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Does transfusion of Asian-type DEL red blood cells to D- recipients cause D alloimmunization?

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Abstract

In 2005, the late George Garratty asked readers of **TRANSFUSION**, "Do we need to be more concerned about weak D antigens?"[1] His question was prompted by his observation that "… there have been increasing numbers of reports of patients who had been transfused with donor blood having 'weak D' or undetectable D (e.g., DEL) who made anti-D." Garratty reviewed the complexity of the D antigen and its variants, case reports of anti-D after transfusion of weak D RBCs to D- recipients, and variable D typing results depending on selection of anti-D reagents. He noted that most available data were from Europe and concluded that "countries with larger Asian or African populations … need to relate to statistics in their own countries."[1] Garratty's question can be answered only when data are available for the many different scenarios in which different categories of weak D RBCs have been transfused to D- recipients. In this commentary, we address one of these scenarios, namely, the potential risk of D alloimmunization when Asian-type DEL (*RHD* DEL1*) RBCs are transfused to D- recipients in the United States. We suggest how this issue can be resolved by a focused study in pertinent communities in the United States.

HISTORICAL ASPECTS

In 1984, Okubo and colleagues[2] reported that "some D-negative red cells, though they were negative in a D^u test after exposure to anti-D, could bind anti-D and yield it on elution". They named the phenotype D_{el} (*D el*uate), which has been renamed DEL in most subsequent reports. DEL phenotypes are D variants with an exceedingly small number of D antigen sites per red blood cell (RBC).[3–5] A typical DEL RBC, for example *RHD* DEL1*, has less than 22 D antigen sites, whereas weak D phenotypes have 1000 to 4000 D antigen sites, and D+ RBCs have 9900 to 33,300 D sites.[5] Unexpectedly, case reports from Austria,[6] Japan,[7]

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CONFLICT OF INTEREST

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Korea,[8,9] China,[10] and Taiwan[11] have described D alloimmunization associated with transfusion of DEL RBCs (which routinely type as D-) to D- recipients (Table 1).

There are no studies quantifying the number of units of DEL RBCs transfused in the United States to D- recipients. A statistical model estimated that the minimum number of units of *RHD*DEL1* RBCs collected from East Asian migrants and transfused annually in the United States may be as few as 68, although the maximum could be 10 times that estimate.[12] There are no peer-reviewed published reports of transfusions of DEL RBCs causing D alloimmunization in the United States. However, there is no active posttransfusion monitoring for formation of anti-D to detect such events, if they do occur.

Thus, the "DEL issue" is that we can assume that *RHD*DEL1* and other DEL RBCs are being transfused as D- to D- recipients in the United States. However, we do not know how many DEL RBCs are actually transfused or whether they have caused D alloimmunization in susceptible transfusion recipients.

MOLECULAR AND DEMOGRAPHIC ASPECTS

More than 40 different molecularly defined DEL variants have been described.[13,14] Most reports of DEL variants have been from East Asian populations of Japan, Korea, China, and Taiwan where *RHD*DEL1* is the most prevalent allele.[12,15,16] *RHD*DEL1* was originally reported and named as *RHD*(K409K),[3] later referred to as *RHD*(1227G>A)[15] and, presently, as *RHD*DEL1* or *RHD*01EL.01* by ISBT nomenclature.[17] The *RHD*DEL1* allele is also referred to as Asian[9] or Asia[18,19] type DEL. Of the 0.5% of Japanese who are D-, 28% express *RHD*DEL1*.[12] Of the 0.3% to 0.5% of Han Chinese who are D-, 30% living in China and 32% in Taiwan, express *RHD*DEL1*.[12] Of the 0.15% of Korean who are D-, 17% express *RHD*DEL1*.[12] The D- phenotype is considerably more prevalent in Caucasians (approximately 15%), although less than 0.1% of Caucasians have been identified as expressing a DEL phenotype.[3,20] DEL alleles have been described in European Caucasians, but their prevalence is considerably lower than *RHD*DEL1* alleles in East Asians. There are no published reports of DEL RBCs in African populations.

A CLOSER LOOK AT REPORTS OF D ALLOIMMUNIZATION

The weak serologic expression of the D antigen by DEL phenotypes, reflecting the small number of D antigen sites on DEL RBCs, caused some early investigators to consider it unlikely that transfusion of DEL RBCs would cause D alloimmunization.[21,22] Nevertheless, multiple case reports of D alloimmunization after transfusion of *RHD*DEL1* RBCs collected from donors in East Asia have been reported (Table 1),[7–11] raising concern for patient safety.[23] Most of these case reports describe "secondary" alloimmunization, that is, an increase in an existing anti-D titer or detection of anti-D too quickly after the transfusion to be considered a primary immune response. The first case report claiming "primary D immunization" by DEL RBCs described an D- Korean man in whom anti-D was detected (only) 9 days after transfusion of RBCs that were retrospectively identified to be *RHD*DEL1*.[8] The short interval between transfusion and detection of anti-D raises a question whether the alloimmunization was primary or secondary. In China, a lookback

study identified 128 transfusion recipients who were D- by molecular methods who had been transfused with DEL *RHD***DEL1* RBCs.[24] None (0%) formed anti-D.[24] These case reports appear to establish that transfusions of *RHD***DEL1* RBCs to D- recipients may elicit a *secondary* immune response. If confirmed, recipients could be at risk for a delayed hemolytic or a delayed serologic transfusion reaction. However, available data are insufficient to conclude evidence-based causation of *primary* D alloimmunization. Additional monitoring and data collection are warranted.

DEL IS ASSOCIATED WITH C AND E ANTIGENS

The original report of a DEL variant by Okubo and colleagues[2] described an association with the C antigen. Subsequent reports from Japan, Taiwan, and Korea describe 100% association of the *RHD***DEL1* allele with the C antigen.[12] Five reports from China describe a similar association (100%); one report describes a 98.8% association (166/168 samples).[12] The association of *RHD***DEL1* with the E antigen in these populations varies from 0% to 38.4%.[12] Among 46,133 first-time blood donors in Germany, 11 *RHD* alleles encoded a DEL phenotype.[20] A DEL allele was detected in 47 donors of which 43 (91.5%) were associated with a C antigen and three (6.4%) were associated with an E antigen.[20] Noteworthy, one (2.1%) DEL allele occurred in a D-C–c+E–e+ phenotype,[20] an association that was not observed previously in this population.[3]

THE TRANSFUSION COMMUNITY HAS A RESPONSIBILITY TO RESOLVE THE DEL ISSUE

These case reports of *RHD***DEL1* DEL-associated D alloimmunization alert us, the transfusion community, that we have a responsibility to address the DEL issue in the United States. Although there are no reports of D alloimmunization associated with transfusion of DEL RBCs in D- recipients in the United States, there has been no routine posttransfusion monitoring for new antibodies that might have detected such events. If, unexpectedly, anti-D is detected in an D- person, it is uncommon for a lookback and a root cause analysis to be performed, although the importance of lookback in such situations is recognized among transfusion medicine specialists.[25] There is neither an AABB nor College of American Pathologists requirement to conduct a lookback when a D- transfusion recipient forms an unexpected anti-D, although many blood centers have internal policies to do so. In Australia, a study of 2017 blood donors estimated that the risk of transfusing D- females not more than 40 years of age with an *RHD***DEL1* DEL RBC unit (labeled as D-) to be one in 149,109 transfusions (range, 100,680–294,490).[26] In Germany, a study estimated that 100 potentially immunogenic units of DEL RBCs would be transfused annually to D- recipients.[20] This concern prompted the implementation of a program that molecularly screens first-time D- donors and transfers any DEL units to the D+ inventory.[20] Blood services in Denmark, Austria, and Switzerland have also avoided he risk of D alloimmunization by using *RHD* genotyping to identify and remove DEL units from the D- inventory.[26]

A FOCUSED STUDY IS FEASIBLE

In our opinion, the available evidence is not adequate for implementing a similar program nationwide in the United States at this time. Before considering how we might implement such a program, we must first resolve whether there is or is not a "DEL issue" in the United States, that is, *are* D- transfusion recipients forming anti-D—undetected—after transfusion with DEL RBCs? A study of *all* molecularly defined DEL variants would be too large to be practical. A *prospective* study would be too large and too expensive and take too many years to be feasible. A *retrospective* study of *RHD* DEL1* RBCs that had been collected from East Asian donors in the United States and transfused to D- recipients could be feasible if testing for anti-D (D alloimmunization) were limited to the relatively few transfusion recipients of a prior transfusion of *RHD* DEL1* RBCs. Such a study could be feasible if 1) current, repeat D- blood donors were screened for C antigens; 2) molecular testing for *RHD* DEL1* were limited to only D-C+ donor samples; and 3) requests for testing for anti-D were limited to D- former recipients of RBC transfusions who, retrospectively, were recognized to have been transfused with *RHD* DEL1* RBCs. Such a study would require institutional review board approval and would be most efficient if conducted in blood centers located in communities with a significant population of East Asians. Blood samples from *all* D- donors would be screened for the C antigen.

It is time to resolve the "DEL issue" in the United States. It is our responsibility, as the transfusion community, to do so. Hopefully, investigators who are located in suitable communities will recognize the responsibility, seize the opportunity and organize and develop a protocol that would answer at least one of the scenarios in Garratty's question, "Do we need to be more concerned about weak D antigens?"

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TABLE 1.

Case reports of D alloimmunization associated with transfusion of *RHD*DEL1* RBCs

Case	Reported alloimmunization	D- recipient	DEL allele	Comment	Reference
1	Secondary	Japanese female	*RHD*DEL1*	Anti-D titer 8 → 128 after transfusion	Yasuda et al.[7]
2	Secondary	Korean male	*RHD*DEL1*	Anti-D detected 9 days after transfusion	Kim et al.[8]
3	Primary	Caucasian male	*RHD*DEL1*	Anti-D detected 5–7 days after transfusion	Yang et al.[9]
4	Primary	Japanese male	*RHD*DEL1*	Anti-D detected 22 days after transfusion	Shao et al.[10]
5	Secondary	Japanese female	*RHD*DEL1*	Anti-D titer increased 8 → 64 after transfusion	Shao et al.[10]
6	Secondary	Japanese male	*RHD*DEL1*	Anti-D titer increased 8 → 64 after transfusion	Shao et al.[10]
7	Not specified	Taiwanese male	D_{el} *	Anti-C+D detected 1 month after transfusion	Chen et al.[11]
8	Not specified	Taiwanese male	D_{el} *	Anti-C+D detected 1 month after transfusion	Chen et al.[11]

* Donors' D_{el} phenotype was based on adsorption-elution and D-C+E- antigen typing.