Other Blood Group Systems

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Introduction to Immunohematology

I. Blood Group Immunology/Pre-transfusion Testing/ABO/Rh

II. Other Blood Group Systems

III. Antibody Identification I&II
Other Blood Group Systems: points to consider

• Most commonly encountered antigens and their respective antibodies

• Which antibodies are clinically significant?

• Impact on the Blood Bank
Blood Groups: Discovery and Elucidation

• 1900s-1950s: serology/family studies

• 1950-1980s: biochemical analysis

• Late 1980s: molecular genetics

• A blood group antigen is defined serologically by antibodies made by a human

• In order to be assigned a number by the ISBT Terminology Working Party the antigen must be shown to be inherited
Today: 36 blood group systems; 300+ antigens

Growth spurt thanks to new technologies
Some favorite “old” antigens (that were detected many years ago) have now become systems
RBC Membrane Components & 35 blood group systems

All 36 blood group genes have been cloned and sequenced

Figure adapted from: Blood Group Antigen FactsBook; 3rd ed
Reid, Lomas-Francis & Olsson
ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology

36 Blood group systems (001 through 036)
A blood group system consists of one or more antigens controlled at a single gene locus, or by two or more very closely linked homologous genes

Blood group collections: antigens are related serologically, biochemically or genetically, but do not fit the criteria required for system status (Cost, Er)

700 series: of low incidence antigens that are not part of a blood group system or collection; incidence of <1% in most population tested (e.g., Bi, Kg)

901 series: of high incidence antigens (> 90%) in most population tested that are not part of a blood group system or collection (e.g., MAM, AnWj)
# ISBT Working Party on Terminology for Red Cell Surface Antigens

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<tr>
<th>Number</th>
<th>System name</th>
<th>ISBT gene name</th>
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<td>033</td>
<td>Lan</td>
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</tbody>
</table>

Criteria for the establishment of new blood group systems:
For an antigen to form a new blood group system it must be:
- Defined by a human alloantibody
- Inherited character
- Gene encoding it must have been identified and sequenced
- Known chromosomal location
- Gene must be different from, and not a closely-linked homologue of, all other genes encoding antigens of existing blood group systems.
Blood group antigens that are sugars

• The antigens of the P1PK (formerly P) and Lewis systems are sugars that are produced by a series of reactions in which enzymes (glycosyltransferases) catalyze the transfer of sugar units to the carrier protein in the RBC membrane

• A person’s DNA determines the type of enzyme and therefore, the immunodominant sugar (and antigen) on the RBCs
Most blood systems are carried on proteins

- Single-pass proteins (e.g., Kell, MNS)
- Multi-pass proteins (e.g., Rh, Duffy)
- Glycosylphosphatidylinositol (GPI)-linked protein (e.g., Dombrock, Cromer)
Blood Group Systems and their Chromosomes

Note: # antigens reflect those identified as of 2009
Other Blood Group Systems: **Review of Key Features**

- **Distinguishing characteristics**
  - Structure/function/disease associations

- **Antigen Prevalence/ISBT number**

- **Antibodies**
  - Reactivity
  - Clinical significance
Points to consider for RBC transfusion

• Is the antibody identified clinically significant?

• What is the antigen prevalence in the donor population
  or
  How difficult is it to find compatible blood for the patient?
“Other” blood group systems (BGS): Non-ABO/D

- P1PK (formerly P)
- Lewis
- Other Rh antigens
  - MNS
  - Kell
  - Duffy
  - Kidd

<table>
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<tr>
<th></th>
<th>Rh-hr</th>
<th>Kell</th>
<th>Kidd</th>
<th>Duffy</th>
<th>Lewis</th>
<th>MNSs</th>
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<td>E</td>
<td>c</td>
<td>e</td>
<td>K</td>
<td>k</td>
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<tr>
<td>I</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
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<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
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<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
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</table>

New York Blood Center
Blood Group Immunization: Most Common Specificities

- Rh
- Kell
- Duffy
- Kidd
- MNSs

*Antibodies that occur without exposure to RBC antigens: ABH, li, Lewis, P1, M, N*
Lewis blood group system

- Lewis antigens are not intrinsic to RBCs
- Carried glycolipids in the plasma that are adsorbed onto the RBC
- The Le gene (*FUT3*) produces a fucosyl-transferase that attaches L-fucose to the sub-terminal chain of the precursor chain to form the Le\(^a\) antigen
- The subsequent action of the enzyme encoded by the Se (secretor) gene (*FUT2*) attaches a fucose to the terminal chain to form Le\(^b\) antigen
- Le(a–b–) individuals make Lewis antibodies
Lewis blood group system (continuation)

• Antibodies are frequently found but are usually NOT clinically significant
• Rare examples of hemolytic anti-Le\textsuperscript{a} and even rarer examples of anti-Le\textsuperscript{b} have been found
• Mostly not necessary to type donor blood Lewis antigens prior to transfusion or crossmatching
  – Reactions obtained in the crossmatch provide a good index of transfusion safety
  – If agglutination and/or hemolysis are observed at 37°C or IAT, then the blood should not be given and antigen-negative blood should be used
P1PK Blood Group system (formerly P system)

- P1 antigen formed on cellular paragloboside with Type II chains
- Immunodominant sugar = D-galactose
- No L-fucose added to subterminal sugar
- P1-positive phenotype = \( P_1 \)
- P1-negative phenotype = \( P_2 \)
- Shares common precursor with P (globoside)
- Anti-P1 NOT clinically significant
- Anti-P1 is mostly IgM, it does not cross the placenta and has not been reported to cause HDFN
  - P1 antigen is poorly expressed on fetal cells
Rh blood group system

- The most polymorphic BGS in humans
  - 56 antigens to date and counting!
  - 2nd most important system after ABO
  - Antigens are highly immunogenic
  - Usually clinically significant: can cause transfusion reactions and HDFN

- Rh antibodies rarely, if ever, bind complement
  - RBC destruction is mediated almost exclusively via macrophages in the spleen
Single antigen prevalence (calculated)

• D 85% Caucasians, 93% Blacks, 99% Asians
  – Therefore HDFN due to anti-D very rare in Asian populations

• C 70% Caucasians, 27% Blacks, 93% Asians
• E 30% Caucasians, 22% Blacks, 39% Asians
• C 80% Caucasians, 96% Blacks, 47% Asians
• e 98% Caucasians, 98% Blacks, 96% Asians
MNS blood group system

• 48 antigens

• Carried on sialoglycoproteins:
  – glycophorin A (GPA) and glycophorin B (GPB)

• Encoded by 2 genes: GYPA, GYPB

  M or N; S or s antigens

• Inherited as a haplotype: MS, Ms, NS or Ns

• Disease associations
  – GPA is a pathogen receptor (E. coli; influenza virus)
  – GPA deficient RBCS are resistant to *P. falciparum* invasion
MNS Blood Group

- Many enzyme cleavage sites along both molecules; useful in antibody studies
- Multiple low incidence antigens caused by point mutations
- Various hybrid molecules define novel antigens

Null phenotypes:

- **En(a−)**  M−N−; cells lack GPA
- **U negative**  S−s−; cells lack GPB or have aberrant molecule [Uvar (S−s−U+W)]
- **Mk**  Cells lack both GPA and GPB
MNS antigens: carrier molecules

Amino Acids 1 to 19 are cleaved from the membrane-bound protein

Met/Thr 48
S/s
U
Glycophorin B

131

Glycophorin A

N-linked sugar
O-linked sugar
MNS System: Phenotypes and Prevalence

<table>
<thead>
<tr>
<th>Reactions with Anti-</th>
<th>Phenotype</th>
<th>Prevalence (%)</th>
<th></th>
<th></th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Whites</td>
<td>Blacks</td>
</tr>
<tr>
<td>+ 0</td>
<td>M+N−</td>
<td>28</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>+ +</td>
<td>M+N+</td>
<td>50</td>
<td>44</td>
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</tr>
<tr>
<td>0 +</td>
<td>M−N+</td>
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Adapted from AABB Technical Manual
## Phenotypes and Prevalence in the MNS System

<table>
<thead>
<tr>
<th>Reactions with Anti-</th>
<th>Pheno-</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td></td>
<td>type</td>
<td>Whites</td>
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<tr>
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<td>S+s–U+</td>
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<tr>
<td>+</td>
<td>S+s+U+</td>
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<td>S–s+U+</td>
<td>45</td>
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<tr>
<td>0</td>
<td>S–s–U–</td>
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</table>

Adapted from AABB Technical Manual
MNS Antibodies: anti-M

Anti-M

- IgG (cold reactive; many direct agglutinins) and IgM
  - React at 24°C (RT) or 4°C; rarely also reactive by IAT
  - M antigen: large quantity (up to 1 million copies) on RBCs so that agglutination in saline test may occur even if the antibody is wholly IgG
  - Anti-M demonstrates dosage

- Generally not clinically significant
  - Rare examples have caused transfusion reactions or HDFN

- If reactivity is at 37°C the anti-M should be considered potentially significant
MNS antibodies: anti-N

Anti-N

- IgM and IgG (some direct agglutinins)
  - typically behave like weakly reactive cold agglutinins
  - Rarely reactive at IAT

- Usually considered clinically insignificant
  (although some powerful and potentially significant IgG examples have been observed)

- Antibodies showing dosage are rarely encountered

- Rare N–S–s–U– people make an antibody that reacts with N on GPA and GPB and may be clinically significant
MNS Antibodies: anti-S, -s, -U

Anti-S and anti-s

- Usually IgG; react by IAT but some anti-S and anti-s are IgM
- Anti-S may be “naturally-occurring” without known RBC stimulation
- RBC units for transfusion must be antigen negative and crossmatch compatible

Anti-U

- IgG; reacts by IAT; reacts with enzyme treated RBCs as U antigen is resistant to enzyme treatment
- May cause HDFN; can be difficult to manage be U–blood is rare
Proteolytic Enzymes

• Useful tools for investigating complex antibody problems
• Papain, ficin, bromelin
• Modify RBC membrane/remove negatively charged molecules
• Enzymes destroy M, N, S antigens
  – however, s antigen may or may not be denatured by enzyme treatment
Kell Blood Group System

• 35 antigens

• 6 antigens encountered most
  – K/k
  – Kp^a/Kp^b
  – Js^a/Js^b

• Rare silent alleles encode K_0 (Kell-null) phenotype; no Kell antigens expressed

• McLeod phenotype (encoded by an X-linked gene, XK) has greatly weakened expression of Kell system antigens and is associated with structural and functional abnormalities of RBCs and leukocytes (if patient has CGD)
Kell Glycoprotein

- Member of Neprilysin (M13) family of zinc endopeptidases
- Kell cleaves big endothelin-3 to release ET-3, a potent vasoconstrictor
- Kell antigen expression greatly reduced when Kx protein (encoded by XK gene) is absent (McLeod phenotype)

Courtesy C. Lomas-Francis, modified
# Kell System: Phenotypes and Prevalence

<table>
<thead>
<tr>
<th>Reactions with Anti-</th>
<th>Pheno-type</th>
<th>Prevalence (%)</th>
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<tr>
<td>+</td>
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<td>K+k−</td>
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<tr>
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<td>K−k+</td>
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Adapted from AABB Technical Manual
## Kell System: Phenotypes and Prevalence

<table>
<thead>
<tr>
<th>Reactions with Anti-</th>
<th>Pheno-type</th>
<th>Prevalence (%)</th>
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<td>Kp&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>Kp(a+b−)</td>
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## Kell System: Phenotypes and Prevalence

<table>
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<tr>
<th>Reactions with Anti-</th>
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<th>Prevalence (%)</th>
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<tr>
<td>+ +</td>
<td>\text{Js}(a+b+)</td>
<td>rare</td>
</tr>
<tr>
<td>0 +</td>
<td>\text{Js}(a−b+)</td>
<td>100</td>
</tr>
</tbody>
</table>

Adapted from AABB Technical Manual
Kell Blood Group Antibodies

• IgG; react by IAT

• Always considered clinically significant
  – Cause severe HTRs and HDFN
  – Anemia of the fetus and newborn due to suppression of erythroid progenitor cells *in utero*

• Anti-K most common antibody (very potent immunogen, second only to D), other specificities are rare

• Some bacteria elicit production of IgM anti-K
HDFN due to Anti-D and to Anti-K

Anti-D

Hydropic

Anti-K

Hydropic and anemic

Pictures courtesy of Dr. Greg Denomme
Duffy Blood Group

- 5 antigens: Fy\(^a\), Fy\(^b\), Fy\(_3\), Fy\(_5\) and Fy\(_6\)
- Most common are Fy\(^a\) and Fy\(^b\)
- The Duffy gene encodes a glycoprotein that is expressed in other tissues, including brain, kidney, spleen, heart and lung
- In Fy\(_{a-b-}\) individuals, transcription in the bone marrow is prevented and Duffy protein is absent from the red cell
- Duffy protein is expressed normally in non-erythroid cells of these Fy\(_{a-b-}\) persons
# Molecular Basis of Duffy (Fya & Fyb) Antigens

![Diagram of RBC lipid bilayer with amino acid variations](image)

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Nucleotide Variation</th>
<th>Amino acid Variation</th>
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<tr>
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<td>42nd Gly</td>
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<tr>
<td>Fyb</td>
<td>“” A</td>
<td>“” Asp</td>
</tr>
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</table>
Duffy Blood Group: Fy(a–b–) phenotype

- Fy(a–b–) red cells resistant to *Plasmodium vivax* invasion
- Is extremely rare in Whites
- The prevalence among African American Blacks is 68% and approaches 100% in some areas of West Africa
# Duffy System: Phenotypes and Prevalence

<table>
<thead>
<tr>
<th>Reactions with Anti-</th>
<th>Phenotype</th>
<th>Prevalence</th>
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<td>Fy(a–b+)</td>
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<tr>
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<td>0</td>
<td>Fy(a–b–)</td>
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</table>

Adapted from AABB Technical Manual
Duffy Blood Group Antibodies

- IgG; react by IAT; clinically significant
- Anti-Fy\textsuperscript{a} stronger and more common than anti-Fy\textsuperscript{b}
- Anti-Fy\textsuperscript{a} and -Fy\textsuperscript{b} are non-reactive with enzyme-treated cells
- Anti-Fy\textsuperscript{3}, sometimes made by Fy(a–b–) people
  - The Fy\textsuperscript{3} antigen is resistant to enzyme treatment
Kidd Blood Group System

- ISBT symbol JK, ISBT number 009
- 3 Antigens Jk\(^a\)/Jk\(^b\) Jk3
- Glycoprotein with 10 membrane spanning domains
- Jk\(^a\)/Jk\(^b\) polymorphisms on the 4\(^{th}\) extracellular loop
- Function = urea transport
- Jk(a–b–) individuals are rare
  - are unable to maximally concentrate urine
Kidd Gene and Protein


Asp→Asn
Jk^a→Jk^b

G838A

ATG

Stop

30 kb
# Kidd System: Phenotypes and Prevalence

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<tr>
<th>Reactions with Anti-</th>
<th>Jk(^a)</th>
<th>Jk(^b)</th>
<th>Phenotype</th>
<th>Prevalence (%)</th>
<th></th>
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<tr>
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<td>+</td>
<td>+</td>
<td>Jk(a+b+)</td>
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<td>34</td>
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<tr>
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<td>+</td>
<td>Jk(a−b+)</td>
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<td>9</td>
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<tr>
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<td>0</td>
<td>Jk(a−b−)</td>
<td>Exceedingly rare</td>
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Adapted from AABB Technical Manual
Kidd Blood Group Antibodies

- IgG; react by IAT and with enzyme-treated cells
- **Always** clinically significant
- Titer drops over time and may be difficult to detect
- Often responsible for delayed hemolytic transfusion reactions
- Partial Jk\textsuperscript{a} and Jk\textsuperscript{b} antigens exist putting patients who are apparently antigen-positive patients at risk for making alloantibody
<table>
<thead>
<tr>
<th></th>
<th>Common</th>
<th>Uncommon</th>
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<tbody>
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<td>Specificities</td>
<td>Rh, MNS, Kell, Fy, Jk</td>
<td>Di, Cr, Do, Yt, Lu, Ch/Rg, Kn</td>
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<td>FDA licensed typing reagents available?</td>
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<td>No</td>
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<tr>
<td>RBCs on commercial panels routinely phenotyped?</td>
<td>Always</td>
<td>Usually not</td>
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<tr>
<td>Antibody easily identified by hospital BB?</td>
<td>Yes</td>
<td>No</td>
</tr>
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</table>
Some other blood group systems

• 010  Diego
• 011  Yt
• 014  Dombrock
• 015  Colton
• 020  Gerbich
• 021  Cromer
Structure and Function of Blood Group Antigens

- Membrane transporters
- Receptors and adhesion molecules
- Complement regulatory glycoproteins
- Structural components
- Enzymes
Antibody Detection: 3-cell screen

<table>
<thead>
<tr>
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<th>Kidd</th>
<th>Duffy</th>
<th>Lewis</th>
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Indicates an antibody is present but must test further to identify!
Multiple alloantibodies: points to consider

• What antibodies are identified?
• How many units will I need to screen to find compatible blood?
• Will I find them in my inventory or need to place an order with Blood Center?
Phenotype Prevalence

• Multiply the individual frequencies (incidence of an antigen negative), since phenotypes are independent of one another
• This number will be the % negative for that particular combination
Phenotype Prevalence Example

What is the incidence (or phenotype frequency) of c- K- Jk(a-) unit?
c neg = .20
K neg = .91
Jk(a-) = .23

(.20 x .91 x .23 = .04)
Therefore 4% or 4/100 units would be c- K- Jk(a-)

If the question reads, how many units would you need to screen to find 2 antigen neg units for surgery, proceed with a further calculation:

4  =  2
100  x
4x=200 and x = 50
Answer: 50 units need to be screened to find the 2 units ordered
Blood Bank Challenges
Serological Challenges

• Multiple alloantibodies
  – Which phase and by which method do the antibodies react?
  – Selected cell panels
  – Other helpful techniques?

• POS DAT/warm autoantibodies
  – Unable to RBC phenotype
  – Underlying alloantibodies?

• ABO discrepancies

• Delayed transfusion reactions
  – RBC phenotype unreliable
Additional resources

  – by M.E. Reid, C. Lomas-Francis and M.L. Olsson

  – by G. Daniels

AABB Technical Manual
18th edition
Questions?