



9. The Duffy blood group

The Duffy glycoprotein is a receptor for chemicals that are secreted by blood cells during inflammation. It also happens to be a receptor for *Plasmodium vivax*, a parasite that invades red blood cells (RBCs) and causes malaria. RBCs that lack the Duffy antigens are relatively resistant to invasion by *P. vivax*. This has influenced the variation in Duffy blood types seen in populations where malaria is common.

Antibodies formed against the Duffy antigens are a cause of both transfusion reactions and hemolytic disease of the newborn.

At a glance

Antigens of the Duffy blood group.

Number of antigens	6: Fy ^a , Fy ^b , Fy3, Fy4, Fy5, Fy6
Antigen specificity	Protein Amino acid sequence determines the specificity of Duffy antigens.
Antigen-carrying molecules	Glycoprotein that is a red cell receptor The Duffy glycoprotein is a receptor that binds cytokines released during inflammation. It also binds the malaria parasite <i>Plasmodium vivax</i> , and RBCs that lack the Duffy Fy ^a and Fy ^b antigens are resistant to invasion. Structurally, the Duffy protein is similar to the family of G-protein coupled receptors, having 7 transmembrane domains.
Molecular basis	The FY gene encodes the Duffy antigens. FY has two major codominant alleles, FYA and FYB, which result from a SNP (125G→A), and the corresponding Fy ^a and Fy ^b antigens differ by a single amino acid (G42D). Individuals who are homozygous for a -33T→C SNP in the erythroid promoter region of the FYB allele have the phenotype Fy(a-b-) and do not express Duffy antigens on their RBCs.
Frequency of Duffy antigens	Fy ^a : 66% Caucasians, 10% Blacks, 99% Asians Fy ^b : 83% Caucasians, 23% Blacks, 18.5% Asians Fy3: 100% Caucasians, 32% Blacks, 99.9% Asians (1).
Frequency of Duffy phenotypes	The Duffy null phenotype, Fy(a-b-), is very rare in Caucasians but is found in 68% of Blacks (1). Fy(a+b+): 49% Caucasians, 1% Blacks, 9% Chinese Fy(a-b+): 34% Caucasians, 22% Blacks, <1% Chinese Fy(a+b-): 17% Caucasians, 9% Blacks, 91% Chinese

Antibodies produced against Duffy antigens.

Antibody type	IgG Mainly IgG, IgM is rare
Antibody reactivity	Does not bind complement

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Transfusion reaction	Typically a moderate, delayed transfusion reaction Anti-Fy ^a and anti-Fy ^b can cause transfusion reactions that range from mild to severe in nature and may occur immediately after the transfusion (rarely) or more commonly, after a delay. Anti-Fy ³ is a cause of mild to moderate, delayed transfusion reactions.
Hemolytic disease of the newborn	Typically mild disease Anti-Fy ^a causes mild HDN (rarely, severe HDN can occur). Anti-Fy ^b and anti-Fy ³ are uncommon causes of mild HDN.

Background information

History

The Duffy blood group was discovered in 1950. It was named for a patient with hemophilia who had received multiple blood transfusions and was the first known producer of anti-Fy^a. A year later, anti-Fy^b was discovered in a woman who had had several children. The remaining Duffy antigens (FY3, FY4, FY5, and FY6) were discovered 20 years later, but from these, only FY3 appears to be clinically significant.

The frequency of the Duffy phenotypes varies in different populations. The Duffy null phenotype, Fy(a-b-), is rare among Caucasian and Asian populations, whereas it is the most common phenotype in Blacks, occurring in over two-thirds of the Black population. The racial variation in the distribution of Duffy antigens is a result of a positive selection pressure—the absence of Duffy antigens on RBCs makes the RBCs more resistant to invasion by a malarial parasite.

Worldwide, of the four *Plasmodium* species that routinely cause malaria in humans, *P. falciparum* is responsible for the majority of fatal cases (2). But in Asia and the Americas, *P. vivax* is a more common cause of malaria. To cause disease, *P. vivax* must first enter the human RBC, which it does by binding to the N-terminal extracellular domain of the Duffy glycoprotein through the cysteine-rich region of the Duffy binding protein (DBP) (3). Individuals with the Duffy null phenotype do not express the Duffy protein on their RBCs and therefore are immune to *P. vivax* infection.

Interestingly, the Fy(a-b-) phenotype is most common in areas where there is little *P. vivax* malaria (4). In areas of West Africa, there is a high frequency of the Fy(a-b-) phenotype and a low incidence of *P. vivax* malaria. This may be because the pre-existence of a high frequency of the Fy(a-b-) phenotype prevented *P. vivax* malaria from becoming endemic in West Africa (4, 5).

Nomenclature

- Number of Duffy antigens: 6
- ISBT symbol: FY
- ISBT number: 008
- Gene symbol: FY
- Gene name: Duffy blood group

Basic biochemistry

The Duffy glycoprotein is encoded by the FY gene, of which there are two main alleles, FYA and FYB. They are codominant, meaning that if the FYA is inherited from one parent and the FYB allele is inherited from the other, both gene products, Duffy Fy^a and Fy^b antigens, will be expressed on the RBCs.

Phenotypes

There are four main Duffy phenotypes:

- Fy(a+b-)
- Fy(a+b+)
- Fy(a-b+)
- Fy(a-b-)

The Fy^a and Fy^b antigens are found relatively frequently in Caucasians (Fy^a 66% and Fy^b 83%) and Asians (Fy^a 99% and Fy^b 18.5%) but are far less common in Blacks (Fy^a 10% and Fy^b 23%). In fact, the Fy(a- b-) phenotype is present in two-thirds of African-American Blacks but is very rare in Caucasians (1).

An important minor Duffy phenotype is the Fy^x [Fy(b+^x)]. The FYX allele encodes the Fy^b antigen, but it is only weakly expressed because a reduced amount of Duffy protein, and it is not always detected by anti-Fy^b.

Expression of Duffy antigens

Duffy antigens are expressed on many different types of cells. Even Fy(a-b-) individuals who do not produce Duffy antigens on their RBCs do express Duffy antigens elsewhere, including endothelial cells that line blood vessels, epithelial cells of kidney collecting ducts, lung alveoli, and Purkinje cells of the cerebellum. Duffy antigens are also expressed in the thyroid gland, the colon, and the spleen.

Function of Duffy glycoprotein

The Duffy glycoprotein is also called the Duffy-Antigen Chemokine Receptor (DARC). As a chemokine receptor, it binds to the chemicals that are secreted by cells during inflammation and recruits other blood cells to the area of damage. These chemokines include C-X-R (acute inflammation chemokine) and C-C (chronic inflammation chemokine), IL-8 (interleukin 8), and RANTES (regulated on activation, normal T-expressed and secreted) (6).

Animal studies suggest that the function of Duffy as a chemokine receptor is not physiologically important because mice that lacked the mouse homolog of the Duffy gene (Dfy) were not more susceptible to infection than mice that expressed Dfy (7). Indeed, individuals with the null Duffy phenotype appear to have normal RBCs and a normal immune system.

Clinical significance of Duffy antibodies

Transfusion reactions

Antibodies against the Duffy antigens Fy^a (8), Fy^b (9, 10), Fy3 (1), and Fy5 (11,12) have all been implicated as the cause of a transfusion reaction. Anti-Fy^a is more commonly found in patients who are of African descent (in whom the Duffy null phenotype is more common) and have sickle cell anemia (and therefore may require multiple blood transfusions).

Hemolytic disease of the newborn

Maternal-fetal incompatibilities within the Duffy blood group system is an uncommon cause of HDN. The disease tends to be mild in nature. The Duffy antigens known to have caused maternal immunization and subsequent hemolytic disease are Fy^a (13-16), Fy^b (17), and Fy3 (1).

Molecular information

Gene

The Duffy locus, FY, is located on chromosome 1 at position q22-q23. It consists of two exons that span over 1,500 bp of genomic DNA. The two main alleles, FYA and FYB, differ by a single nucleotide at position 125 (G and A, respectively) and they likewise encode Fy^a and Fy^b antigens that differ by a single amino acid at residue 42 (glycine and aspartic acid, respectively).

View the sequences of FY alleles at the [dbRBC Sequence Alignment Viewer](#)

There are two genetic backgrounds that give rise to the Duffy negative phenotype Fy(a-b-) (18). Most commonly, a mutation in the promoter region of the FYB allele abolishes the expression of the Duffy glycoprotein in RBCs, but the protein is still produced in other types of cells. This erythroid-specific mutation is found in African Americans (70%) and West Africans (approaching 100%) (19). Perhaps because the Duffy antigens are expressed in other tissues, these patients do not generally make anti-Fyb or anti-Fy3 (20).

Less commonly, the Fy(a-b-) phenotype is a result of point mutation that introduces a premature stop codon into the coding sequence. It is unlikely that the truncated Duffy protein is transported to the cell surface, and it is likely that the Duffy protein would be absent from all tissues in individuals who carry this type of mutation. There may be strong anti-Fy3 in these patients (20).

The molecular basis of the F^x [Fy(b+x)] phenotype is a mutation in the coding sequence 265C→T (Arg897Cys), which always occurs with another mutation, 298G→A (Ala100Thr) (18).

Protein

The Duffy glycoprotein is a transmembrane protein that spans the RBC membrane seven times and has an extracellular N-terminal domain and a cytoplasmic C-terminal domain. It shares structural similarity with G-protein coupled receptors but so far, it has not been shown to be a member of this family.

The binding site for chemokines, the binding site for *P. vivax*, and the major antigenic domains are all located in overlapping regions in the extracellular N-terminal domain.

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