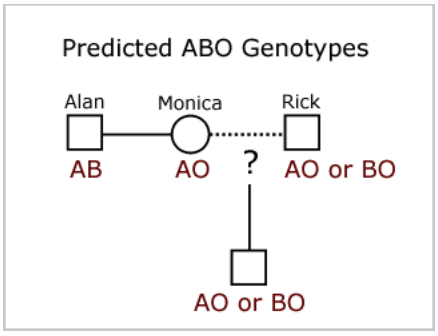
6. The Hh blood group

The Hh blood group contains one antigen, the H antigen, which is found on virtually all RBCs and is the building block for the production of the antigens within the ABO blood group.

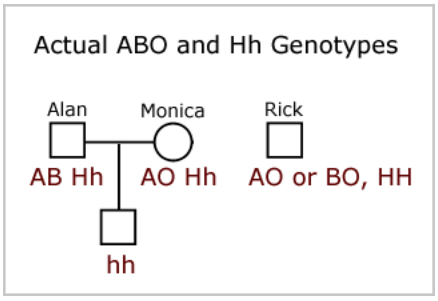
H antigen deficiency is known as the "Bombay phenotype" (h/h, also known as Oh) and is found in 1 of 10,000 individuals in India and 1 in a million people in Europe. There is no ill effect with being H deficient, but if a blood transfusion is ever needed, people with this blood type can receive blood only from other donors who are also H deficient. (A transfusion of "normal" group O blood can trigger a severe transfusion reaction.)

Because the H antigen is the precursor of the ABO blood group antigens, if it is not produced, the ABO blood group antigens are also not produced. This can be misleading in paternity cases, a fact that has been exploited in soap opera story lines!

In the show "General Hospital", the father of Monica's child was in doubt. Monica had blood type A (genotype AO) and her child had blood type O (genotype OO). Because the child must inherit an O allele from the father, the father could have the genotype AO, BO, or OO. In other words, the child's father could have blood group A or B or O, which rules out Monica's husband Alan (type AB) and implicates Rick (type O).



However, Alan is the father! This is possible because both he and Monica are carriers of incomplete H deficiency (H/h). Their h/h child is unable to produce any ABO blood group antigens and so despite inheriting the A or B allele from Alan, the child's RBC's lack the A and B antigens as in blood type O.



At a glance

Antigens of the Hh blood group

Number of antigens	**1: the H antigen**
Antigen specificity	**Carbohydrate** The specificity of the H antigen is determined by the sequence of oligosaccharides. More specifically, the minimum requirement for H antigenicity is the terminal disaccharide fucose-galactose, where the fucose has an alpha-(1-2)- linkage.
Antigen-carrying molecules	**Glycoproteins and glycolipids of unknown function** The H antigen is attached to oligosaccharide chains that project above the RBC surface. These chains are attached to proteins and lipids that lie in the RBC membrane.
Molecular basis	**The FUT1 gene indirectly encodes the H antigen expressed on RBCs.** FUT1 encodes a fucosyltransferase that catalyzes the final step in the synthesis of the H antigen. The FUT2 gene indirectly encodes a soluble form of the H antigen, which is found in bodily secretions.
Frequency of the H antigen	**Present on 99.9% of RBCs in all populations** H deficiency is rare: it is found in 1 of 8,000 in Taiwan, 1 of 10,000 in India, and 1 per million in Europe (1).
Frequency of the H phenotype	**Blood group O: 45% in Caucasians, 49% in Blacks, 43% in Asians, and 55% in Mexicans** The frequency of the H antigen is equivalent to the frequency of blood group O in which the H antigen remains unaltered (1).

Antibodies produced against the H antigen

Anti-H type	**IgM is more common than IgG** Anti-H is naturally occurring in people with H antigen deficiency.
Anti-H reactivity	**Capable of hemolysis** Anti-H can activate the complement cascade which lyses RBCs while they are still in the circulation (intravascular hemolysis).
Transfusion reaction	**Yes—can cause an acute hemolytic transfusion reaction**
Hemolytic disease of the newborn	**Possible** HDN could arise in mothers with the Bombay phenotype (Oh, h/h)

Background information

History

In Bombay, India, an individual was discovered to have an interesting blood type that reacted to other blood types in a way that had not been seen before. Serum from this individual contained antibodies that reacted with all RBCs from normal ABO phenotypes (i.e., groups O, A, B, and AB). The individual's RBCs appeared to lack all of the ABO blood group antigens plus an additional antigen that was previously unknown.

In 1952, a paper about the "new blood group character related to the ABO blood group" was published (2). This new blood group character is the H antigen and it is the building block for the antigens of the ABO blood group.

Named for the city in which it was first discovered, the "Bombay phenotype" describes individuals whose RBCs lack the H antigen. Because the A and B antigens cannot be formed without the H antigen precursor, their RBCs also lack these antigens. As a result, these individuals produce anti-H, anti-A, and anti-B and can therefore be transfused only with RBCs that also lacks the H, A, and B antigens i.e., they can only receive blood from another person with the Bombay phenotype. Because of the rarity of this blood type, this normally means using blood donations from a suitable relative.

Nomenclature

- Number of H antigens: 1
- ISBT symbol: H
- ISBT number: 018
- Gene symbol: FUT1
- Gene name: Fucosyltransferase 1

Basic biochemistry

The biosynthesis of the H antigen and the A and B antigens involves a series of enzymes (glycosyltransferases) that transfer monosaccharides. The resulting antigens are oligosaccharide chains, which are attached to lipids and proteins that are anchored in the RBC membrane.

The H antigen is produced by a specific fucosyltransferase. Depending upon a person's ABO blood type, the H antigen is converted into either the A antigen, B antigen, or both. If a person has blood group O, the H antigen remains unmodified. Therefore, the H antigen is present in the highest amounts in blood type O and in the least amounts in blood type AB.

Two regions of the genome encode two enzymes with very similar substrate specificities—the H locus (FUT1) and the Se locus (FUT2).

The H locus contains the FUT1 gene, which is expressed in RBCs. At least one functioning copy of FUT1 needs to be present (H/H or H/h) for the H antigen to be produced on RBCs. If both copies of FUT1 are inactive (h/h), the Bombay phenotype results.

The Se locus contains the FUT2 gene, which is expressed in secretory glands. Individuals who are "secretors" (Se/Se or Se/se) contain at least one copy of a functioning enzyme. They produce a soluble form of H antigen that is found in saliva and other bodily fluids. "Non-secretors" (se/se) do not produce soluble H antigen. The enzyme encoded by FUT2 is also involved in the synthesis of antigens of the Lewis blood group.

Common H phenotypes

The two common H phenotypes are "secretor" and "non-secretor".

Secretor (common)

- H antigen is expressed on RBCs.
- H antigen is expressed in saliva.
- No anti-H is produced.
- Genotype: H/H or H/h; Se/Se or Se/se

Non secretor (common)

- H antigen is present on RBCs.
- H antigen is absent from saliva.
- No anti-H is produced.
- Genotype: H/H or H/h; se/se

Uncommon H Phenotypes

The Bombay phenotype and para-Bombay phenotype are relatively rare. In India, where H deficiency was first discovered, the frequency of both phenotypes combined is 1 in 10,000 (1). H deficiency is slightly more common in Taiwan, affecting 1 of 8,000 people (1). A relatively large number of H-deficient individuals were found on Reunion Island, which is a small French Island 800 km east of Madagascar in the Indian Ocean (3). Both the classical Bombay phenotype and a new variant type of partial H deficiency was seen in the islanders (4). In Europe, 1 per million people are H deficient (1).

Bombay phenotype

- H antigen is not expressed on RBCs.
- H antigen is not found in saliva.
- Serum contains anti-H.
- Genotype: h/h se/se

Para-Bombay phenotype

- H antigen is weakly expressed on RBCs.
- H antigen may be present or absent in saliva.
- Serum contains anti-H.
- Genotype: (H), Se/Se or Se/se or se/se

Expression of the H antigen

The H antigen shares the same broad tissue distribution as the A and B antigens. Likewise, in individuals who are "secretors", a soluble form of the H antigen is found in saliva and all fluids except cerebrospinal fluid.

Function of the H antigen

The function of the H antigen, apart from being an intermediate substrate in the synthesis of ABO blood group antigens, is not known although it may be involved in cell adhesion (5). People who lack the H antigen do not suffer any deleterious effects, and being H-deficient is only an issue if they were to need a blood transfusion because they would require H-deficient blood.

Clinical significance of H antibodies

Transfusion reactions

If patients with anti-H in their circulation receive transfusions of blood that contains the H antigen (e.g., blood group O), they are at risk of suffering an acute hemolytic transfusion reaction.

Hemolytic disease of the newborn

In theory, the maternal production of anti-H during pregnancy could cause hemolytic disease in a fetus who did not inherit the mother's Bombay phenotype. In practice, cases of HDN caused in this way have not been described, possibly because of the rarity of the Bombay phenotype.

Molecular information

The H blood group locus (containing FUT1) and the secretor locus (containing FUT2) are located on chromosome 19 at q.13.3. FUT1 and FUT2 are tightly linked, being only 35 kb apart. Because they are highly homologous, they are likely to have been the result of a gene duplication of a common gene ancestor.

The H locus contains four exons that span more than 8 kb of genomic DNA. Both the Bombay and para-Bombay phenotypes are the result of point mutations in the FUT1 gene (6, 7).

The classical Bombay phenotype is caused by a Tyr316Ter mutation in the coding region of FUT1 (1, 8). The mutation introduces a stop codon, resulting in a truncated enzyme that lacks 50 amino acids at the C-terminal end, rendering the enzyme inactive. In Caucasians, the Bombay phenotype may be caused by a number of mutations (9, 10). Likewise, a number of mutations have been reported to underlie the para-Bombay phenotype (11).

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