Blood Groups – Duffy, and MNSs Group Systems

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2009-03-12
Duffy Blood Group System
History

- 1950: Mrs. Duffy, a multiply transfused hemophiliac woman, developed an antibody not reacting with the known RBC antigens. Corresponding antigen was named after Mrs. Duffy.
- 1951: Fyb antibody was described in a woman with 3 pregnancies.
- 1955: Majority of blacks tested Fy(a-b-).
- 1975: Fy(a-b-) RBCs were shown to resist infection by malaria organism Plasmodium vivax.
- Later: more Duffy antigens (Fy3, Fy4, Fy5, Fy6) were discovered.
- ISBT: 008 for the Duffy Blood Group.
Duffy Antigens

- Most common: Fya and Fyb.
- Present at 6 weeks of gestation, well developed at birth – anti-Fy can cause hemolytic disease of newborn
- Duffy antigens can be destroyed by enzymes such as ficin, papain, bromelain, chymotrypsin, ZZAP
- When compared to Rh or Kell antigens, Duffy antigens are not very immunogenic. So, anti-Fya or anti-Fyb is not common.
- Fy (a-b-) is not Fy null, but homozygous for Fyb gene, they express Fyb antigen in other tissues, but not on RBCs → only will produce anti-Fya, not anti-Fyb.
- Fy (a-b-) is negative for Fy⁶ antigen which is the receptor for P. vivax (Fy⁶ is + when Fya + or Fyb+)
# Duffy Antigens

## Phenotype Frequencies

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Whites %</th>
<th>Blacks %</th>
<th>Chinese %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fy (a+b-)</td>
<td>17</td>
<td>9</td>
<td>90.8</td>
</tr>
<tr>
<td>Fy (a+b+)</td>
<td>49</td>
<td>1</td>
<td>8.9</td>
</tr>
<tr>
<td>Fy (a-b+)</td>
<td>34</td>
<td>22</td>
<td>0.3</td>
</tr>
<tr>
<td>Fy (a-b-)</td>
<td>rare</td>
<td>68</td>
<td>0</td>
</tr>
</tbody>
</table>

**Fya:** 66% Caucasians, 10% Blacks, 99% Asians  
**Fyb:** 83% Caucasians, 23% Blacks, 18.5% Asians  
**Fy3:** 100% Caucasians, 32% Blacks, 99.9% Asians  

White donor population:  
Fya – units: 35%  
Fyb – units: 15%
Duffy Antigens

- **Biochemistry:** glycoprotein, transmembrane (7 times, 3 extracellular loops)
- **Function:** amino acid is similar to interleukin-8 receptor on WBCs, receptors of cytokines
- **Gene:** chromosome 1q22-23. Rh gene also located on chromosome 1, but not linked
- **Fyx gene:** produced weak Fyb antigen – react with some not all anti-Fyb, it can be typed as Fy(b-), can cause confusion in paternity testing
Figure 1 – Schematic representation of the Duffy blood group gene Fy, including the promoter region and the two exons. Black circles represent nucleotide substitutions (nucleotide numbers are given according to reference 13), and arrows indicate the location and orientation of the allele-specific oligonucleotide primers (FYAB2, GATAFY2, FYAREV, FYBREV) used for genotyping and the FY3 and FY4 primers used for amplifying a 661-bp fragment for sequence analysis. Primer sequences (from 5' to 3') are as follows: FYAB2, CTC ATT AGT CCT TGG CTC TTA T; GATAFY2, CTC ATT AGT CCT TGG CTC TTA C; FYAREV, AGC TGC TTC CAG GTT GGC AC; FYBREV, AGC TGC TTC CAG GTT GGC AT (note that these two pairs of forward and reverse allele-specific primers differ in a single nucleotide [T or C] at the 3' end); FY3, CCC TCT TGT GTC CCT CCC TTT, and FY4, CAG AGC TGC GAG TGC TAC CTA. The nucleotide replacements C265T and G298A in exon 2, marked with asterisks, may be detected by restriction fragment length polymorphism analysis using the restriction enzymes AcII and MwoI, respectively.
Blood, Vol. 89 No. 9 (May 1), 1997: pp. 3077-3091

From **Malaria to Chemokine Receptor**: The Emerging Physiologic Role of the Duffy Blood Group Antigen

By Terence J. Hadley and Stephen C. Peiper

From the Departments of Medicine, Pathology, and Biochemistry, Henry Vogt Cancer Research Institute, James Graham Brown Cancer Center, University of Louisville; and the Department of Veterans Affairs Medical Center, Louisville, KY.
This thin film Giemsa stained micrograph reveals a mature *Plasmodium vivax* trophozoite.

*P. vivax trophozoites* show amoeboid cytoplasm, large chromatin dots, and fine, yellowish-brown pigment. RBCs are enlarged 1 1/2 - 2X, and may be distorted. If visible, Schüffner's dots may appear finer than those seen in *P. vivax*. 
Anti-Fya and Anti-Fyb

- IgG, clinically significant, warm-reacting, exposure-requiring antibody
- Transfusion reactions: acute or delayed hemolytic transfusions
- HDN cases are usually mild
- Anti-Fya is more common than anti-Fyb (Fya is more immunogenic than Fyb)
- Anti-Fya or anti-Fyb do not react with enzyme treated RBCs (useful tech in ID)
- Dosage effect is not as strong as anti-Jk
- Antibody titers can fade over time, causing delayed hemolytic transfusion reaction
- People with Fy (a-, b-) phenotype can make anti-Fy3 (anti-Fya & anti-Fyb reactivity)
Uncommon Duffy Antigen and Antibody

- **Fy3**: 1971 a case reported that anti-Fy3 was found in an Fy(a-b-) white. It reacted with all RBCs except Fy(a-b-) cells. Fy3 antigen is part of the Fya and Fyb antigen (one of the 3 extracellular loops)

- **Fy4**: 1973 a Fy(a+b+) black made anti-Fy4 reacted with all Fy(a-b-) blacks, Fy(a+b-), and Fy(a-b+) blacks, but not with Fy(a+b+) blacks and not with whites of any Duffy type. Fy(a-b-) blacks carry Fy4Fy4 antigens
Uncommon Duffy Antigen and Antibody

- **Fy5**: 1973 an Fy(a-b-) black child made anti-Fy5 which reacted with cell from a Fy(a-b-)Fy3-, but did not react with Fy(a+) or Fy(b+) Rh\textsubscript{null} red cells. Fy5 antigen is the result of Duffy and Rh genes.

- **Fy6**: 1987, marine monoclonal antibody, much like anti-Fy3, but destroyed by enzymes (Fy3, Fy4, Fy5 antigens resist enzymes). **Fy6 is the receptor for** *P. vivax* **and present on all Fy + cells.**
MNSs (002) Blood Group System
MNSs Antigens

- Total 46 antigens

- Antigen Biochemistry:
  - Glycophorin A (GPA) forms the M, N antigens
  - Glycophorin B (GPB) forms the S, s antigens and U antigen. U antigen is the common core of S, s antigens
  - The glycophorins cross the RBC membrane once and have an external N-terminal and a intracellular C-terminal (linked to spectri skeleton)
  - GPA (1 million copies) is much more abundant than GPB (200,000 copies)

- Tight linkage between GPA and GPB

- GPA is an erythroid marker and is the receptor for Plasmodium falciparum

- M antigen is receptor of E. coli
Figure 15-1. Schematic diagram of glycophorin A and glycophorin B. The amino acid sequences that determine M, N, S, and s are given. ● indicates an O-linked oligosaccharide side chain, ◄ indicates an N-linked polysaccharide side chain. Approximate locations of protease cleavage sites are indicated. (Courtesy New York Blood Center)
MNSs Antigens

- Destroyed by common enzymes (Papain, Ficin, Bromelin, Pronase), but U antigen is resistant
- Trypsin: M, N sensitive, S, s resistant
- Alpha-chymotrypsin: M, N partially sensitive, S, s very sensitive
- S-s-U- phenotype: 2% of Black American and a higher proportion of Black African, due to deletion of the GPB gene, will produce anti-S, s, U
- S- units in White donors: 50%
- S- units in White donors: 10%
MNSs Antibodies

- Anti-M, anti-N: IgM, insignificant, cold-reacting, naturally occurring. Anti-M is common, but anti-N is rare.
- When anti-M, anti-N is reactive at 37°C, antigen negative units should be provided.
- Rare case of anti-M associated severe HDFN has been reported:
  - Lost 2 previous pregnancies, the third baby survived because of intrauterine transfusion.
  - Fetus ruled out other causes of hemolysis.
  - M+ radio-labeled RBCs were destroyed within 3 days after transfusion.
  - M- radio-labeled RBCs survived 30 days after transfusion to the mother (anti-M +).
- Rare case of auto-anti-N causing fatal autoimmune hemolytic anemia.
- Anti-N is associated with hemodialysis, because N antigen is modified by formaldehyde in the dialysis machine.
MNSs Antibodies

- Anti-S, anti-s, & anti-U: IgG, significant, warm-reacting, exposure-requiring
- Whites – 100% S+, s+, 1% of blacks -- S-, s-, and U- (make anti-U)
- GP.Mur phenotype in Southeast Asia: hybrid gene of GPA and GPB produce an unusual amino acid sequence (antigen Mur = MNS10), immunogenic.
- Anti-Mur is the most common antibody after anti-A and anti-B in Hong Kong and Taiwan
Gerbich System

- **Antigens:**
  - Located on Glycophorin C and D
  - 8 antigens, 3 high prevalence (Ge 2, 3, 4), 5 low prevalence
  - Glycophorin C is the receptor for *P. falciparum*.

- **Antibodies**
  - IgG, react at AHG phase,
  - Clinically insignificant, but anti-Ge3 has been reported to cause HDFN, tend to manifest 2-4 wks after birth
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<thead>
<tr>
<th>RBC Antigens</th>
<th>Functions</th>
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<tbody>
<tr>
<td>Duffy</td>
<td>Receptor for chemokins, <em>Plasmodium vivax</em></td>
</tr>
<tr>
<td>Kidd</td>
<td>RBC urea transport (not kidney urea transport)</td>
</tr>
<tr>
<td>Chido/Rodgers</td>
<td>C4</td>
</tr>
<tr>
<td>Knops</td>
<td>Receptor for C3/C4b</td>
</tr>
<tr>
<td>Colton, Co&lt;sup&gt;a&lt;/sup&gt;, Co&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RBC water transport</td>
</tr>
<tr>
<td>Cartwright, Yt&lt;sup&gt;a&lt;/sup&gt;, Yt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RBC AchE</td>
</tr>
<tr>
<td>Cromer</td>
<td>CD55 = DAF (decay accelerating factor)</td>
</tr>
<tr>
<td>MN, Gerbich antigen</td>
<td>Receptor for <em>P. falciparum</em></td>
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