantly produced by the α-1,2-fucosyltransferase 2 (α2FucT2) enzyme in secretory cells of the digestive and respiratory tracts. The α-1,2-fucosyltransferase 1 (α2FucT1) enzyme is a single-pass type II transmembrane glycoprotein found in the Golgi apparatus that forms the H antigen on type 2 precursor chains in erythroid tissues and vascular endothelial cells.[6,7] The carbohydrate chain including the H antigen is then the substrate of the glycosyltransferases encoded by the *ABO* gene to produce A and/or B antigens. Subsequently, in blood group O individuals, the H antigen is not converted to A or B and is strongly detectable on RBCs.

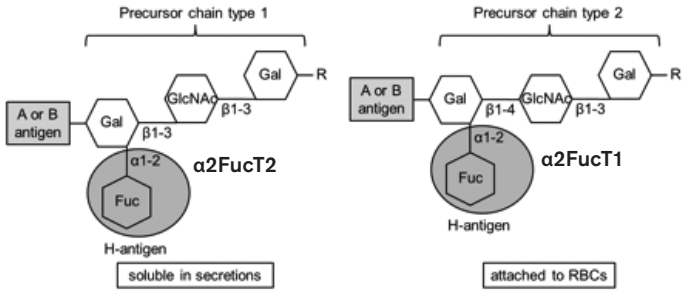

Fig. 1 Schematic illustration of the carbohydrate precursor chains used as substrates by the α2FucT1 and α2FucT2 enzymes encoded by the *FUT1* and *FUT2* genes, respectively. RBCs = red blood cells.

H is found in highest amounts in group O individuals and in least amounts in group A, B, and AB individuals. This is because when the A and/or B enzymes are present, H antigen is converted to A and/or B antigen, resulting in less H antigen present on the cell membrane. H therefore varies in quantity according to the blood group as follows: $O > A_2 > B > A_2B > A_1 > A_1B$.

Antibodies in the H Blood Group System

Anti-H is the only antibody specificity found in the H blood group system. This antibody is naturally occurring in individuals who lack H, as is the case with ABO blood group antibodies. The serum of O_h individuals always contains anti-H, -A, and -B. Occasionally, A_1, A_1B, and (less commonly) B individuals expressing only a low quantity of H can produce anti-H, but the antibody is mostly weakly reactive and usually

considered clinically insignificant, unlike the anti-H in H– individuals, which can cause severe intravascular hemolysis.

Anti-H is most often type IgM, but it can have an IgG component. Like the isoagglutinins, it is best reactive by the saline room temperature method, but can also react in the indirect antiglobulin test (IAT), especially when an IgG component is present. Anti-H can activate complement, and is capable of causing intravascular hemolysis of RBCs. When anti-H is identified in pregnant women, tests using dithiothreitol can be performed to determine the presence or absence of IgG antibodies, and, if present, the titer of the IgG component.

Anti-H produced by Bombay phenotype individuals recognizes H on both type 1 (secretions) and type 2 (RBCs) chains, whereas the anti-H produced by Bombay secretors (hh, Se) reacts preferentially with type 2H. Anti-H lectin (*Ulex europaeus*) can be used to type individuals for the presence of H antigen. It is notable that the lectin reacts best with type 2H individuals, but has some specificity for type 1H. There are other lectins (*Lotus tetragonolobus, Anguilla anguilla, Cysticus sessifolius,* and *Laburnum alpinum*) that recognize H antigen and also monoclonal antibodies with 1H and H specificity.

Autoanti-H and autoanti-IH are primarily autoantibodies that are encountered in a blood transfusion setting often in group A_1 and B patients. These antibodies have been reported in individuals with cold agglutinin syndrome and should be considered in the presence of cold agglutinin testing by including RBCs of different ABO groups and with varying amounts of H and I antigens. The antibody reacts more avidly with samples with enhanced I and H antigens such as group A_2 and O RBCs, and should be most compatible with group A_1 and cord RBCs (having the least quantity of H and I antigen).

Molecular Basis

The *FUT1* and *FUT2* genes are closely linked and located on chromosome 19q13.3.[8] In genomic sequence annotation release 107 from March 2015, the two genes are in opposite orientation with a distance of approximately 42,000 base pairs (bp) (Fig. 2). The *SEC1P* pseudogene upstream of *FUT2* is highly homologous to the *FUT* genes but inactive because of deletions and mutations in the coding region. The molecular cloning and characterization of the *FUT1* gene was first reported in 1990.[2] The genomic structure of the *FUT1* gene includes four exons spanning a region of approximately 7800 bp. The entire coding sequence (CDS) is located within exon 4 and encodes a 365–amino acid polypeptide.[2] The encoded α2FucT1 enzyme adds α-L-fucose to the type 2 precursor chain on RBCs and other cells. The 5′-untranslated region with exons 1–3 contains two distinct promoters with transcription start sites upstream of exon 1 and exon 2.[9] Alternative splicing of the *FUT1* transcripts was reported for different cell types. Recently, it was shown that the transcription factor c-jun binds to an AP-1 site in the promoter region upstream of exon 1 and thereby activates transcription of the *FUT1* gene.[10] The *FUT2* gene has only two exons, and the entire CDS is in exon 2. The encoded α2FucT2 enzyme adds α-L-fucose to the type 1 precursor chain in secretions.[3] Two transcript variants with an upstream and a downstream translation initiation site encode a 343– and a 332–amino acid protein, respectively. The smaller protein is considered to be the active enzyme. This transcriptional regulation by c-jun was not found for the *FUT2* gene.[10]

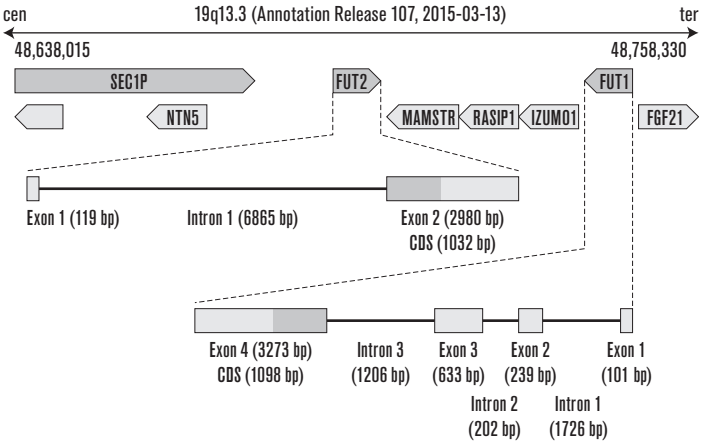

Fig. 2 Gene map of the chromosome 19q13.3 region from centromer (cen; left) to telomer (ter; right) including the *SEC1P, CA11, NTN5, FUT2, MAMSTR, RASIP1, IZUM01, FUT1* and *FGF21* genes according to the National Center for Biotechnology Information (NCBI) genome database annotation release 107 (March 2015). The genomic organization of *FUT1* and *FUT2* indicates that the coding sequence (CDS; dark gray box) of each gene is located within one exon (exon 4 of *FUT1* and exon 2 of *FUT2*).

At least one functioning copy of *FUT1* needs to be present (H/H or H/h) for H to be expressed on RBCs. If both copies of *FUT1* are inactive (h/h), the Bombay phenotype (O_h) results, and there is no expression of A, B, or H antigens on the RBCs. The inactive null alleles of *FUT1* (*FUT1*01N*) are characterized by nonsense mutations causing a stop codon and a truncated protein or by missense mutations causing a single amino acid exchange in the catalytic domain of the enzyme (Table 1).[11,12] Homozygosity or compound heterozygosity for null alleles leads to the h/h phenotype, which is characterized by absence of a functional fucosyltransferase adding fucose to the precursor chain type 1 on RBCs. Many missense

Table 1. Null alleles of the *FUT1* gene leading to a lack of H-antigens on red blood cells

Allele name (ISBT)	Nucleotide change	Amino acid change	Type of mutation	Reference
*FUT1*01N.01*	422G>A	Trp141Ter	Nonsense	27
*FUT1*01N.02*	461A>G	Tyr154Cys	Missense	19, 28
*FUT1*01N.03*	462C>A	Tyr154Ter	Nonsense	29
*FUT1*01N.04*	513G>C	Trp171Cys	Missense	28
*FUT1*01N.05*	538C>T	Gln180Ter	Nonsense	27
*FUT1*01N.06*	547_548delAG	183fs	Frameshift	20
*FUT1*01N.07*	586C>T	Gln196Ter	Nonsense	30
*FUT1*01N.08*	695G>A	Trp232Ter	Nonsense	31
*FUT1*01N.09*	725T>G	Leu242Arg	Missense	19, 32
*FUT1*01N.10*	776T>A	Val259Glu	Missense	28
*FUT1*01N.11*	785G>A; 786C>A	Ser262Lys	Missense	33
*FUT1*01N.12*	826C>T	Gln276Ter	Nonsense	10
*FUT1*01N.13*	880_882delTT	294fs	Frameshift	20
*FUT1*01N.14*	944C>T	Ala315Val	Missense	28
*FUT1*01N.15*	948C>G	Tyr316Ter	Nonsense	10
*FUT1*01N.16*	980A>C	Asn327Thr	Missense	34
*FUT1*01N.17*	1047G>C	Trp349Cys	Missense	28
*FUT1*01N.18*	684G>A	Met228Ile	Missense	12
*FUT1*01N.19*	694T>C	Trp232Pro	Missense	12
*FUT1*01N.20*	764_768delC	256fs	Frameshift	35
*FUT1*02N.01*	423G>A 392T>C 668-670delACT	Trp141Ter Leu131Pro Tyr224del	Nonsense Nonsense In-frame del	35 36 36

ISBT = International Society of Blood Transfusion; del = deletion.

Table 2. Missense mutations of the *FUT1* gene leading to a weak expression of H antigens on red blood cells

Allele name (ISBT)	Nucleotide change	Amino acid change	Reference
*FUT1*01W.01*	293C>T	Thr98Met	37
*FUT1*01W.02*	328G>A	Ala110Thr	30
*FUT1*01W.03*	349C>T	His117Tyr	19
*FUT1*01W.04*	442G>T	Asp148Tyr	31
*FUT1*01W.05.01*	460T>C	Tyr154His	20, 31
*FUT1*01W.05.02*	460T>C; 1042G>A	Tyr154His; Glu348Lys	31
*FUT1*01W.07*	491T>A	Leu164His	10
*FUT1*01W.08*	522C>A	Phe174Leu	38, 39
*FUT1*01W.09*	658C>T	Arg220Cys	20, 39, 40
*FUT1*01W.10*	659G>A	Arg220His	12, 39
*FUT1*01W.11*	661C>T	Arg221Cys	41
*FUT1*01W.12*	682A>G	Met228Val	42, 43
*FUT1*01W.13*	689A>C	Gln230Pro	27
*FUT1*01W.14*	721T>C	Tyr241His	31
*FUT1*01W.15*	801G>C	Trp267Cys	44
*FUT1*01W.16*	801G>T	Trp267Cys	44
*FUT1*01W.17*	832G>A	Asp278Asn	44
*FUT1*01W.19*	917C>T	Thr306Ile	27
*FUT1*01W.21*	235G>C	Gly79Arg	40
*FUT1*01W.22*	991C>A	Pro331Thr	45
*FUT1*01W.23*	424C>T	Arg142Trp	46
*FUT1*01W.24*	649G>T	Val217Phe	35
*FUT1*01W.25*	235G>C	Gly79Arg	40
*FUT1*01W.26*	545G>A	Arg182His	11, 12
*FUT1*01W.27*	958G>A	Gly320Arg	11, 12
*FUT1*01W.28*	896A>C	Gln299Pro	47
*FUT1*01W.29*	655G>C	Val219Leu	48
*FUT1*02W.01*	269G>T	Gly90Val	12
*FUT1*02W.02*	371T>G	Phe124Cys	12
*FUT1*02W.04*	980A>C	Asn327Thr	12, 39
*FUT1*02W.05*	748C>T 366-398del33	Arg250Trp Val123-Pro133del	12 49

ISBT = International Society of Blood Transfusion; del = deletion.

mutations of *FUT1* (*FUT1*01W*) have been described (Table 2), leading to a weak expression of H on RBCs typical for the para-Bombay phenotype (H+^{W}).[11,12]

The *FUT2* gene encodes α2FucT2, which synthesizes the H antigen found in body fluids, and is associated with a secretor (Se) status. Homozygosity or compound heterozygosity for null alleles is associated with the nonsecretor (se) status. In Europeans, the 428G>A nonsense mutation (Trp143ter) is the most common cause of the nonsecretor status. All other null alleles and *FUT2* gene deletions are rare variants (Table 3).[11,12] Because of the sequence homology with *SEC1P,* unbalanced recombination leading to *SEC1P-FUT2* hybrid genes or *FUT2* gene deletions have been reported as the molecular basis of the nonsecretor status.[13,14] Additionally, nonsecretors express only the Le^{a} antigen of the Lewis blood group system because the α1,3/4-fucosyltranferase encoded by the *FUT3* gene uses the type 1 precursor. In secretors, the type 1 precursor carries the H antigen, and the carbohydrate structure can be converted to A or B blood group antigens as well as to the Le^{b} antigen. Interestingly, *FUT2* mutations leading to an inefficient α2FucT2 enzyme such as 385A>T (Ile129Phe) are associated with the Le^{ab} phenotype because less H type 1 results in less Le^{b}, and the *FUT3* enzyme more efficiently converts type 1 precursor to Le^{a}.[15]

In summary, for the genotype–phenotype correlation in the H blood group system, it is important to consider the genotype of both genes, *FUT1* and *FUT2*. For the classic

Table 3. Null alleles of the *FUT2* gene conferring the nonsecretor status

Allele name (ISBT)	Nucleotide change	Amino acid change	Type of mutation	Reference
*FUT2*01N.01*	244G>A; 385A>T	Ala82Thr; Ile129Phe	Missense Missense	50
*FUT2*01N.02*	428G>A; 739A>G	Trp143Ter; Gly247Ser	Nonsense Missense	19, 45, 51
*FUT2*01N.03*	569G>A	Arg190His	Missense	50
*FUT2*01N.04*	571C>T	Arg191Ter	Nonsense	52
*FUT2*01N.05*	628C>T	Arg210Ter	Nonsense	14
*FUT2*01N.06*	658C>T	Arg220Ter	Nonsense	53
*FUT2*01N.07*	664C>T	Arg222Cys	Missense	52
*FUT2*01N.08*	685_686delGT	230fs234Ter	Frameshift	
*FUT2*01N.09*	688_690delGTC	del230Val	In-frame del	54, 55
*FUT2*01N.10*	400G>A; 760G>A	Val134Ile; Asp254Asn	Missense Missense	52
*FUT2*01N.11*	778delC	259fs275Ter	Frameshift	56
*FUT2*01N.12*	849G>A	Trp283Ter	Nonsense	57
*FUT2*01N.13*	868G>A	Gly290Arg	Missense	52
*FUT2*01N.14*	950C>T	Pro317Leu	Missense	50
*FUT2*01N.15*	302C>T	Pro101Leu	Missense	58
*FUT2*01N.16*	960A>G	Gly247Ser	Missense	45, 51, 52
*FUT2*01N.17*	412G>A	Gly138Ser	Missense	45
*FUT2*01N.18*	818C>A	Thr273Asn	Missense	59
*FUT2*0N.01*	Gene deletion		Deletion	19, 32, 60
*FUT2*0N.02*	Coding region deleted		Deletion	61
*FUT2*0N.03*	Fusion gene 1 between *FUT2* and *SEC1P*		Recombination	14, 50, 62
*FUT"*0N.04*	Fusion gene 2 between *FUT2* and *SEC1P*		Recombination	50

ISBT = International Society of Blood Transfusion; del = deletion.

Bombay phenotype (O_h), both genes are inactive (genotype: *h/h* and *se/se*) and no H antigens are expressed on RBCs or in secretions. For the para-Bombay phenotype ($H+^W$), two types can be distinguished:

(1) lack of H on RBCs caused by inactive *FUT1* null alleles (*FUT1*01N*) and presence of H in secretions caused by an active *FUT2* gene (Se);
(2) weak expression of H on RBCs caused by *FUT1* mutant alleles (*FUT1*01M*) encoding weakly active fucosyltransferases in combination with active or inactive *FUT2* (Se or se).

Particularly for the type 1 para-Bombay phenotype, it is important to note that the H antigens produced by *FUT2* in secretions can be absorbed by RBCs. The $H+^W$ cells can be converted to $A+^W$ or $B+^W$ when the corresponding glycosyltransferases are encoded by the ABO locus.

Table 4. Distribution of O_h phenotype cases reported from different states of India

State	Number of O_h phenotype cases
Andhra Pradesh	8
Bihar	2
Goa	6
Gujarat	5
Karnataka	14
Kerala	4
Madhya Pradesh	4
Maharashtra	112
North India (unclassified)	2
Orissa	1
Pondichery	1
Rajasthan	2
South India (unclassified)	1
Tamil Nadu	2
Uttar Pradesh	5
Not Known	10
Total	**179**

Compiled from Lowe.[6]

Populations

The Bombay phenotype is almost unique to Indian ethnic groups, with a prevalence of about 0.7 percent, and is rare in most populations. The greater numbers of cases are situated in the southern states of India (Table 4).[16] Further studies published in 2007 of the Bhuyan tribal population of Orissa, India, revealed the average prevalence of the Bombay phenotype to be 1 in 278.[17] The prevalence therefore varies depending on the number of global migrants originating from these regions. A study on people living on Reunion Island (east of Madagascar) revealed a second geographic "hot spot" of the O_h phenotype with a high prevalence (1:1000).[18,19] Interestingly, although the largest series of H– phenotypes in Bombay and Natal were of Indian ethnicity, 85 percent of the Reunion O_h phenotype were of European descent (mostly of French origin). The O_h and para-Bombay phenotype has also been found in other ethnic groups such as Taiwanese (1:8000), Hong Kong Chinese (1:15,620), and those of European origin (1:1,000,000).[20,21]

In summary, *FUT1* mutant alleles are rare, and their geographic distribution varies greatly. The frequency of *FUT2* null alleles may be 20 percent or higher. A linkage disequilibrium of mutations in *FUT1* and *FUT2* was observed, and is attributable to the close proximity of both genes on chromosome 19q13.3.[19] Individuals of particular ethnic groups have a unique set of mutations: in India, *FUT1* 725T>G with *FUT2* deletion; on Reunion Island (Caucasian), *FUT1* 349C>T with *FUT2* 428G>A.

Clinical Significance

Anti-H in O_h individuals can cause severe hemolytic transfusion reactions with intravascular hemolysis. Anti-H and anti-IH, which are sometimes found in the serum of A1 people, although generally not considered clinically significant, have been reported to cause hemolytic transfusion reactions when the antibodies are demonstrable and reactive by the IAT.[22,23] Such patients should receive cross-match compatible A1 (type-specific) RBC concentrates.

Theoretically, anti-H during pregnancy could cause hemolytic disease of the fetus and newborn (HDFN) in a non-O_h fetus. In practice, however, cases of HDFN have not been described. In an evaluation performed in South Africa of 21 O_h pregnancies/births, only one baby required transfusion, and none were seen to have HDFN.

The function of the H antigen, besides being a precursor for the synthesis of ABO blood group antigens, is not well known; although, it may be involved in cell adhesion. Individuals lacking H do not seem to suffer any ill effects.

The leukocyte adhesion deficiency II (LADII) is a rare inherited primary immunodeficiency disorder resulting from a defect in fucose metabolism. Patients with this disorder are unable to fucosylate glycoproteins, including the H blood group polysaccharide and, therefore, present serologically as O_h blood group. This disorder is characterized by recurrent infections in the patients, persistent leucocytosis, and severe mental and growth retardation.[24] Treatment with oral L-fucose reverses most of the symptoms in these patients, but has no effect on true O_h individuals.

Recent reports indicate that *FUT1* significantly contributes to angiogenesis in the context of rheumatoid arthritis and ovarian cancer.[9,25,26] It is speculated that the higher degree of fucosylation of molecules important for cell adhesion, such as the Lewis antigens, promotes inflammatory and angiogenic mechanisms.

Summary

The H blood group system currently consists of the antigen H. Complete lack of H results in the Bombay (O_h) phenotype and weak expression of H is known as the para-Bombay phenotype. There are a number of genetic mutations that have been found to be responsible for the O_h (*FUT1*01N* alleles) and the para-Bombay (*FUT1*01W* alleles) types. The *FUT1* locus and *FUT2* locus are closely linked, which can result in individuals who may have weak expression or no H expressed on their RBCs, although H may be found in secretions. The H antigen is the precursor for the ABO blood group antigens, and therefore plays a significant role in the serologic blood type of an individual. As with ABO, the antibodies produced by individuals who lack H can cause severe hemolytic reactions, although there have not been many reported cases of obstetric significance.

References

1. Bhende YM, Deshpande CK, Bhatia HM, et al. A new blood group character related to the ABO system. Lancet 1952;1: 903–4.
2. Larsen RD, Ernst LK, Nair RP, et al. Molecular cloning, sequence, and expression of a human GDP-L-fucose: beta-D-galactoside 2-alpha-L-fucosyltransferase cDNA that can form the H blood group antigen. Proc Natl Acad Sci U S A 1990;87: 6674–8.
3. Kelly RJ, Ernst LK, Larsen RD, Bryant JG, Robinson JS, Lowe JB. Molecular basis for H blood group deficiency in Bombay (Oh) and para-Bombay individuals. Proc Nat Acad Sci U S A 1994;91:5843–7.
4. Reid ME, Lomas-Francis C, Olsson ML. The blood group antigen factsbook. 3rd ed. New York: Elsevier Academic Press, 2012.
5. Daniels G. Human blood groups. 3rd ed. Hoboken, NJ: Wiley-Blackwell, 2013.
6. Lowe JB. 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. New York: Plenum Press, 1995:5–115.
7. Oriol R. ABO, Hh, Lewis and secretion: serology, genetics and tissue distribution. In: Cartron J-P, Rouger P, eds. Molecular basis of human blood group antigens. New York: Plenum Press, 1995:37–73.
8. Rouquier S, Lowe JB, Kelly RJ, et al. Molecular cloning of a human genomic region containing the H blood group alpha (1,2) fucosyltransferase gene and two H locus–related DNA restriction fragments: isolation of a candidate for the human Secretor blood group locus. J Biol Chem 1995;270:4632–9.
9. Koda Y, Soejima M, Kimura H. Structure and expression of the gene encoding secretor-type galactoside 2-alpha-L-fucosyltransferase (FUT2). Eur J Biochem 1997;246:750–5.

10. Gao N, Liu J, Liu D, et al. c-Jun transcriptionally regulates alpha 1, 2-fucosyltransferase 1 (FUT1) in ovarian cancer. Biochimie 2014;107:286–92.
11. dbRBC. H blood group system. http://www.ncbi.nlm.nih.gov/projects/gv/rbc/xslcgi.fcgi?cmd=bgmut/systems_info&system=hh.
12. ISBT. Red cell immunogenetics and blood group terminology. http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/.
13. Soejima M, Fujihara J, Takeshita H, Koda Y. Sec1-FUT2-Sec1 hybrid allele generated by interlocus gene conversion. Transfusion 2008;48:488–92.
14. Koda Y, Soejima M, Liu Y, Kimura H. Molecular basis for secretor type alpha(1,2)-fucosyltransferase gene deficiency in a Japanese population: a fusion gene generated by unequal crossover responsible for the enzyme deficiency. Am J Hum Genet 1996;59:343–50.
15. Henry S, Mollicone R, Fernandez P, Samuelsson B, Oriol R, Larson G. Molecular basis for erythrocyte Le(a+ b+) and salivary ABH partial-secretor phenotypes: expression of a FUT2 secretor allele with an A-->T mutation at nucleotide 385 correlates with reduced alpha(1,2) fucosyltransferase activity. Glycoconj J 1996;13:985–93.
16. Balgir RS. Detection of a rare blood group "Bombay Oh Phenotype" among the Kutia Kondh primitive tribe of Orissa, India. Indian J Hum Genet 2005;5:193–8.
17. Balgir RS. Identification of rare blood group in Bhuyan tribe of Orissa, India. Indian J Hum Genet 2007;13:109 –13.
18. Gerard G, Vitrac D, Le Pendu J, Muller A, Oriol R. H-deficient blood groups (Bombay) of Reunion Island. Am J Hum Genet 1982;34:937–47.
19. Fernandez-Mateos P, Cailleau A, Henry S, et al. Point mutations and deletion responsible for the Bombay H null and the Reunion H weak blood groups. Vox Sang 1998;75:37–46.
20. Yu LC, Yang YH, Broadberry RE, Chen YH, Lin M. Heterogeneity of the human H blood group alpha(1,2)fucosyltransferase gene among para-Bombay individuals. Vox Sang 1997;72:36–40.
21. Chi Q, Tang W, Wang CQ, Chen Y, Chen GL, Guo YJ. Molecular genetics analysis and frequency survey of H deficient phenotype. Chin J Blood Transfus (Chinese) 2006;19:445–8.
22. Irani MS, Richards C. Haemolytic transfusion reaction due to anti-IH. Transfusion 2011;51:2676–8.
23. Campbell SA, Shirey RS, King KE, Ness PM. An acute haemolytic transfusion reaction due to anti-IH in a patient with sickle cell disease. Transfusion 2000;40:828–31.
24. Becker DJ, Lowe JB. Leukocyte adhesion deficiency type II. Biochim Biophys Acta 1999;1455:193–204.
25. Isozaki T, Ruth JH, Amin MA, et al. Fucosyltransferase 1 mediates angiogenesis, cell adhesion and rheumatoid arthritis synovial tissue fibroblast proliferation. Arthritis Res Ther 2014;16:R28.
26. Wang H, Deng L, Cai M, et al. Annexin A4 fucosylation enhances its interaction with the NF-kB p50 and promotes tumor progression of ovarian clear cell carcinoma. Oncotarget (in press) doi: 10.18632/oncotarget.10226.
27. Storry JR, Johannesson JS, Poole J, et al. Identification of six new alleles at the FUT1 and FUT2 loci in ethnically diverse individuals with Bombay and para-Bombay phenotypes. Transfusion 2006;46:2149–55.
28. Wagner FF, Flegel WA. Polymorphism of the h allele and the population frequency of sporadic nonfunctional alleles. Transfusion 1997;37:284–90.
29. Ogasawara K, Nakata K, Watanabe J, et al. New FUT1(H) alleles identified from H-deficient phenotype individuals. Vox Sang 2000;78(Suppl 1):4.
30. Guo ZH, Xiang D, Zhu ZY, et al. Analysis on FUT1 and FUT2 gene of 10 para-Bombay individuals in China. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2004;21:417–21.
31. Kaneko M, Nishihara S, Shinya N, et al. Wide variety of point mutations in the H gene of Bombay and para-Bombay individuals that inactivate H enzyme. Blood 1997;90:839–49.
32. Koda Y, Soejima M, Johnson PH, Smart E, Kimura H. Missense mutation of FUT1 and deletion of FUT2 are responsible for Indian Bombay phenotype of ABO blood group system. Biochem Biophys Res Commun 1997;238:21–5.
33. Wagner T, Vadon M, Staudacher E, et al. A new h allele detected in Europe has a missense mutation in alpha(1,2)-fucosyltransferase motif II. Transfusion 2001;41:31–8.
34. Luo G, Wei L, Wang Z, et al. The summary of FUT1 and FUT2 genotyping analysis in Chinese para-Bombay individuals including additional nine probands from Guangzhou in China. Transfusion 2013;53:3224–9.
35. Cai XH, Jin S, Liu X, Fan LF, Lu Q, Xiang D. Molecular genetic analysis for the para-Bombay blood group revealing two novel alleles in the FUT1 gene. Blood Transfus 2011;9:466–8.
36. Zanjani DS, Afzal Aghaee M, Badiei Z, et al. Molecular basis of Bombay phenotype in Mashhad, Iran: identification of a novel FUT1 deletion. Vox Sang 2016;111:88–92.
37. Yan L, Zhu F, Xu X, Hong X, Lv Q. Molecular basis for para-Bombay phenotypes in Chinese persons, including a novel nonfunctional FUT1 allele. Transfusion 2005;45:725–30.
38. Yip SP, Chee KY, Chan PY, Chow EY, Wong HF. Molecular genetic analysis of para-Bombay phenotypes in Chinese: a novel non-functional FUT1 allele is identified. Vox Sang 2002;83:258–62.
39. Chen DP, Tseng CP, Wang WT, et al. Two prevalent h alleles in para-Bombay haplotypes among 250,000 Taiwanese. Ann Clin Lab Sci 2004;34:314–8.
40. Xu X, Tao S, Ying Y, et al. A novel FUT1 allele was identified in a Chinese individual with para-Bombay phenotype. Transfus Med 2011;21:385–93.
41. Samuelsson J, Staples N, Condon J, et al. First example of the para-Bombay phenotype in an Australian proband is encoded by a novel FUT1 allele. In: Annual meeting of Australian and New Zealand Society for Blood Transfusion, Sydney, Australia, October 2005: Abstract 47.
42. Yan LX, Xu XG, Hong XZ, Wu JJ, Zhu FM, Fu QH. Identification of a novel FUT1 allele derived from the alpha-(1,2)-fucosyltransferase gene through a nucleotide substitution 682A>G. Transfus Med 2006;16:447–9.
43. Tao SD, He YM, Hong XZ, et al. Study on the expression stability of mutant alpha-1,2 fucosyltransferase gene 293C to T and 658C to T in eukaryotic cells. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2011;28:521–4.
44. Johnson PH, Mak MK, Leong S, et al. Analysis of mutations in the blood-group H gene in donors with H-deficient phenotypes. Vox Sang 1994;67(Suppl 2):25.

45. Matzhold EM, Helmberg W, Wagner T, et al. Identification of 14 new alleles at the fucosyltransferase 1, 2, and 3 loci in Styrian blood donors, Austria. Transfusion 2009;49:2097–108.
46. Chi Q, Zhang A, Ren B, Guo Y. Genetic analysis of 16 para-Bombay phenotype individuals: a novel non-functional FUT1 allele and a new evidence of genetic linkage within FUT1 and FUT2 gene. Vox Sang 2011;101(Suppl 2):108.
47. Liang W, Xu H, Liu YY, et al. Molecular genetic analysis of para-Bombay phenotype in Chinese persons: a novel FUT1 allele is identified. Transfusion 2015;55:1588.
48. He Z, Liu F. Two novel α 1,2-fucosyltransferase alleles in an H-deficient phenotype individual. Transfus Med Hemother 2014;41:375–9.
49. Su Yq, Wei TL, Yu Q, Liang YL, Li DC. Molecular genetic analysis of FUT1 and FUT2 gene in para-Bombay Chinese: a novel FUT1 allele is identified. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2007;24:520–3.
50. Soejima M, Nakajima T, Fujihara J, Takeshita H, Koda Y. Genetic variation of FUT2 in Ovambos, Turks, and Mongolians. Transfusion 2008;48:1423–31.
51. Yip SP, Lai SK, Wong ML. Systematic sequence analysis of the human fucosyltransferase 2 (FUT2) gene identifies novel sequence variations and alleles. Transfusion 2007;47: 1369–80.
52. Koda Y, Ishida T, Tachida H, et al. DNA sequence variation of the human ABO-secretor locus (FUT2) in New Guinean populations: possible early human migration from Africa. Hum Genet 2003;113:534–41.
53. Liu YH, Koda Y, Soejima M, et al. The fusion gene at the ABO-secretor locus (FUT2): absence in Chinese populations. J Hum Genet 1999;44:181–4.
54. Yu LC, Lee HL, Chu CC, Broadberry RE, Lin M. A newly identified nonsecretor allele of the human histo-blood group alpha(1,2)fucosyltransferase gene (FUT2). Vox Sang 1999;76:115–9.
55. Yu LC, Chu CC, Chan YS, et al. Polymorphism and distribution of the Secretor alpha(1,2)-fucosyltransferase gene in various Taiwanese populations. Transfusion 2001;41:1279–84.
56. Liu Y, Koda Y, Soejima M, Pang H, Schlaphoff T, du Toit ED, Kimura H. Extensive polymorphism of the FUT2 gene in an African (Xhosa) population of South Africa. Hum Genet 1998;103:204–10.
57. Yu LC, Broadberry RE, Yang YH, Chen YH, Lin M. Heterogeneity of the human Secretor alpha(1,2)fucosyltransferase gene among Lewis(a+b-) non-secretors. Biochem Biophys Res Commun 1996;222:390–4.
58. Chang JG, Yang TY, Liu TC, et al. Molecular analysis of secretor type alpha(1,2)-fucosyltransferase gene mutations in the Chinese and Thai populations. Transfusion 1999;39:1013–7.
59. Soejima M, Fujimoto R, Agusa T, et al. Genetic variation of FUT2 in a Vietnamese population: identification of two novel Se enzyme-inactivating mutations. Transfusion 2012;52: 1268–75.
60. Koda Y, Soejima M, Johnson PH, Smart E, Kimura H. An Alu-mediated large deletion of the FUT2 gene in individuals with the ABO-Bombay phenotype. Hum Genet 2000;106:80–5.
61. Pang H, Fujitani N, Soejima M, et al. Two distinct Alu-mediated deletions of the human ABO-secretor (FUT2) locus in Samoan and Bangladeshi populations. Hum Mutat 2000;16:274.
62. Mitani T, Tsujita H, Sonoda S, Akane A. Se genotyping following allele-specific polymerase chain reaction amplification. Leg Med (Tokyo) 2002;4:193–6.

Erwin Andreas Scharberg, MD (corresponding author), Director of Immunohematology, Institute of Transfusion Medicine and Immunohematology, German Red Cross Blood Service Baden-Württemberg-Hessen, gGmbH Gunzenbachstr. 35, 76530 Baden-Baden, Germany, A.Scharberg@blutspende.de; Coral Olsen, Senior Biomedical Scientist Immunohaematology Specialised Laboratory Services, South African National Blood Service, South Africa; and Peter Bugert, PhD, Associate Professor, Institute of Transfusion Medicine and Immunology, Heidelberg University, Medical Faculty Mannheim, and German Red Cross Blood Service Baden-Württemberg-Hessen, Mannheim, Germany.