Uncommon Blood Groups: The Diego System

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Objectives:

1. Discuss case studies detailing the history of Diego system antigens and antibodies.
2. Describe the characteristics of antigens and antibodies of the Diego System.
3. Evaluate clinical significance and disease association of Diego System antibodies.

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Recognized blood group systems

- The International Society of Blood Transfusion (ISBT) Working Party for Red Cell Immunogenetics and Blood Group Terminology
- Currently 43 recognized blood group systems
- Containing 345 red blood cell antigens

ISBT International Society of Blood Transfusion

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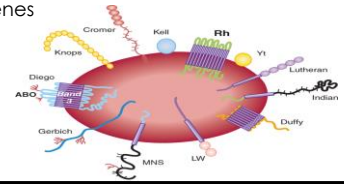
Red blood cell antigens

- Systems of one or more antigens governed by a single gene or complex of two or more closely linked genes



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Discovery of red cell antigens

- Historically due to antibody presence/detection or involvement in transfusion reaction or hemolytic disease of the fetus and newborn (HDFN)
- New antigens discovered today due to advances in genomic testing
- Important that laboratorians are aware of "uncommon" antigens/antibodies

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Common versus uncommon

Common: antigens to which antibodies are commonly encountered

FDA requirements for antigen makeup of commercial red blood cells for antibody detection and identification

Uncommon groups have high and/or low prevalence antigens, so the corresponding antibodies are not commonly encountered

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Antigen frequency/prevalence

- **High prevalence**: antigens carried by 98 – 99% of the population
  - Will not be stimulated to produce the corresponding antibody
- **Low prevalence**: antigens carried by <1 – 2% of the population
  - Very few donor units would contain the antigen

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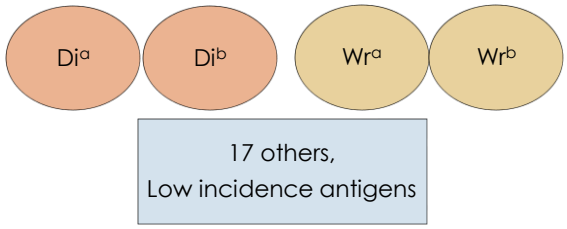
Diego blood group antigens



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Discovery of Di^a

- 1953 Venezuela, South America
- Miguel Layrisse and co-workers are studying the serum of an infant who died from severe jaundice
- Blood specimens from the mother and the infant were sent to Philip Levine in New York
- The infant's RBC were strongly coated with antibody
- No antibody was demonstrable in the mother's serum

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Discovery of Di^a

- ABO and Rh incompatibility were excluded
- In October 1953, the father visits Levine in New York
- The father's RBC were tested against the maternal serum, and a strong agglutination reaction occurred
- Levine and the father agreed to name this mysterious blood factor "Diego" after their family name

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Discovery of Di^a

- 1955 Venezuela
- Mrs. Diego consults Layrisse about a new pregnancy
- Di^a antigen was found in 4 generations of this family
- Evidence of family mixture with South American Indians
- Further study showed the Di^a antigen in groups of Native Americans in the US and in people of Chinese and Japanese ancestry

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Layrisse, Levine, and Diego

Miguel Layrisse

Diego Blood System

Philip Levine

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Discovery of Di^b

- Studied in 1964-65, published in 1967
- Mrs. Luebano, group B, Rh-positive, Mexican-Indian heritage
  - Experienced jaundice after 3-unit transfusion during elective surgery
  - Has delivered 5 infants with no evidence of HDFN
  - Previous transfusion in 1943
- Mrs. Ramirez, group A, Rh-positive, Mexican-Indian heritage
  - Pre-surgery crossmatches reacted with all donors at AHG
  - Has delivered 9 normal infants
  - No prior transfusion history

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Discovery of Wr antigens

- First described in 1953
- Implicated in a case of HDFN
- Named after the family in which the antibody was found
- Assigned to the Diego blood group in 1995
- Antithetical Wright antigens, Wr^a and Wr^b
- Wr^a is low-prevalence in all ethnic groups <0.01%
- Wr^b is high-prevalence with universal expression in all groups

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Frequency of Diego antigens

- Diego blood group is very interesting, especially to anthropologists
- 21 known antigens in the Diego system
- Di^a, Di^b, Wr^a are the most significant
- Di^a found mainly in populations of Mongolian descent but is rare in Whites and Blacks
- Di^b found universally in most populations

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Frequency of Diego phenotypes

Phenotype	Whites	Blacks	Asians
Di(a=b+)	>99%	>99%	>90%
Di(a+b+)	<0.1%	<0.1%	10%
Di(a+b=)	<0.1%	<0.1%	<0.1%
Di(a=b=)	Extremely rare among all races		

Di^a antigen is low prevalence among Whites and Blacks
Di^b antigen is high prevalence among all races

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Linking people of Asia to the Americas

- Di^a antigen has been used as an anthropologic population migration marker

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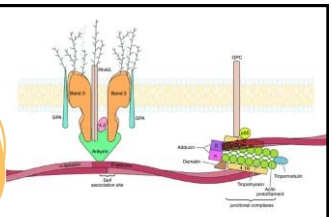
Where are the Diego antigens?



- On the RBC membrane
  - Associated with Band 3 and Glycophorin A

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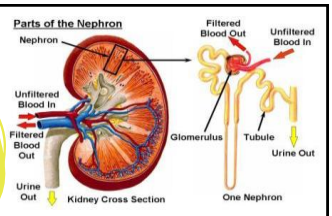
Where are the Diego antigens?



- In the kidneys
  - On alpha-intercalated cells lining the distal tubules and collecting ducts of nephron

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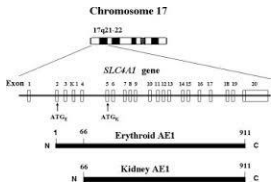
Molecular basis of Diego antigens



- *SLC4A1* gene on chromosome 17
- Anion exchanger 1 proteins
- Chloride/bicarbonate exchange
- 2 versions of AE1 protein:
  - Long – on the RBC
  - Short – in the kidney

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Long AE1 proteins (RBC)

- Band 3 protein on the RBC
- Major anion exchanger
- Structural framework (cytoskeleton) of the RBC
- Interacts with Glycophorin A

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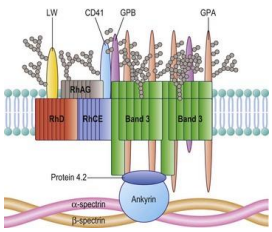
Band 3 on the RBC membrane

- Most abundant membrane protein in human RBC
- Physically linked to ankyrin
- Facilitates exchange of CO_2 and HCO_3
- Associated with Glycophorin A
- ABO, H/h, I/i antigens



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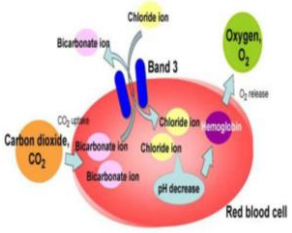
Anion exchange across the RBC

- Exchange one Cl^- for one HCO_3
- CO_2 diffuses across and is converted into HCO_3
- Direction of exchange depends on the concentration of ions on either side of the RBC



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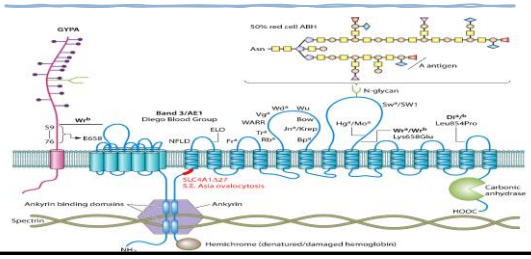
Diego proteins of Band 3



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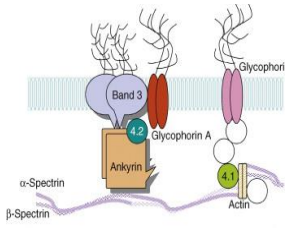
What's up with Glycophorin A?

- Major intrinsic membrane protein of RBC
- Required for high activity of Band 3 anion exchange



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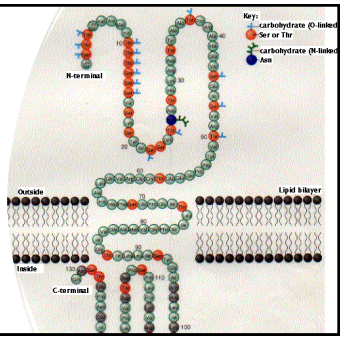
Glycophorin A structure

- Site of M and N antigens
- Associates with Band 3 to form the Wr^b antigen



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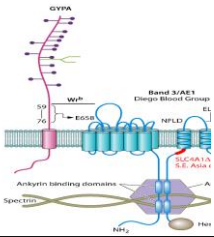
Wr^b proteins of Band 3

- Evidence suggests the Wr^b antigen is formed by linkage between Band 3 and Glycophorin A
- Both are required for expression of the Wr^b antigen
- Wr^b will be absent from RBC that lack GYPA



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Hematological disease associations

- Mutations in the *SLC4A1* gene can cause several blood disorders
- Autosomal dominant inheritance
- Leads to reduction of AE1 proteins or development of abnormal AE1 proteins
  - Hereditary spherocytosis
  - Hereditary stomatocytosis
  - Southeast Asian ovalocytosis

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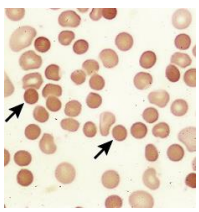
Hereditary spherocytosis

- Mutation to *SLC4A1* gene
- Overly rigid, misshapen cells
- Spherical instead of disc shaped
- Cells cannot flex and change shape to travel through blood vessels
- Spherocytes removed from circulation and broken down in the spleen



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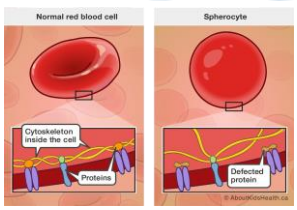
Hereditary spherocytosis



- Anemia
- Jaundice
- Splenomegaly
- High risk for developing gallstones

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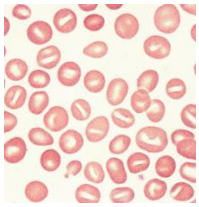
Hereditary stomatocytosis

- Abnormal AE1 proteins
- Allow sodium and potassium to leak out of cell
- RBC are unstable and are broken down more quickly than usual



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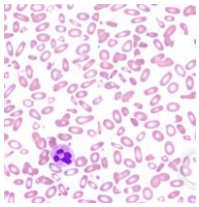
Southeast Asian ovalocytosis

- Most common in regions where malaria is endemic
- Deletion of 9 amino acids in AE1 protein
- Reduction of AE1 on surface of RBC
- Cells are unusually rigid and oval shaped
- May be lethal if mutation is homozygous



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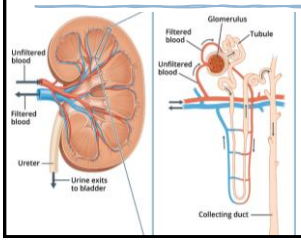
Short AE1 proteins (kidney cells)



- Specialized kidney cells
- Alpha-intercalated cells
- Distal tubules and collecting ducts
- Resorb substances that are needed
- Eliminate wastes

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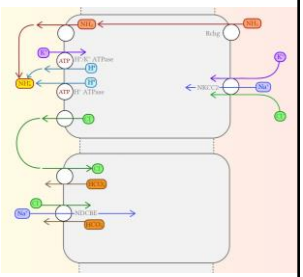
Diego proteins on kidney cells

- Exchange of bicarbonate through AE1 protein allows acid to be released from cell into urine for excretion
- Renal tubules return useful substances to blood circulation



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Kidney disease associations

***SLC4A1*-associated distal renal tubular acidosis**

- At least 18 different mutations to *SLC4A1* gene
- Leads to buildup of acid in the blood (metabolic acidosis)
- Autosomal dominant and autosomal recessive forms

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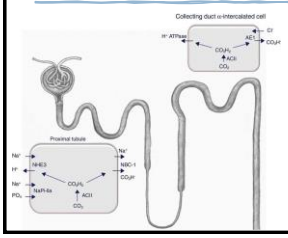
Distal renal tubular acidosis



- Altered AE1 proteins either stuck inside the cell or trafficked to the wrong side of the cell
- Disrupts bicarbonate exchange = acid buildup in blood
- Soft, weak bones, calcium deposits, kidney stones

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Clinical significance of Diego antibodies

- May be IgM or IgG
- Capable of causing Hemolytic Disease of the Fetus and Newborn (HDFN)
- Capable of causing immediate and delayed hemolytic transfusion reactions

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Anti-Di^a and Anti-Di^b

- Immune (red-cell) stimulated
- Primarily IgG1 plus IgG3
- Best detected at 37°C/AHG phase

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Anti-Di^a and Anti-Di^b

- Clinically significant for transfusion practice and pre-natal testing
- Will cause mild to severe HDFN
- Few cases of hemolytic transfusion reaction
- Selected units should be Diego antigen negative and crossmatch compatible

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Anti-Wr^a

- Often occurs naturally
- May also be immune (red-cell) stimulated
- IgM with or without an IgG component
- IgG1 and IgG3 subclasses

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Anti-Wr^a

- Clinically significant for transfusion practice and pre-natal testing
- Occurs in up to 2% of blood donors
- Frequently found in patients with autoimmune hemolytic anemia
- Often found in association with other antibodies

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Anti-Wr^a

- Will cause mild to severe HDFN
- Known to cause acute and delayed hemolytic transfusion reactions, sometimes severe
- Selected units should be Wr^a antigen negative and crossmatch compatible

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Transfusion practice

- FDA mandates that commercial cell panels include RBCs with D, C, E, c, e, M, N, S, s, P1, Le^a, Le^b, K, k, Fy^a, Fy^b, Jk^a and Jk^b antigens
- Currently no requirement for Diego system antigens
- Routine donor antigen typing may not include the Diego system antigens

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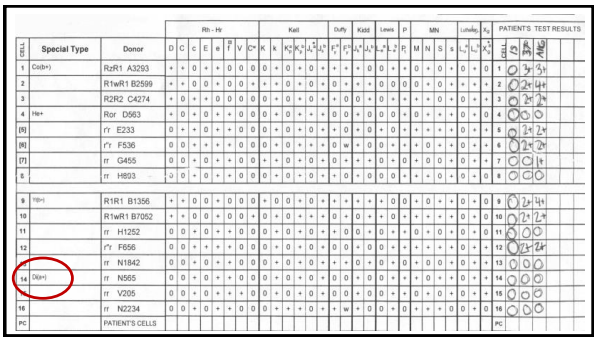

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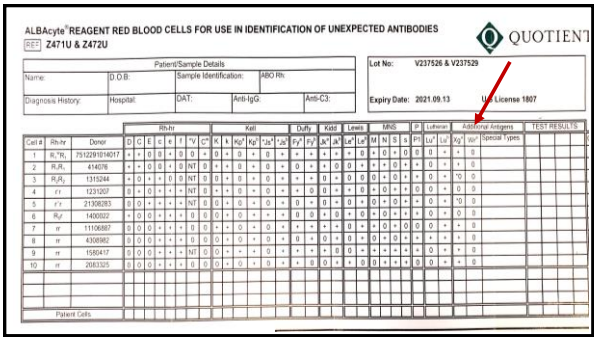

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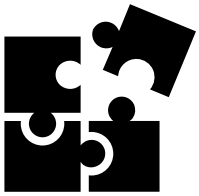
Applications to patient management

- Rare donor files
- Select cell panels
- Consider Diego system when antibody to high incidence antigen found in Japanese and other non-White populations



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Thank you!

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