The Redelberger antigen: a family study, a family story

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The Redelberger antigen (Rb^a) was first discovered in 1974 on the RBCs of a blood donor who was an employee of the Community Blood Center in Dayton, Ohio. The discovery was made as a result of the investigation of a reagent contamination problem. Two examples of the Rb^a antigen were subsequently identified in the United Kingdom, but no "new" examples have been identified in the United States or Europe. Anti-Rb^a is a commonly occurring antibody, often found in combination with other antibody specificities, especially in combination with other antibodies to low-incidence antigens. ***Immunohematology*** **2006;22:48–51.**

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The discoveries of antigens of low incidence have historically occurred as a result of one of several scenarios. These scenarios include the following: an infant suffering from HDN due to a maternal antibody against a low-incidence antigen of paternal origin, a patient who experiences an unexpected transfusion reaction, a patient whose serum has an unexpected antibody detected in a screening or compatibility test, an individual whose RBCs react unexpectedly with routine blood grouping reagents, and the antithetical antigen to a defined high-incidence antigen. Investigations of low-incidence antigens are often time-consuming, and, unfortunately, often dismissed by blood bankers because low-incidence antigens are perceived as only of academic, not practical, interest.

This article will review the discovery of a very rare antigen, Redelberger, or Rb^a. It will also document the subsequent discoveries of the Rb^a antigen in the United States and how all of the individuals in the United States whose RBCs carry Rb^a can be traced back to the original propositus.

Background

In March 1974, Richard Redelberger donated a unit of blood at the Community Blood Center in Dayton, Ohio. Mr. Redelberger was a frequent blood donor who was employed, quite coincidentally, by the Community Blood Center of Dayton as a donor services coordinator. Mr. Redelberger's RBCs routinely typed as group B, D–, but on this particular donation, his RBCs reacted 3+ at the antihuman globulin phase of testing with a commercial anti-CDE reagent supplied by Gamma Biologicals, Inc., of Houston, Texas. Other lot numbers of Gamma anti-CDE reagent did not react with Mr. Redelberger's RBCs nor did anti-CDE reagents from other commercial manufacturers. Gamma was contacted about this potential contamination problem and the unidentified antibody was traced to the anti-E component of the reagent.[1]

The anti-E component of the anti-CDE reagent and samples of Mr. Redelberger's RBCs were sent to many reference laboratories around the world. Initially, it was thought that the antigen present was the previously identified Bishop antigen (Bp^a). However, with further testing, all investigators soon agreed that the antigen present on the Redelberger RBCs was unique. Mr. Redelberger's RBCs reacted with the Tillett serum (which contains many antibodies to low-incidence antigens), as did the RBCs of a random donor from the North London Blood Transfusion Center in London, England. RBCs from this donor, Mrs. NM, gave the same pattern of reactions with a battery of antisera for low-incidence antigens as did those from Redelberger; Mrs. NM was subsequently determined to be the second individual identified as possessing RBCs with the "new" antigen. A third donor, Mrs. SR, was found at the Wales Blood Transfusion Center in Cardiff. The RBCs from this donor reacted with only one of several anti-E sera. Further investigation revealed that her RBCs gave the same pattern of reactions with antibodies to low-incidence antigens as did those of Redelberger and Mrs. NM.[1]

The Redelberger antigen was studied in all three families and was found to be autosomal dominant in its inheritance.[1] Richard Redelberger was thrilled to learn that a "new" antigen had been discovered on his RBCs. Always the master of the one-liner, Richard declared that he knew all along that he could "never be a

bishop!" The antigen was subsequently named in his honor and abbreviated as Rb^a according to the conventions of the time.

No new examples of the Redelberger antigen were reported for many years in either the United States or Europe. However, anti-Rb^a was found with some frequency, suggesting that the antibody is usually naturally occurring. It has been demonstrated that most examples of anti-Rb^a are direct agglutinins and predominantly IgM. In one study, 6200 donor sera were screened for the presence of anti-Rb^a and six examples were found.[1,2] The incidence of anti-Rb^a is much higher in sera containing multiple antibodies, especially when multiple antibodies to low-incidence antigens are present. Anti-Rb^a is especially common in sera that contain anti-Bp^a and anti-Wr^a.[1]

At the American Red Cross/AABB Immunohematology Reference Laboratory (IRL) conference held in Memphis, Tennessee, in April 2004, Marilyn Moulds of Gamma reported that an apparent new Rb^a propositus had been identified. The individual, RT, was a healthy blood donor who had donated a unit of RBCs at the Blood Connection in Greenville, South Carolina. The most probable Rh genotype of his RBCs was R_2R_2 and they were subsequently used by Gamma as part of a reagent RBC screening duet. Within days of the release of the screening duet, Gamma received numerous customer complaints about this particular RBC reacting with many patient sera when subsequent antibody identification studies did not detect any alloantibodies. One hospital reported seven reactive sera with four of the seven patients reporting no history of transfusion. A second hospital reported that five of six patient sera reacted with the RBC over a weekend! Marilyn's investigation focused on the identification of an antigen of low incidence on the RBCs in question and, with the assistance of Gail Coghlan of the Rh Laboratory, University of Manitoba, Winnipeg, in Manitoba, Canada, they were found to be Rb(a+)

In the audience at the IRL conference that day was Nancy Lang, the lead technologist in the IRL at the Community Blood Center/Community Tissue Services in Dayton, Ohio. Nancy listened to the facts of Marilyn's discovery with particular interest since she personally knew of the discovery of the Redelberger antigen in Dayton. Upon returning to work on the Monday morning after the conference, Nancy opened an e-mail message from a local blood donor, GK. The message, in part, read:

"I received an e-mail from my sister in Greensboro, NC, who indicated that her son in Greenville, SC, was recently told that he had a particular antigen in his blood associated with the Diego Blood Group . . . I know that many years ago the Dayton Blood Center told my mother that she was a carrier of some rare type of blood component but none of us knew what this meant . . . I was wondering if you would be willing to test my blood for this antigen since I am a regular donor. Apparently, the test involves Rb(a)—whatever that may be."

What timing! Nancy called GK and was able to confirm that GK's mother was Richard Redelberger's sister. Nancy's second phone call was to Marilyn Moulds to tell her the Rb^a discovery was not a "new" family in the United States!

A Manufacturer's Perspective

Often, blood bankers are simply annoyed at the finding of an antibody directed at a low-incidence antigen when performing routine serologic procedures. Very little, if any, effort is put forth in attempting to identify the specificity of this antibody. Seen as an isolated event, identification seems unnecessary and not useful, so the reactivity is ignored unless a pattern or trend is noted. As a result, potential "new" low-incidence antigens are not identified as frequently as they might be. There is one instance where identification might be pursued, however, and that is in the case of potential for clinical HDN in a current pregnancy or for future pregnancies.

Manufacturers of commercial RBC products and antisera have an entirely different perspective, however. As illustrated in the case of the R_2R_2 donor above, an antibody to a low-incidence antigen can be quite common, although the incidence of the antigen itself is very low. Anti-Wr^a, for example, is analogous to anti-Rb^a in that the antibody is quite common while the antigen itself is very uncommon. The use of a screening or panel (antibody identification) RBC that possesses a low-incidence antigen can prove to be quite frustrating for the unsuspecting customer of the product when the corresponding antibody occurs with some frequency. Complaints are generated and sent to the manufacturer, which launches an investigation of the antigen on the RBC.

The presence of an antibody to a low-incidence antigen is not of great concern to the manufacturer of commercial antisera if the incidence of the antigen is extremely low. In fact, commercial reagent antisera

only need to be screened for the presence of antibodies directed at rare antigens that occur in 1 percent or more of the random population. However, commercial antisera "contaminated" with anti-Rb^a led to the initial discovery of the Rb^a antigen and the accidental discovery of the Rb^a antigen in another member of the Redelberger family was also the result of an anti-D contamination problem. That story follows.

AR was a female blood donor from Florida who had donated to the 6-gallon benchmark. Donor records showed that she had been typed as D– on all donations until the last. At that time, in August 2003, the RBCs of AR reacted weakly in the weak D test with one source of anti-D reagent, which was a human polyclonal reagent. Her RBCs did not react with anti-D reagent used in an automated test and did not react in tube tests that used monoclonal blend anti-D reagent.

An investigation was launched by the manufacturer of the anti-D reagent that caused the positive weak D test result. The RBCs of AR did not react with six monoclonal anti-D reagents from different manufacturers but did react with three of 12 human sera containing multiple antibodies directed at low-incidence antigens. Several antibodies were in all three reactive sera. After testing with her standard panel of sera containing multiple antibodies, Gail Coghlan of the Rh Laboratory suggested that this donor's RBCs might also be Rb(a+). Donor RBCs, known to be D–, Rb(a+), from a liquid nitrogen collection were then tested and found to react with the same human polyclonal anti-D reagent that reacted with AR's RBCs. Another lot number of anti-D reagent that contained serum from the same donor was also found to react with AR's RBCs and with the D–, Rb(a+) frozen RBCs.

The referring donor center in Florida was contacted to obtain more information on AR. AR indicated that she knew she was positive for the Redelberger antigen and produced the paperwork from the original study. Her mother was a sister of Richard Redelberger!

The Rb^a Antigen and Antibody Today

The Rb^a antigen was assigned to the Diego blood group system in 1996 and its ISBT symbol (number) is DI6 (010006).[3] The molecular basis for the Rb^a antigen was published by Jarolim et al. in 1997.[4] They showed that individuals whose RBCs carry the antigen have a point mutation in anion exchanger 1 that leads to the replacement of proline with leucine at amino acid 548. The antigen is expressed on cord RBCs and the effect of enzymes on the antigen is variable. The antigen deteriorates upon storage at 4°C but survives storage in liquid nitrogen.[1] Anti-Rb^a is predominantly IgM but can also be IgG.[1,3] The antibody does not bind complement and its clinical significance is doubtful.[3] Five Rb(a–) women, who gave birth to Rb(a+) children, did not make anti-Rb^a.[1,2] No other data are available.

Summary

The Rb^a antigen is of extremely low incidence and has only been discovered in three families in the world.[3] All examples of the Rb^a antigen found in the United States since 1974 can be traced back to the original propositus, Richard Redelberger, for whom the antigen is named (Fig. 1). Anti-Rb^a has been found to be a frequent, naturally occurring antibody, however, and is often found in combination with other antibodies, especially those directed to antigens of low incidence.

Addendum

The authors have been in contact with the Redelberger family in regard to the publishing of this article. While completing the article, an e-mail message was received from family member JS, a grandnephew of Richard Redelberger. The message, in part, read as follows:

> "…It made me start thinking about the bone marrow donation that I did a couple years ago. The recipient was a non-relative that matched antigens with mine. Do you think that it could mean that the recipient also has the Redelberger antigen?"

No, JS, the recipient did not have the Redelberger antigen at the time you were selected as the marrow donor. But the recipient does have the Redelberger antigen now!

Who says blood banking is boring????

Acknowledgments

We thank the family of Richard Redelberger for its enthusiastic cooperation over the years in the study of the Rb^a antigen. The Redelberger family's altruism has been demonstrated by several generations of faithful volunteer blood donors throughout the United States. Their spirit and dedication to providing the gift of life to others is a great legacy to Richard and to his mission of donor recruitment. We also want to acknowledge the

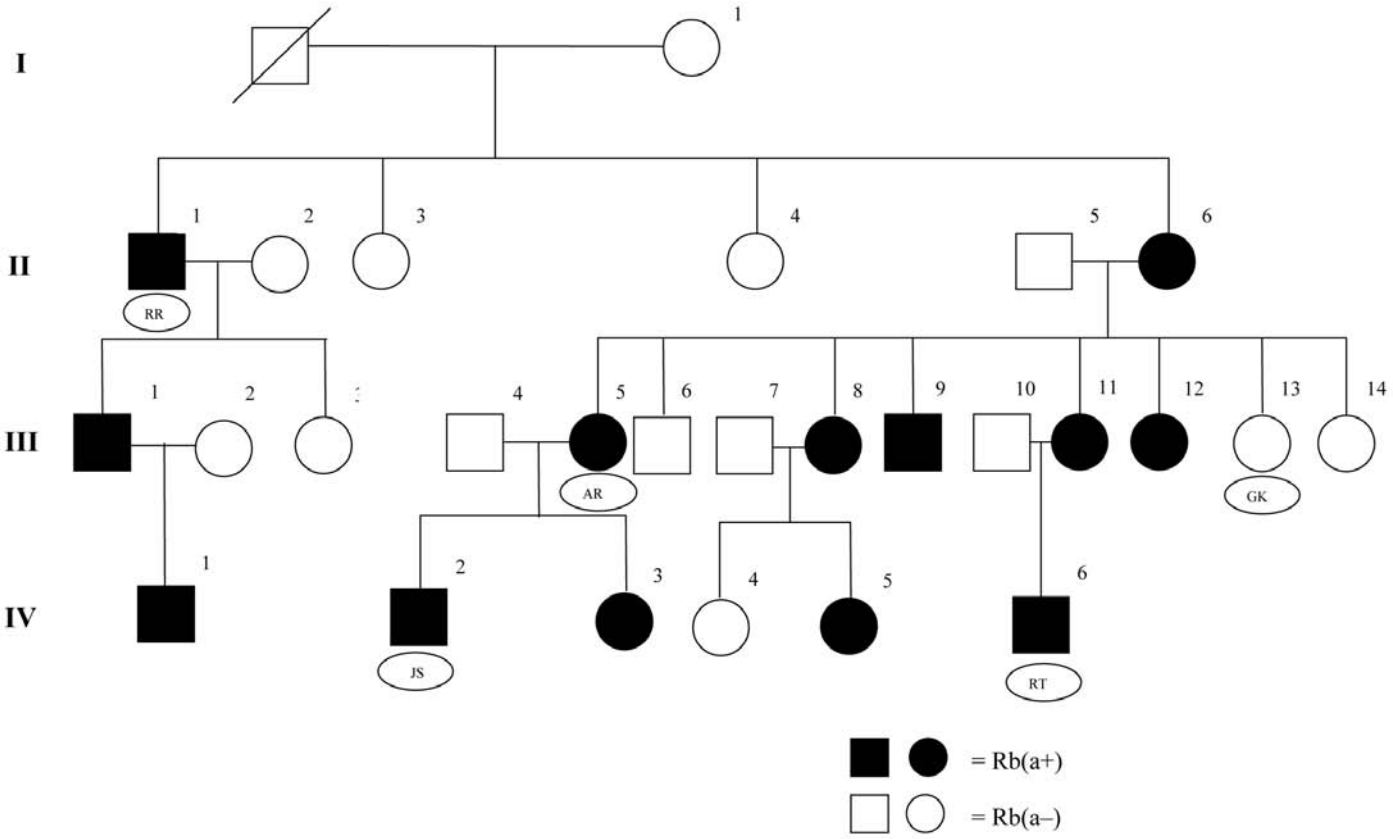

Fig. 1. Pedigree chart of the Redelberger family.

efforts of Delores Mallory and Joan Bare of the Community Blood Center in Dayton for all their hard work in the initial investigation of this "new" low-incidence antigen and for their sharing of samples with other investigators all over the world. Delores continues to keep in touch with the family even today.

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