Duffy Blood Group System

Number of antigens 5

Polymorphic	Fy[a], Fy[b]
High prevalence	Fy3, Fy5, Fy6

Terminology

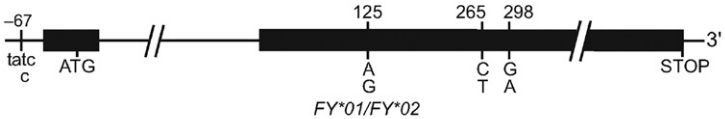
ISBT symbol (number)	FY (008)
CD number	CD234
History	Named after the family of the first proband who made anti-Fy[a].

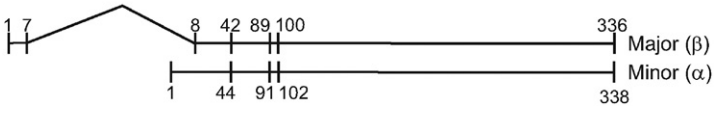
Expression

Other blood cells	Not on granulocytes, lymphocytes, monocytes, platelets
Tissues	Endothelial cells of capillary and postcapillary venules, the epithelial cells of kidney collecting ducts, lung alveoli, and Purkinje cells of the cerebellum

Gene

Chromosome	1q23.2
Name	*FY* (*DARC*)
Organization	2 exons distributed over 1.5 kbp of gDNA
Product	Major (β) Duffy glycoprotein (DARC) Minor (α) Duffy glycoprotein





The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00010-7

Database accession numbers

GenBank	X85785 (gene); U01839 (mRNA); NM_002036
Entrez Gene ID	2532

Molecular basis of Duffy phenotypes

Two Duffy mRNA are translated from *FY*: a less abundant splice form (α) that encodes a protein of 338 residues that was discovered first and used for cloning (Accession number U01839, amino acid sequence MASSGYVLQAE. . .), and a more abundant splice form (β) that encodes a protein of 336 residues[1] (amino acid sequence MGNCLHRAE. . .). *FY*02* (Accession number U01839) is used as the reference allele, but the numbering by Iwamoto et al. is changed to conform with numbering from the codon for the initiator Met.

The reference allele *FY*02* or *FY*B* (Accession number U01839[1]) encodes Fy^b (FY2), FY3, FY5, FY6. The nucleotide difference from this reference allele, and the amino acid affected, are given.

Allele encodes	Allele name	Exon	Nucleotide	Restriction enzyme	Amino acid	Ethnicity (prevalence)
Fy(a+b–) or FY:1	*FY*01* or *FY*A*	2	125A>G	*Ban*I+	Asp42Gly	Asians> Caucasians> Blacks (Common)

Molecular bases of silencing of *FY*

Homozygosity or compound heterozygosity leads to the FY_{null} [FY:–3; Fy(a–b–)] phenotype. Nucleotide changes from the *FY*01* or *FY*02* backgrounds, and amino acids affected, are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*FY*01N.01*	Promoter	–67t>c^	Protein absent from RBCs	Papua New Guinea (Rare)
*FY*01N.02*	2	281_295del	fs, Stop	Caucasians (Rare)
*FY*01N.03*	2	408G>A	Trp136Stop	(Rare)
*FY*01N.04*	2	287G>A	Trp96Stop	(Rare)

(*Continued*)

(Continued)

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*FY*01N.05*	2	327delC	fs, Stop[2]	(Rare)
*FY*02N.01*	Promoter	–67t>c^	Protein absent from RBCs	Blacks (Common);Arabs, Jews, Romany (Several);Caucasians (Rare)
*FY*02N.02*	2	407G>A	Trp136Stop	(Rare)

^=This GATA-1 nucleotide change has been reported previously as –33 and –46. The gene is silenced only in erythroid cells.

Molecular bases of the FY_{mod} (Fy^x) phenotype

Nucleotide changes from the *FY*02* background, and amino acids affected, are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*FY*02M.01*	2	265C>T 298G>A	Arg89Cys Ala100Thr	Caucasians (Many), Blacks (Few)
*FY*02M.02*	2	145G>T 265C>T 298G>A	Ala49Ser Arg89Cys Ala100Thr	Caucasians (Few), Blacks (Rare)

Amino acid sequence of Fy^{b} [1,3]

Major product:

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MGNCLHRAEL  SPSTENSSQL  DFEDVWNSSY  GVNDSFPDGD  YDANLEAAAP   50
CHSCNLLDDS  ALPFFILTSV  LGILASSTVL  FMLFRPLFRW  QLCPGWPVLA  100
QLAVGSALFS  IVVPVLAPGL  GSTRSSALCS  LGYCVWYGSA  FAQALLLGCH  150
ASLGHRLGAG  QVPGLTLGLT  VGIWGVAALL  TLPVTLASGA  SGGLCTLIYS  200
TELKALQATH  TVACLAIFVL  LPLGLFGAKG  LKKALGMGPG  PWMNILWAWF  250
IFWWPHGVVL  GLDFLVRSKL  LLLSTCLAQQ  ALDLLLNLAE  ALAILHCVAT  300
PLLLALFCHQ  ATRTLLPSLP  LPEGWSSHLD  TLGSKS               336
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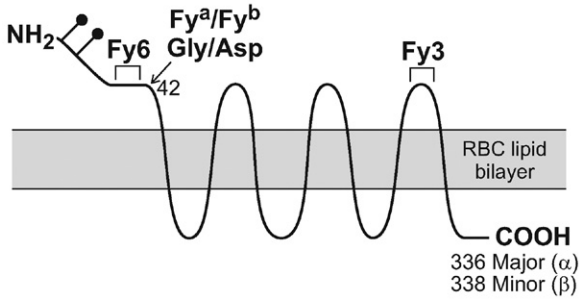
At the N-terminus, the minor product of 338 amino acids has 9 amino acids, MASSGYVLQ, in place of the first 7 amino acids, MGNCLHR, of the major product.

Carrier molecule

A multipass membrane glycoprotein.



M_r (SDS-PAGE)	35,000–45,000
CHO: N-glycan	2 potential sites
CHO: O-glycan	No sites
Copies per RBC	6,000 to 13,000

Function

DARC is a promiscuous receptor for chemokines of both the C-X-C and C-C families, which have pleiotropic functions in innate and chronic immunobiology: IL-8 (interleukin-8), MGSA (melanoma growth stimulatory activity); MCP-1 (monocyte chemotactic protein 1); RANTES (regulated on activation, normal T-expressed and secreted). Clears proinflammatory peptides[4,5]. Fy(a–b–) RBCs do not bind chemokines, and RBCs with suppressed Fy^b antigen expression encoded by *FY*02M.01* bind reduced levels of chemokines.

Disease association

Receptor for *Plasmodium vivax*, *P. knowlesi* malarial parasites: Fy(a–b–) RBCs resist invasion.

The –67t>c change in *FY* (*DARC*) has been associated with a survival advantage in leukopenic HIV-infected persons, as well as low neutrophil counts, which in turn was associated with a three-fold higher risk of HIV susceptibility[6,7]. FY antigens may act as minor histocompatibility antigens in renal allograft rejection[8].

Duffy glycoprotein (DARC) has been reported to regulate prostate cancer growth, and its presence on vascular endothelium interacts with CD82 on cancer cells to inhibit the spread of cancer to remote sites and also may induce cancer cell senescence[9,10].

Phenotypes (% occurrence)

Phenotype	Caucasians	Blacks	Chinese	Japanese	Thai
Fy(a+b–)	17	9	90.8	81.5	69
Fy(a–b+)	34	22	0.3	0.9	3
Fy(a+b+)	49	1	8.9	17.6	28
Fy(a–b–)	Very rare	68	0	0	0
25% of Israeli Arabs and 4% of Israeli Jews have Fy(a–b–) RBCs					
Null: Fy(a–b–)					
Unusual: Fy^x expresses weak Fy^b antigen not detected by all anti-Fy^b					

Comments

Fy(a–b–) is also present in Arabs, Jews, Brazilians, and Romanies.
The polymorphism 298G>A (Ala100Thr) occurs (without 265C>T) in ~15% of all *FY*02* alleles in Caucasians, and does not reduce expression of Fy^b.

References

[1] Iwamoto, S., et al., 1996. Identification of a novel exon and spliced form of Duffy mRNA that is the predominant transcript in both erythroid and postcapillary venule endothelium. Blood 87, 378–385.

[2] Tsuneyama, H., et al., 2000. Deletion in the Duffy gene of an apparently healthy individual with the Fy(a−b−) phenotype [abstract]. Transfusion 40 (Suppl.), 116S.

[3] Pogo, A.O., Chaudhuri, A., 2000. The Duffy protein: a malarial and chemokine receptor. Semin Hematol 37, 122–129.

[4] Darbonne, W.C., et al., 1991. Red blood cells are a sink for interleukin 8, a leukocyte chemotaxin. J Clin Invest 88, 1362–1369.

[5] Neote, K., et al., 1994. Functional and biochemical analysis of the cloned Duffy antigen: identity with the red blood cell chemokine receptor. Blood 84, 44–52.

[6] Kulkarni, H., et al., 2009. The Duffy-null state is associated with a survival advantage in leukopenic HIV-infected persons of African ancestry. Blood 114, 2783–2792.

[7] Ramsuran, V., et al., 2011. Duffy-null-associated low neutrophil counts influence HIV-1 susceptibility in high-risk South African black women. Clin Infect Dis 52, 1248–1256.

[8] Lerut, E., et al., 2007. Duffy and Kidd blood group antigens: minor histocompatibility antigens involved in renal allograft rejection? Transfusion 47, 28–40.

[9] Bandyopadhyay, S., et al., 2006. Interaction of KAI1 on tumor cells with DARC on vascular endothelium leads to metastasis suppression. Nat Med 12, 933–938.
[10] Shen, H., et al., 2006. The Duffy antigen/receptor for chemokines (DARC) regulates prostate tumor growth. FASEB J 20, 59–64.

Fy^a Antigen

Terminology

ISBT symbol (number)	FY1 (008001 or 8.1)
History	Antibody identified in 1950 in the serum of Mr. Duffy, who was a multi-transfused hemophiliac. The last two letters of his name were used for the antigen name.

Occurrence

Caucasians	66%
Blacks	10%
Asians	99%
Thai	97%

Antithetical antigen

Fy^b (**FY2**)

Expression

Cord RBCs	Expressed

Molecular basis associated with Fy^a antigen[1–4]

Amino acid	Gly42 (44 in minor isoform)
Nucleotide	G at bp 125 in exon 2

Effect of enzymes and chemicals on Fy^a antigen on intact RBCs

Ficin/Papain	Sensitive
Trypsin	Resistant
α-Chymotrypsin	Sensitive
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-Fy^a

Immunoglobulin class	IgG; IgM rarely
Optimal technique	IAT
Complement binding	Rare

Clinical significance of alloanti-Fy^a

Transfusion reaction	Mild to severe (rare); immediate/delayed
HDFN	Mild to severe (rare)

Autoanti-Fy^a

Autoantibodies mimicking alloanti-Fy^a have been reported[5].

Comments

Fy^a has been demonstrated on fetal RBCs as early as 6 weeks gestation. Adult level of Fy^a expression is attained approximately 12 weeks after birth.

References

[1] Chaudhuri, A., et al., 1995. The coding sequence of Duffy blood group gene in humans and simians: restriction fragment length polymorphism, antibody and malarial parasite specificities, and expression in nonerythroid tissues in Duffy-negative individuals. Blood 85, 615–621.

[2] Iwamoto, S., et al., 1995. Genomic organization of the glycophorin D gene: Duffy blood group Fy^a/Fy^b alloantigen system is associated with a polymorphism at the 44-amino acid residue. Blood 85, 622–626.

[3] Mallinson, G., et al., 1995. Mutations in the erythrocyte chemokine receptor (Duffy) gene: the molecular basis of the Fy^a/Fy^b antigens and identification of a deletion in the Duffy gene of an apparently healthy individual with the Fy(a−b−) phenotype. Br J Haematol 90, 823–829.

[4] Tournamille, C., et al., 1995. Molecular basis and PCR-DNA typing of the Fy^a/Fy^b blood group polymorphism. Hum Genet 95, 407–410.

[5] Harris, T., 1990. Two cases of autoantibodies that demonstrate mimicking specificity in the Duffy blood group system. Immunohematology 6, 87–91.

Fy^b Antigen

Terminology

ISBT symbol (number)	FY2 (008002 or 8.2)
History	Named in 1951 when the antigen was shown to be antithetical to Fy^a.

Occurrence

Caucasians	83%
Blacks	23%
Chinese	9.2%
Asians	18.5%
Thai	31%

Antithetical antigen

Fy^a (**FY1**)

Expression

Cord RBCs	Expressed
Altered	Weak on RBCs with the Fy^x phenotype

Molecular basis associated with Fy^b antigen[1–4]

Amino acid	Asp42 (44 in minor isoform)
Nucleotide	A at bp 125 in exon 2

Effect of enzymes and chemicals on Fy^b antigen on intact RBCs

Ficin/Papain	Sensitive
Trypsin	Resistant (weakened)
α-Chymotrypsin	Sensitive
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-Fy^b

Immunoglobulin class	IgG; IgM rarely
Optimal technique	IAT
Complement binding	Rare

Clinical significance of alloanti-Fy^b

Transfusion reaction	Mild to severe (rare); immediate (rare); delayed
HDFN	Mild (rare)

Autoanti-Fy^b

Several examples of autoantibody mimicking alloanti-Fy^b have been reported; one caused AIHA.

Comments

Fy^b is a poor immunogen and has been estimated to be 20 times less immunogenic than Fy^a.

Black individuals who have Fy(a–b–) RBCs invariably possess an allele that encodes Fy^b on cells other than RBCs. When the allele encoding RBC Fy^b antigen is silenced by a GATA box mutation (*FY**–67t>c)[5], patients do not make anti-Fy^b.

References

[1] Chaudhuri, A., et al., 1995. The coding sequence of Duffy blood group gene in humans and simians: restriction fragment length polymorphism, antibody and malarial parasite specificities, and expression in nonerythroid tissues in Duffy-negative individuals. Blood 85, 615–621.

[2] Iwamoto, S., et al., 1995. Genomic organization of the glycophorin D gene: Duffy blood group Fy^a/Fy^b alloantigen system is associated with a polymorphism at the 44-amino acid residue. Blood 85, 622–626.

[3] Mallinson, G., et al., 1995. Mutations in the erythrocyte chemokine receptor (Duffy) gene: the molecular basis of the Fy^a/Fy^b antigens and identification of a deletion in the Duffy gene of an apparently healthy individual with the Fy(a−b−) phenotype. Br J Haematol 90, 823–829.

[4] Tournamille, C., et al., 1995a. Molecular basis and PCR-DNA typing of the Fy^a/Fy^b blood group polymorphism. Hum Genet 95, 407–410.

[5] Tournamille, C., et al., 1995b. Disruption of a GATA motif in the *Duffy* gene promoter abolishes erythroid gene expression in Duffy-negative individuals. Nature Genet 10, 224–228.

Fy3 Antigen

Terminology

ISBT symbol (number)	FY3 (008003 or 8.3)
Obsolete names	Fy^{ab}; Fy^aFy^b
History	Anti-Fy3, found in 1971, was made by a pregnant Australian Fy(a–b–) woman who had been transfused. The specificity was named anti-Fy3 (and not anti-Fy^{ab}) because the antigenic determinant was resistant to enzyme treatment.

Occurrence

Caucasians	100% [Fy(a–b–) found in 4 Caucasians and one Cree Indian]
Blacks	32%
Asians	99.9%
Yemeni Jews	99%
Israeli Jews	96%
Israeli Arabs	75%

Expression

Cord RBCs	Expressed; increases after birth
Altered	Weak on RBCs with the Fy^x phenotype

Molecular basis associated with Fy3 antigen

See System pages for molecular basis associated with an absence of Fy3.
The third extracellular loop of the Duffy glycoprotein contains sequences necessary for binding of monoclonal anti-Fy3.

Effect of enzymes and chemicals on Fy3 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Resistant
α-Chymotrypsin	Resistant
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-Fy3

Immunoglobulin class	IgG
Optimal technique	IAT; enzymes
Complement binding	Rare

Clinical significance of alloanti-Fy3

Transfusion reaction	Mild to moderate; immediate (rare); delayed/ hemolytic
HDFN	Mild (rare)

Comments

The anti-Fy3 made by three non-black women reacted strongly with cord RBCs, whereas the anti-Fy3 made by black people does not react or reacts very weakly with cord RBCs.
Formation of anti-Fy3 is usually preceded by formation of anti-Fy^a. In spite of the high percentage of the Fy:–3 phenotype among blacks, anti-Fy3 is a rare specificity. To date, no black Fy(a–b–) individual has made anti-Fy^b, which is due to a GATA-box nucleotide change that silences *FY*B* only in the erythroid lineage.
Anti-Fy3 agglutinates Rh_{null} RBCs, while anti-Fy5 does not.
Fy:–3 [Fy(a–b–)] RBCs resist invasion by *P. vivax* and *P. knowlesi* malarial parasites.

Fy5 Antigen

Terminology

ISBT symbol (number)	FY5 (008005 or 8.5)
History	Reported in 1973, and given the next Fy number when the antibody was shown to detect a novel antigen. Antibody was made by a black Fy(a–b–) boy with leukemia.

Occurrence

Blacks	32%
Most populations	99.9%

Expression

Cord RBCs	Expressed
Altered	Weak on Fy^x and D−− RBCs; absent from Rh_{null} RBCs

Molecular basis associated with Fy5 antigen

Not known; possible interaction between Duffy and Rh proteins[1].

Effect of enzymes and chemicals on Fy5 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Not reported
α-Chymotrypsin	Not reported
DTT 200 mM	Resistant

In vitro characteristics of alloanti-Fy5

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Fy5

Transfusion reaction	Mild, delayed in one case
HDFN	No data

Comments

Several examples of anti-Fy5 have been found. All are in black, multiply-transfused (mostly because of sickle cell disease) Fy(a–b–) patients.
Fy(a–b–) RBCs from black individuals are FY:–3,–5; from a Caucasian (AZ; a.k.a. Findlay) are FY:–3,5, while Rh_{null} RBCs are FY:3,–5.

Reference

[1] Colledge, K.I., et al., 1973. Anti-Fy5, an antibody disclosing a probable association between the Rhesus and Duffy blood group genes. Vox Sang 24, 193–199.

Fy6 Antigen

Terminology

ISBT symbol (number)	FY6 (008006 or 8.6)
History	Reported in 1987. This antigen, although numbered by the ISBT, has only been defined by murine monoclonal antibodies. No human anti-Fy6 has been described.

Occurrence

Blacks	32%
Most populations	100%

Expression

Cord RBCs	Expressed
Altered	Weak on RBCs with the Fy^x phenotype

Molecular basis associated with Fy6 antigen[1]

Anti-Fy6 binds to amino acid residues ^{19}Gln-Leu-Asp-Phe-Glu-Asp-Val-Trp^{26}.

Effect of enzymes and chemicals on Fy6 antigen on intact RBCs

Ficin/Papain	Sensitive
Trypsin	Resistant
α-Chymotrypsin	Sensitive
DTT 200 mM	Resistant
Acid	Resistant

Comments

Amino acid residues 8 (Ala) to 43 (Asp) are critical for *Plasmodium vivax* binding[2].

References

[1] Wasniowska, K., et al., 2002. Structural characterization of the epitope recognized by the new anti-Fy6 monoclonal antibody NaM 185-2C3. Transfus Med 12, 205–211.

[2] Pogo, A.O., Chaudhuri, A., 2000. The Duffy protein: a malarial and chemokine receptor. Semin Hematol 37, 122–129.