Review

DEL phenotype

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DEL red blood cells (RBCs) type as D– by routine serologic methods and are transfused routinely, without being identified as expressing a very weak D antigen, to D– recipients. DEL RBCs are detected only by adsorption and elution of anti-D or by molecular methods. Most DEL phenotypes have been reported in population studies conducted in East Asia, although DEL phenotypes have been detected also among Caucasian individuals. Approximately 98 percent of DEL phenotypes in East Asians are associated with the *RHD*DEL1* or *RHD*01EL.01* allele. The prevalence of DEL phenotypes has been reported among D– Han Chinese (30%), Japanese (28%), and Korean (17%) populations. The prevalence of DEL phenotypes is significantly lower among D– Caucasian populations (0.1%). Among the 3–5 percent of African individuals who are D–, there are no reports of the DEL phenotype. Case reports from East Asia indicate that transfusion of DEL RBCs to D– recipients has been associated with D alloimmunization. East Asian immigrants constitute 2.1 percent of the 318.9 million persons residing in the United States, and an estimated 2.8 percent are blood donors. Using these statistics, we estimate that 68–683 units of DEL RBCs from donors of East Asian ancestry are transfused as D– annually in the United States. Given the reports from East Asia of D alloimmunization attributed to transfusion of DEL RBCs, one would expect an occasional report of D alloimmunization in the United States following transfusion of DEL RBCs to a D– recipient. If such cases do occur, the most likely reason that they are not detected is the absence of active post-transfusion monitoring for formation of anti-D. ***Immunohematology* 2017;33:125–132.**

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In 1984, Okubo and colleagues at the Osaka Red Cross Blood Center reported their observation 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."[1] They named the phenotype of these red blood cells (RBCs) Del (D eluate), adding that "most phenotypes with Del had C, c, and e antigens, but no cells of an *EE* homozygote have yet adsorbed anti-D."[2] During the subsequent 30 years, these observations have been confirmed by several investigators. The Del phenotype has been renamed DEL and is, in D– East Asians, predominantly caused by the *RHD(1227G>A)* allele, which has since been termed *RHD*DEL1* or *RHD*01EL.01* (International Society of Blood Transfusion [ISBT] terminology). This review summarizes the current status of molecular science and demographic distribution of the DEL phenotype.

Molecular Investigations of DEL Phenotypes

In 1997, investigators at the Osaka Red Cross Blood Center reported that polymerase chain reaction with sequence-specific primers (PCR-SSP) for *RHD* exons 7, 4, and 10 detected PCR products in all 102 DEL blood samples, but not in 204 non-DEL samples from D-seronegative donors.[3] Among a total of 306 D– donor samples, Fukumori and colleagues found 102 donors with the DEL phenotype associated with *CCee* (4 of 5), *CcEe* (45 of 66), and *Ccee* (53 of 86). No DEL phenotypes were detected among D– samples that were *ccee*—that is, none were C+ or E+.[3] The authors concluded that DEL RBCs have exons 4, 7, and 10 of *RHD* present in some form. In 2001, three DEL alleles were characterized in German blood donors by Wagner and coworkers.[4] One of the alleles, *RHD*(K409K) (G1227A) or *RHD*DEL1,* was soon shown to be prevalent among D– East Asians[5] and later termed "Asia type DEL" by Shao et al.[6] Also, in 2001, Singleton and colleagues described in abstract form the partial nucleotide sequences for the alleles *IVS1+1A* and *G1227A* in three Japanese donors with the DEL phenotype,[7] a terminology consistent with Human Genome Variation Society nomenclature.[8]

In 2004, J.-C. Chen and colleagues reported detection of *RHD*DEL1* in all (100%) of 94 D– Taiwanese blood donors.[9] Additional DEL variants were reported in blood donors in Germany[4] and in China.[10] The report of genomic deletion of *RHD* exon 9 by Chang et al. in 1998[11] has not been confirmed and is not considered to be an established basis for any DEL phenotype.[12] Instead, *RHD*DEL1* is the result of a single nucleotide polymorphism in a splice-site on exon 9 that leads to reduced D antigenic density, but may retain the intact D protein.[12] This mechanism has been well studied for *RHD*DEL1,* in which a "silent" 1227G>A substitution in *RHD* codon 409 is immediately adjacent to the exon 9/intron 9 boundary.[13] To emphasize the structural basis of the (unchanged) protein, a novelty at the time, this allele was originally called *RHD*(K409K).[4] Later, the term *RHD*(1227G>A), based on the allele's nucleotide structure, became more widely used[13] and, presently, updated to *RHD*DEL1* by ISBT nomenclature.

To date, investigators have identified more than 40 alleles that are associated with a DEL phenotype.[14] The *RHD*DEL1* allele,[4] which accounts for up to 98 percent of DEL phenotypes

in East Asians,[15,16] is the most prevalent variant *RHD* allele in the D– East Asian population. For consistency, we will use *RHD*DEL1* for the "Asia type DEL" allele for the remainder of this review.

DEL Phenotype in East Asian Populations

The *RHD*DEL1,* or as in the original report, *RHD(K409K),* allele[4] is the most prevalent variant *RHD* allele in D– East Asian populations,[5] and *RHD*DEL2* (*RHD 3G>A*) was thought to be the second most common DEL allele, at least in Chinese populations.[17] Ji and van der Schoot observed that *RHD*DEL1* was the most common DEL allele among D– Han Chinese in the southern region of China.[18] The prevalence of DEL phenotypes among the 0.3–0.5 percent of Han Chinese who are D–[19,20] is 30 percent for native Chinese[15] and 32 percent for those living in Taiwan.[9] Among Japanese, 0.5 percent are D–,[2] and of these, 28 percent express a DEL phenotype.[21] In Korean populations, 0.15 percent are D–, and of these, 17 percent express a DEL phenotype.[12,22,23] The prevalence of DEL phenotypes is significantly lower in Caucasian populations, of whom approximately 15 percent are D– and only 0.1 percent of these express a DEL phenotype.[24] Among the 3–5 percent of African populations who are D–,[25] there are no reports of DEL phenotypes, but few population studies have been conducted.

DEL Phenotype in Caucasian Populations

More than 40 DEL alleles are currently listed in the human RhesusBase,[14] and all belong in the Eurasian D cluster.[26] Most of these DEL alleles have been reported as individual cases in Caucasian populations. Except for *RHD*DEL1,* all DEL alleles are rare in any population, particularly in Caucasian and African populations. The cumulative prevalence of all DEL phenotypes that are associated with DEL alleles, other than *RHD*DEL1,* is small in any population when compared with the prevalence of DEL phenotypes associated with *RHD*DEL1* in East Asian populations. Although other rare DEL alleles add to the risk of D alloimmunization, we conclude that the overall risk of D alloimmunization in the United States is defined by the prevalence of *RHD*DEL1*.

Transfusion of DEL RBCs to D– Recipients Has Been Associated with Secondary D Alloimmunization and May Be Associated with Primary D Alloimmunization

Recognizing the very weak serologic expression of D by DEL phenotype RBCs, early investigators considered it unlikely that RBCs expressing a DEL phenotype would elicit D alloimmunization.[27] Subsequently, cases of D alloimmunization by DEL RBCs have been reported. In 2005, T. Wagner et al. proposed D alloimmunization in a D– female patient after she had been transfused with RBCs from an Austrian donor who tested D– and weak D test negative by serologic methods.[28] The authors identified a deletion in the donor's *RHD* that they described as *"RHD* IVS5-38del4" and linked it to expression of the DEL phenotype.[28] Subsequent studies determined that the deletion IVS5-38del4 does not cause a DEL phenotype and is common in European and Asian populations.[29] The cause of a DEL phenotype in the implicated Austrian blood donor remains unknown, and the deletion presently designated as *RHD*(IVS5-38del4) is thought to be unrelated.[29]

In 2005, Yasuda et al. described a D– Japanese woman who developed a secondary D alloimmunization after transfusion with 2 units of RBCs that were subsequently determined to be from Japanese donors with the *RHD*DEL1* allele.[30] In 2009, K. Kim et al. described a D– Korean man who developed anti-D 9 days after transfusion with 1 unit of RBCs that was subsequently determined to express the *RHD*DEL1* allele.[23]

In 2012, Shao et al. described one case of primary immune response and two cases of secondary immune responses in a total of 11 recipients in central China who had been transfused with RBCs from DEL phenotype donors with the *RHD*DEL1* allele.[15] This study of 11 recipients included seven pre-transfusion anti-D–negative patients, who were at risk for a primary immune response following transfusion of DEL RBCs, and four pre-transfusion anti-D–positive patients. One of the seven at-risk recipients, who tested negative for anti-D on admission and had no transfusion history, was transfused twice with DEL RBCs. On day 22 after the first transfusion, he formed anti-D (titer 2), which the authors interpreted to be "characteristic of primary anti-D alloimmunization." Two of the four anti-D–positive recipients demonstrated a 50 percent increase in anti-D titer after the transfusion, describing secondary immune response. The authors concluded "that blood centers and blood banks need to identify the presence of the DEL variant in apparent D-negative donors and recipients. A truly D-negative recipient should not receive DEL

transfusion in an effort to protect him or her from primary alloimmunization or severe DHTR."[15]

In 2015, H.S. Yang et al. reported detection of anti-D between days 5 and 7 after transfusion of 2 units of RBCs from Korean donors to a Caucasian male patient.[16] Retrospective studies of RBCs from the Korean donors confirmed that the donors' RBCs tested as D– by serologic anti-D and weak D testing. *RHD* genotyping identified the *RHD*DEL1* allele in both donors.[16] The short time interval between transfusions and detection of anti-D in the recipient suggests that these events were more likely secondary immune responses.

Transfusion Recipients with a DEL Phenotype and an *RHD*DEL1* Allele Are Not at Risk of Forming Anti-D Following Transfusion of D+ RBCs

In 2005, Körmöczi and colleagues proposed that the absence of D alloimmunization by transfusion recipients with a DEL phenotype following transfusion of D+ RBCs was explained by serologic studies showing that the *RHD*DEL1* allele expresses a complete repertoire of D epitopes.[31] In 2006, Flegel suggested that East Asians expressing a DEL phenotype and carrying the *RHD*DEL1* allele might not form anti-D after exposure to D+ RBCs.[32] The extremely weak expression of D by serologic testing is caused by significantly fewer D antigen sites per RBC (<22) compared with normal RBCs (*CcDdee* with 10,429) and weak D phenotypes (922).[31] In 2014, Q.P. Wang et al. conducted a retrospective study of 227 D– transfusion recipients in southeast China who had been transfused with RBCs, presumably some of which were D+.[33] Eleven recipients developed anti-D. None of the transfusion recipients with anti-D had a DEL phenotype associated with the *RHD*DEL1* allele. The time interval between transfusions and testing for anti-D was not specified. Wang et al. concluded that "people in East Asian populations who carry Del variants can safely receive transfusions from RhD-positive donors. Our findings would apply to East Asian transfusion recipients in Europe, North America, and elsewhere and could be implemented easily when genetic crossmatching becomes a reality."[33]

Pregnant Women with a DEL Phenotype Who Delivered a D+ Newborn Did Not Form Anti-D, But Pregnant Women with Certain Partial or Hybrid DEL Alleles Have Formed Anti-D

In 2010, Shao et al. reported a retrospective study of 104 D– pregnant Chinese women who formed anti-D after delivery.[10] Based on the prevalence of DEL phenotypes in the local Han Chinese population, these investigators anticipated that 30 percent of the women who formed anti-D would have a DEL phenotype, but none did (0%).[10] In the same report, Shao et al. described a prospective study of 44 pregnant women with the DEL phenotype who did not receive Rh immune globulin (RhIG) immunoprophylaxis and did not form anti-D. During the 2-year study period, 38 of 155 (24.5%) D– (*dccee*) mothers formed anti-D. The authors concluded that women with *RHD*DEL1* do not appear to be at risk of alloimmunization to the D antigen and "DEL recipients can be transfused safely with Rh-positive blood."[10] The authors also concluded that RhIG prophylaxis is unnecessary (in women with an *RHD*DEL1* allele).[10]

In 2014, Q.P. Wang et al. studied D alloimmunization in 416 D– pregnant women. Anti-D was detected in 61 of these 416 D– pregnant women (14.66%) and in 11 of 227 D– transfusion recipients (4.85%). None of the 72 D– pregnant women or transfusion recipients with anti-D had a DEL phenotype. The time interval from delivery to follow-up was not reported. The authors concluded that antenatal and postpartum Rh immunoprophylaxis with RhIG was unnecessary in pregnant women with a DEL phenotype.[33] In 2015, M. Wang et al. described the outcome of 142 pregnant Han Chinese women with a DEL phenotype who delivered a D+ newborn.[34] None of 130 women (0%) with a DEL phenotype caused by *RHD*DEL1* formed anti-D. There were six women with a DEL phenotype who formed anti-D after delivery. All six of these women had a DEL phenotype associated with *RHD-CE-D* hybrid alleles[34] encoded by *RHD* exons replaced by counterparts from *RHCE* genes, with a resultant loss of one or more D epitopes.[4] The authors cite the proposal by Körmöczi and colleagues[31] for defining partial DEL phenotypes by drawing an analogy with the definition for partial D variant antigens (i.e., an *RHD/RHCE* gene recombination event that affects exofacial D sections and loss of one or more D epitopes). Thus, M. Wang et al. refer to DEL antigens resulting from these recombinations as partial DEL phenotypes and concluded that "individuals with a partial DEL phenotype should be treated as RhD-negative...and receive only RhD-negative RBCs." Also, "pregnant women [with a partial DEL phenotype] should be administered antenatal and postpartum anti-D prophylaxis, whereas patients with a complete DEL type can safely receive RhD-positive blood...and do not need RhD immunoglobulin prophylaxis."[34]

In 2015, Xu et al. reported the outcomes of 168 pregnant Chinese women with a DEL phenotype of the *RHD*DEL1* allele and 8 women with the *RHD*(3G>A) allele who delivered a D+ newborn.[35] None developed anti-D. Two pregnant women with a DEL phenotype and the *RHD-CE(4-9)-D* or *RHD-*

CE(2-5)-D allele did form anti-D; one was associated with mild hemolytic disease of the fetus and newborn (HDFN). The authors concluded that the observation of anti-D in the two women with absent D epitopes confirms that their RBCs express partial DEL phenotypes and pregnant women with these alleles are at risk for forming anti-D.[35]

Within Caucasian populations, there are DEL phenotypes arising from changes at the intron exon splice boundaries;[4] at least one of these has been associated with anti-D and another has been associated with mild HDFN.[36]

DEL Phenotype Is Associated with the C Blood Group Antigen

The association of the DEL phenotype and the C antigen, first described by Okubo et al. in 1984,[1] has been confirmed by subsequent studies and provides a promising strategy for a low-cost, efficient method to screen large numbers of donors for DEL phenotypes. RBCs from as many as 18 percent of D– Japanese donors express C,[21] whereas only 1 in 1818 (0.055%) RBCs from D– Caucasian donors express C.[4] A 6-year study of D– European individuals demonstrated that the prevalence of the DEL phenotype is much higher among D– blood donors whose RBCs express C and/or E, concluding that the DEL phenotype was associated with a *Cde* or *cdE* haplotype.[14] The longstanding observations that the presence of *Ce* in *cis* with a variant *RHD* allele had a suppressive effect resulting in a DEL-like phenotype further strengthens the apparent relationship between C and the DEL phenotype.[1] D– East Asian populations have a high association of *RHD*DEL1* with C (99–100%), as originally observed among five individuals,[4] because *RHD*DEL1* is linked to an *RHCE*Ce* allele in one haplotype (in *cis* configuration on one chromosome).

The association with the E antigen (i.e., an *RHCE*cE* allele in *trans*) shows considerable ethnic variability. The association with E in Chinese and Taiwanese individuals is 3.7 and 2.6 percent, respectively, whereas the association in Korean and Japanese individuals is 28.6 and 38.4 percent, respectively (Table 1). This variation in linkage has resulted in different proposals for managing clinical aspects of the DEL phenotype. Y.H. Wang et al. proposed screening for the DEL phenotype by testing RBCs from apparent D– donors for C, followed by genotyping for *RHD*DEL1*.[37] Seo et al. demonstrated that RBCs testing negative for C and E by serology safely predicts

Table 1. *RHCE* predicted genotypes in East Asians associated with the *RHD*DEL1* allele

		Number of individuals								Association with *Cc* or *CC* (%)	Association with *Ee* or *EE* (%)
Reference	Country	*Ccee*	*CCee*	*CeEe*	*CCEe*	*ccEe*	*CcEE*	*ccEE*	*ccee*		
J.-C. Chen et al. (2004)[9]	Taiwan *N* = 94	78	14	1	1	0	NA	NA	NA	100	2.6
Luettringhaus et al. (2006)[12]	Korea *N* = 16	15	NA	1	NA	NA	NA	NA	NA	100	6.3
Q.P. Wang et al. (2014)[33]	China *N* = 151	85	66	NA	NA	NA	NA	NA	NA	100	0
Xu et al. (2015)[35]	China *N* = 168	150	10	2	4	2	NA	NA	NA	98.8	4.8
Y.H. Wang et al. (2005)[37]	China *N* = 126	105	18	2	1	NA	NA	NA	NA	100	2.4
Seo et al. (2016)[38]	Korea *N* = 14	7	3	4	NA	NA	NA	NA	NA	100	28.6
Ogasawara et al. (2015)[39]	Japan *N* = 318	166	30	121	1	NA	NA	NA	NA	100	38.4
Gu et al. (2014)[40]	China *N* = 37	32	3	1	1	NA	NA	NA	NA	100	5.4
Q. Li et al. (2008)[41]	Chinese minority *N* = 14	12	1	1	NA	NA	NA	NA	NA	100	7.1
J.J. Wu et al. (2006)[42]	China *N* = 41	32	8	1	NA	NA	NA	NA	NA	100	2.4
Total	(*N* = 979)	682	153	134	8	2	0	0	0		
	(%)	69.7	15.6	13.7	0.8	0.2	0	0	0		

NA = not applicable.

true D– RBCs (100% positive predictive value) (*N* = 4407), and RBCs testing negative by anti-D, but testing C+ and/or E+ by serology, can be tested for DEL by *RHD* genotyping, including promoter, intron 4, exon 7, and exon 10.[38] In 1984, Okubo et al. considered the possibility that the specificity of the antibody formed by D– individuals exposed to D–, C+ RBCs could be anti-G. They excluded anti-G, confirming the serologic anti-D specificity using r^G-reagent RBCs.[1] In 2005, Yasuda and colleagues also considered the possibility that the specificity of the antibody formed when D– individuals were exposed to DEL RBCs that were D–, C+ could be anti-G.[30] They excluded anti-G and confirmed anti-D specificity by adsorption and elution studies.

Potential Risk of D Alloimmunization by Transfusion of DEL RBCs with an *RHD*DEL1* Allele in the United States

There are inadequate data on the number of East Asian and other blood donors in the United States for an accurate calculation of the risk of D alloimmunization in D– recipients who are transfused, unknowingly, with DEL RBCs. There are data, however, that make it possible to calculate a reasonable range (maximum and minimum estimates). East Asians constitute 2.2 percent of 318.9 million people residing in the United States (4.01 million Chinese, 1.71 million Korean, and 1.3 million Japanese).[43] The prevalence of D– phenotypes in East Asians ranges from 0.1 to 0.5 percent,[1,10,27] although the genotypic prevalence may be increased to 1 percent if mixed ethnic populations in the United Stated are considered. The percent of DEL phenotypes among D– East Asians is approximately 17.7 percent based on population surveys (Table 2; 2047 individuals with the *RHD*DEL1* allele among 11,592 D– individuals surveyed translates to a prevalence of 17.7%). According to a multi-institution 10-year study, 2.8 percent of blood donors were Asians on average.[48] Using these data, we estimate that 68–683 units of "Asian-type" (RHD*DEL1)-DEL RBCs are transfused annually in the United States (Table 3). Yazer et al. emphasized the importance of minority donor recruitment and collection programs to maintain an adequate blood supply in response to the diversity of the U.S. population.[48,49]

Table 2. *RHD*DEL1* allele in serologic D– East Asian populations

Reference	Country	Subjects (*N*)	Subject type	RHD(1227G>A) *n* (%)
J.-C. Chen et al. (2004)[9]	Taiwan	294	Blood donor	94 (32.0)
Luettringhaus et al. (2006)[12]	Korea	126	Blood donor	16 (12.7)
Q. Li et al. (2009)[17]	China	1585	Blood donor	268 (16.9)
Y.E. Yang et al. (2007)[20]	Han Chinese living in Taiwan	294	Blood donor	108 (36.7)
Y.J. Kim et al. (2005)[22]	Korea	264	Blood donor	43 (16.3)
Yasuda et al. (2005)[30]	Japan	57	Blood donor	2 (3.5)
Q.P. Wang et al. (2014)[33]	China	643 (*n* = 416) (*n* = 227)	 Pregnant woman Blood recipient	151 (23.5)
Xu et al. (2015)[35]	China	808	Pregnant woman	168 (20.8)
Y.H. Wang et al. (2005)[37]	China	395	Blood donor	126 (31.9)
Seo et al. (2016)[38]	Korea	110	Blood donor	14 (12.7)
Ogasawara et al. (2015)[39]	Japan	3526	Blood donor	318 (9.0)
Gu et al. (2014)[40]	China	165	Blood donor	37 (22.4)
Q. Li et al. (2008)[41]	Chinese minority	150	Blood donor	14 (9.3)
J.J. Wu et al. (2006)[42]	China	143	Blood donor	41 (28.7)
X. Wu et al. (2014)[44]	China	2385	Blood donor	516 (21.6)
J.H. Li et al. (2012)[45]	China	374	Blood donor	61 (16.3)
Q. Chen et al. (2012)[46]	China	155	Blood donor	32 (20.6)
Sun et al. (2008)[47]	Taiwan	118	Blood donor	38 (32.2)
Total		11,592		2047 (17.7)

Table 3. Estimated number of RBC units with the *RHD*DEL1* allele transfused per year in the United States

	Calculation				
	RBC units transfused per year (*N*)	Asians in the U.S. (2.8% of the donor population)	Prevalence of D– phenotype in East Asians (0.1–1%)	Prevalence of *RHD*DEL1* allele in D– East Asians (17.7%)	RBC units with DEL phenotype (*N*)
Estimate					
Minimum	13,785,000	× 0.028	× 0.001	× 0.177	68
Maximum	13,785,000	× 0.028	× 0.01	× 0.177	683

RBC = red blood cell.

Discussion

Considering the number of DEL RBCs that are transfused in the United States annually, one may ask, "Where are these transfusion recipients with D alloimmunization in the United States?" and "Why has DEL-related D alloimmunization been reported only in East Asia, but not in the United States and elsewhere?" The same questions can be asked about any infrequent outcome of blood transfusion for which there is no active monitoring. Without active and timely follow-up for formation of anti-D by D– transfusion recipients, it is not possible to determine the true risk of D alloimmunization.[50] DEL-related D alloimmunization is another example of an infrequent, but potentially adverse, outcome of blood transfusion that is not recognized because it is not actively monitored.

One option for addressing the potential risk that DEL RBCs may pose to D– transfusion recipients in the United States would be to initiate active post-transfusion monitoring for formation of anti-D. The intent would be to identify the incidence of D alloimmunization by documenting the number of DEL units of RBCs transfused in the United States and the number of D– patients who form anti-D after an RBC transfusion. Such an approach, however, would result in continued exposure of D– women and others to the risks of D alloimmunization. The delay in addressing measures to prevent transfusion of DEL phenotype RBCs to D– recipients should raise ethical questions.

An alternative and more timely resolution would be to follow the model of the German Red Cross Blood Donor Service in Baden-Württemberg-Hessen and begin testing donated blood to exclude RBC units with a DEL phenotype in one or more blood centers in communities with a sizeable East Asian population.[12] Beginning in 2002, blood samples from serologically D– first-time blood donors in Baden-Württemberg-Hessen were tested by *RHD* PCR in pools of 20. Samples detected to contain *RHD* were further tested by PCR and nucleotide sequencing to identify the specific *RHD* allele. That program cost approximately $5 per first-time D– donor, or $0.08 per unit of whole blood.[24] Similar approaches are routine at the National Institutes of Health Blood Bank in the Department of Transfusion Medicine since 2009 and at the Swiss Red Cross Blood Service since 2013. Alternatively, the cost of identifying most Asian-type DEL units could be reduced by serologic screening of D– units for C and, possibly, E. This approach is based on the finding that DEL phenotypes occur when linked to the *Ce* allele or, less frequently, if at all, to the *cE* allele. This screening could be performed by PCR, or even less expensively, by testing with anti-C and, possibly, anti-E using an automated blood typing analyzer. In all scenarios, units of D– RBCs detected to contain an *RHD* allele, or a C or E antigen, would be added to the D+ inventory. In 2005, Garratty noted that the DEL phenotype was usually associated with D–, C+ phenotypes and questioned whether we need to be more concerned about weak D antigens.[51] In 2008, Denomme and Flegel identified numerous opportunities for integrating advances in molecular immunohematology, including screening for low-copy number of D antigens (e.g., weak D or DEL) into routine transfusion practice.[52]

Considering the multiple case reports of DEL-related D alloimmunization in Asian countries, and recognizing the significant number of blood donors of Asian descent in the United States, it is imperative to analyze the risk of transfusing DEL RBCs to D– recipients in the United States. If there is a confirmed risk, it is critical to develop a timely strategy to reduce the risk to D– transfusion recipients and, most urgently, to all female patients of child-bearing potential.

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views expressed do not necessarily represent the view of the National Institutes of Health, the Department of Health and Human Services, or the U.S. Federal Government.

Conflict of Interest

DHK and SGS declare having no conflicts of interest relevant to this article. WAF receives royalties for *RHD* genotyping.

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