11. The Diego blood group

The antigens of the Diego blood group are carried on an important protein, called the band 3 protein, which lies in the red blood cell (RBC) membrane. This protein is a chloride/bicarbonate exchanger involved in carbon dioxide transport from tissues to lungs. It also is found in the kidney, where it is involved in acid secretion.

Many mutations in the gene that encodes the Diego antigens, SLC4A1, are known. These mutations can result in RBCs with an abnormal membrane (hereditary ovalocytosis and spherocytosis) and kidneys that are defective in secreting acid (renal tubule acidosis). Other SLC4A1 mutations that do not give rise to disease may result in new blood group antigens that belong to the Diego blood group system.

At a glance

Antigens of the Diego blood group

Number of antigens	**21: Di^a, Di^b, and Wr^a are among the most significant**
Antigen specificity	**Protein** Amino acid sequence determines the specificity of Diego antigens
Antigen-carrying molecules	**Glycoprotein that transports anions** The Diego protein is a transmembrane, multi-pass protein that is integral to the RBC membrane. It is an anion antiporter that exchanges Cl^- and $HCO3^-$ across the RBC membrane.
Molecular basis	**The SLC4A1 gene encodes the Diego antigens.** Located on chromosome 17 (17q21-22), the SLC4A1 gene contains 20 exons that span more than 18 kbp of DNA. The alleles Di^b and Di^a result from a SNP (2561C→T), and the corresponding Di^b and Di^a antigens differ by a single amino acid (P854L).
Frequency of Diego antigens	**Di^a is found mainly in populations of Mongolian descent.** It is found in 36% of South American Indians, 12% of Japanese, and 12% of Chinese, whereas it is rare in Caucasians and Blacks (0.01%). **Di^b is found universally in most populations** (1).
Frequency of Diego phenotypes	**Di(a-b+) is found in >99.9% of Caucasians and Blacks and >90% of Asians.** Di(a+b+) found in <0.1% of Caucasians and Blacks and in 10% Asians. Di(a+b-) found in <0.01% Caucasians, Blacks, and Asians. Di(a-b-) found in 1 case only (1).

Antibodies produced against Diego antigens	
Antibody type	**IgG or IgM** Anti-Di^a and anti-Di^b is IgG; anti-Wr^a is IgG or IgM (1).
Transfusion reaction	**Yes** Anti-Di^a and anti-Di^b are capable of causing a moderate to severe delayed transfusion reaction. Anti-Wr^a can cause an immediate hemolytic transfusion reaction (1).
Hemolytic disease of the newborn	**Yes** Anti-Di^a and anti-Wr^a can cause severe disease. Anti-Di^b tends to cause mild hemolytic disease (1).

Background information

History

The Diego blood group was discovered in 1955 and was named for the first patient to produce an antibody against the new blood system's antigens. The patient, Mrs. Diego, had given birth to a child affected by HDN. Her serum was found to contain an antibody (now called anti-Di^a) which, during her pregnancy, had crossed the placenta to attack the RBCs of her fetus (which expressed the Di^a antigen).

In 1967, a second Diego antigen, Di^b, was discovered. It wasn't until 1995 that other Diego antigens began to be discovered.

At present, 21 Diego antigens are known, but it is the presence or absence of Di^a and Di^b that is of importance in determining a person's Diego blood type.

Nomenclature

- Number of Diego antigens: 21 (2)
- ISBT symbol: DI
- ISBT number: 010
- Gene symbol: SCLA1
- Gene name: Solute Carrier family 4, Anion exchanger, member 1

Note: The alternate gene symbol is AE1, which stands for Anion Exchanger 1. The alternate gene name is erythrocyte membrane protein band 3.

Basic biochemistry

Common phenotypes

The most common Diego phenotype is Di(a-b+), which is found in over 99.9% Caucasians and Blacks, and over 90% of Asians. The Di(a+b+) is found in 10% of Asians. Whereas the Di^a antigen is universally expressed in most populations, the prevalence of the Di^a antigen differs among races, making the Diego blood group of great interest to anthropologists (3).

In the USA, the Di^a antigen has not been found in Caucasian or Black blood donors (4). The Di^a antigen is more commonly found in Oriental people of Mongolian descent, being more common in the Japanese (12%) and the Chinese (5%). In South American Indians, up to 54% of the population carries the Di^a antigen (1).

Interestingly, the Di^a antigen is less rare in the Polish population (0.47%) (5) compared to most Caucasian populations (0.01%). This may reflect the gene admixture that resulted from the invasion of Poland by Tatars (Mongolian heritage) many centuries ago (6).

Expression of Diego antigens

The expression of Diego antigens is limited to RBCs and the kidney (in the distal tubule and the collecting tubule).

Function of Diego protein

Anion exchange across the RBC membrane

The SLCA41 protein is an anti-porter that plays an essential role in enabling the RBC to transport the waste product CO_2 to the lungs, where it can be removed from the body.

The SLCA41 protein exchanges one Cl^- for one $HCO3^-$. The direction of the exchange depends on the concentration of the ions on either side of the RBC membrane. When levels of waste CO_2 are high, CO_2 diffuses across the RBC membrane and is converted into $HCO3^-$ which is transported out of the RBC in exchange for Cl^-. If anion exchange did not occur, $HCO3^-$ would accumulate inside the RBC and reach toxic levels, altering the intracellular pH. In the lungs, the lower level of CO_2 encourages the direction of the exchange to reverse. Once inside the RBC, the $HCO3^-$ yields CO_2 which diffuses out of the RBC and is exhaled from the body.

Integral protein of the RBC membrane

The SLCA1 protein is an integral part of the RBC membrane. It helps anchor the membrane to the underlying spectrin skeleton. It helps the RBC to be stable and flexible, and maintain its biconcave shape.

Mutations of SLC4A1 can cause abnormally shaped RBCs that may be spherical (spherocytes, seen in hereditary spherocytosis), oval shaped (ovalocytes, seen in Southeast Asian ovalocytosis), or elliptical (elliptocytes). Because these RBCs are more fragile, they are prematurely removed from the circulation (hemolytic anemia).

Anion exchange across in the kidney tubule

SCLA1 is expressed in the kidney, where it also mediates the exchange of anions. Mutations that disrupt its function can cause a renal tubular acidosis in which the kidney fails to adequately excrete acid anions, allowing them to accumulate.

Clinical significance of Diego antibodies

Transfusion reactions

Anti-Di^a and anti-Di^b are more commonly associated with HDN than transfusion reactions. However, these antibodies are capable of causing immediate (9) and delayed hemolytic transfusion reactions (2, 8).

Hemolytic disease of the newborn

HDN caused by Diego antibodies are more common in South East Asia and South America.

Anti-Di^a is capable of causing moderate to severe HDN, and cases have been reported in Japan (9), China (10, 11), and Poland (5).

Anti-Di^b typically causes mild HDN. Cases have been reported in Japan (12), China (13), Poland (6), and in a mother of South American descent (14).

Molecular information

Gene

The SLC4A1 gene, also known as the AE1 gene, is a member of the anion exchanger (AE) gene family. SLC4A1 is located on chromosome 17q21-q22 and consists of 20 exons that are distributed over almost 18 kbp of genomic DNA.

The Di^a and Di^b antigens are produced as a result of a single nucleotide polymorphism (SNP) of the SLC4A1 gene. The result is at amino acid position 854; the common (wild-type) Di^b antigen has a proline residue, and the Di^a antigen has a leucine residue.

Protein

The band 3 protein encoded by SLC4A1 is an important integral protein of the RBC membrane. It is 911 amino acids in length, and it loops across the RBC membrane 12 times.

The N terminal domain of the protein lies in the cytoplasm of the RBC, where it interacts with hemoglobin (influencing the exchange of anions) and also interacts with metabolic enzymes (influencing the metabolism of glucose inside the RBC).

Its C-terminal domain spans across the membrane of the RBC and mediates the exchange of chloride and bicarbonate anions across the membrane.

References

1. Reid ME and Lomas-Francis C. The Blood Group Antigen Facts Book. Second ed. 2004, New York: Elsevier Academic Press..

2. Daniels GL, Fletcher A, et al. Blood group terminology 2004: from the International Society of Blood Transfusion committee on terminology for red cell surface antigens. Vox Sang 2004; 87(4):304-316.

3. Daniels G. Human Blood Groups, Second ed. 2002, Blackwell Science.

4. Komatsu F, Hasegawa K, Yanagisawa Y, Kawabata T, Kaneko Y, Watanabe S, Miyagi S, Sakuma M,

Kagawa Y, Kajiwara M. Prevalence of diego blood group Dia antigen in Mongolians: comparison with that in Japanese. Transfus Apheresis Sci 2004; 30:119-24.

5. Kusnierz-Alejska G, Bochenek S. Haemolytic disease of the newborn due to anti-Dia and incidence of the Dia antigen in Poland. Vox Sang 1992; 62:124-6.

6. Lenkiewicz B, Zupanska B. The first example of anti-Diego(b) found in a Polish woman with the Di(a+b-) phenotype and haemolytic disease of the newborn not requiring treatment. Transfus Med 2003; 13:161-3.

7. Hinckley ME, Huestis DW. Case report. An immediate hemolytic transfusion reaction apparently caused by anti-Dia. Rev Fr Transfus Immunohematol 1979; 22:581-5.

8. Yamane K, Yagihashi A, Sasaki M, Kuwashima K, Morio A, Watanabe N. A delayed hemolytic transfusion reaction (DHTR) with multiple alloantibodies (Anti-E, Jka, Dia, Fyb, and S) induced by E-antigen-negative, crossmatch-compatible blood. Immunopharmacol Immunotoxicol 1998; 20:531-9.

9. Alves de Lima LM, Berthier ME, Sad WE, DiNapoli J, Johnson CL, Marsh WL. Characterization of an anti-Dia antibody causing hemolytic disease in a newborn infant. Transfusion 1982; 22:246-7.

10. Ting JY, Ma ES, Wong KY. A case of severe haemolytic disease of the newborn due to anti-Di(a) antibody. Hong Kong Med J 2004; 10:347-9.

11. Yung CH, Lin JS, Hu HY, Lyou JY, Chen YR, Chen CR, Hao TC, Peng CS, Tzeng CH. [Hemolytic disease of the newborn caused by maternal anti-Di(a): a case report in Taiwan]. Zhonghua Min Guo Wei Sheng Wu Ji Mian Yi Xue Za Zhi 1995; 28:146-50.

12. Uchikawa M, Shibata Y, Tohyama H, Mori H, Aisaka K, Nakagawa M. A case of hemolytic disease of the newborn due to anti-Dib antibodies. Vox Sang 1982; 42:91-2.

13. Chen CC, Broadberry RE, Chang FC, Ding F, Lin M. Hemolytic disease of the newborn caused by maternal anti-Dib: a case report in Taiwan. Zhonghua Yi Xue Za Zhi (Taipei) 1993; 52:262-4.

14. Donato E, Guinot M, Vilar C, Garcia R, Canigral G. rHuEPO in the management of pregnancy complicated by anti-Dib. Transfusion 2003; 43:681-2.