Review Article

Molecular genetics of the Rh blood group system: alleles and antibodies—a narrative review

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Objective: This work proposes a review of the antibodies which have been associated with variant *RHD* and *RHCE* alleles, except null alleles.

Background: The data on this topic is dispersed in the literature.

Methods: A review of the articles referenced in PubMed and of abstract books from major conferences was performed. Most antibodies have been published in full-length articles, and several more have been reported in conference abstracts. The anti-D antibodies reported in carriers of D variants and the antibodies to CE antigens reported in carriers of CE variants were listed, including antibodies to low prevalence antigens. The *RHCE* alleles for which the RH10 (V) and RH20 (VS) phenotypes have been reported were also collected. The reports of antibody formation were compared to the prevalence evaluated by the Erythrogene database in the 1000 Genomes dataset.

Conclusions: It is noted in this review that studies reporting anti-D or antibodies to CE antigens associated with Rh variants only rarely include detailed serological descriptions of the findings. This review lists several alleles which are not exceptional, and for which no carrier has been reported to form the antibody to the expressed antigen(s) (e.g., no allo-anti-D has been reported so far in carriers of *RHD*01EL.01*, c.1227A). Considering the antibody reports in carriers or absence thereof and the prevalence for each *RH* allele, it may become possible to propose case-by-case recommendations for more *RH* alleles in the near future.

Keywords: RH blood group system; immunogenomics; alloimmunization; variant RH antigens; partial RH antigens

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Introduction

Nearly a century after the first publications which would lead to the recognition of the Rh blood group system (1,2), and 40 years after the molecular basis of the Rh antigens (Ag) were discovered (3,4), 55 Rh Ag, over 400 *RHD* and over 150 *RHCE* alleles are recognized by the International Society of Blood Transfusion (ISBT) (5). Many more alleles can be found in the Genbank database (6), published articles and conference abstracts. The Human RhesusBase inventories over 600 *RHD* alleles (7), and the recent RHeference database, over 700 (8). Which alleles to detect and how to manage allele carriers are recurring questions for immunohematologists.

There are 5 conventional alleles in the Rh system: *RHD*01* (standard *RHD*) for the *RHD* gene, *RHCE*01 (RHCE*ce)*, *RHCE*02 (RHCE*Ce)*, *RHCE*03 (RHCE*cE)* and *RHCE*04 (RHCE*CE)* for the *RHCE* gene (9). *RHD*01* and *RHCE*01* are considered to be the reference sequences for the *RHD* and *RHCE* genes, respectively. The reference sequences have only recently been updated in RefSeq (10)

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to reflect this (NG_007494.1 for *RHD* and NG_009208.3 for *RHCE*). Formerly, RefSeq listed the *RHD*10.00* (*RHD*DAU0*) and *RHCE*01.01* (*RHCE*ce48G*) alleles. The broad term "Rh variants" (11,12) is commonly used to designate the products of alleles in the Rh blood group system differing from the conventional.

The allele repartition in different populations is far from homogeneous. Erythrogene database (13) presents an interesting overview through the analysis of blood group systems, including Rh, from the 1000 Genomes project. This approach has limitations, e.g., none of the *RHCE*02* (*RHCE*Ce*) alleles were assigned a prevalence, probably because of the sequence identity between exon 2 of *RHD*01* (conventional *RHD*) and *RHCE*02*. Some genetic variations are associated as if constituting an allele but could be explained by the association of two alleles, e.g., *RHD* c.186G>T, c.410C>T, c.455A>C, c.1048G>C and c.1136C>T are associated with a 0.91% prevalence in Africans, but do not constitute a known *RHD* allele, whereas the variations could be explained at the heterozygous state by the association of two alleles *RHD*10.00* (*RHD*DAU0*, with the single substitution c.1136C>T) and *RHD*04.01* (*RHD*DIVa*, associating c.186G>T, c.410C>T, c.455A>C and c.1048G>C), alleles common in Africans (37.75% and 1.06%, respectively, according to Erythrogene).

The clinical significance of blood group alleles and Rh variants is not easy to establish, for several reasons. Locating the reports in the vast literature is a tedious task. Individual variability to alloimmunization remains poorly understood (14,15), and most available evidence amount to case reports of antibody (Ab) formation, transfusion reactions, or hemolytic disease of the fetus and the newborn (HDFN). As the reports are real-life data, they are often incomplete, particularly regarding serology. Whether the Ab is an allo- or auto-Ab and the imputability of an Ab in a hemolytic reaction may be difficult to ascertain (16,17). The most robust way to demonstrate that an Ab is an allo-Ab is to show that it cannot be auto-adsorbed with the patient's own red blood cells (RBCs) (18). However, auto-adsorptions cannot be performed in a recently transfused patient and may be inconclusive for very weakly expressed Ag.

Several definitions have been proposed for "partial" Rh Ag (12). In this work, we will use the term as a synonym for "at risk for Ab formation to the corresponding Rh Ag" (i.e., a partial D is at risk for allo-anti-D if exposed to the standard D Ag). Ab formation to the corresponding Ag is theoretically impossible in a heterozygous individual, because no epitopes of the Ag would be missing (i.e., a carrier of a conventional D Ag and a partial D variant has all D epitopes thanks to their conventional D; a carrier of a conventional C and a partial C variant has all C epitopes, etc.). Genotyping has become key to detect variants in the Rh system and resolve difficulties in laboratories, as serology cannot reliably distinguish all the subtleties of the Rh system (12,19,20).

One of two main conducts are adopted by most transfusion specialists for the management of Rh variants in recipients. The first could be called a "preventive" attitude and consists in avoiding the exposure of carriers of partial Rh variants to the standard Ag, to prevent alloimmunization [in women of childbearing age and certain types of patients, e.g., with sickle cell disease (SCD)]. The second could be called a "palliative" attitude and consists in taking measures only when a patient has produced the Ab. Most countries recommend the preventive approach for variants at a high risk for Ab formation. Several countries recommend the preventive approach for Rh variants for which the risk for Ab formation is unknown. The choice between the preventive and palliative may be made on a case-by-case basis for each variant and this requires easily accessing the available evidence for Ab formation. The choice will also depend on the allele prevalence in the country or region, the alloimmunization risk that carriers face, the availability of anti-D immunoglobulins and of RBC units of different phenotypes, e.g., in a country where partial D variants and D negative RBC units are rare, the attitude will probably be different than in a country where partial D variants are common and D negative units are more readily available.

The present review gathers the current published evidence regarding allo-Ab formation associated with *RHD* and *RHCE* alleles. Null alleles are not discussed, as, by definition, they do not express the Ag and carriers are consequently able to form Ab when exposed to the Ag, e.g., individuals with *RHD* null alleles are at risk for anti-D as much as homozygous *RHD*01N.01* (*RHD* deletion) individuals are.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aob-20-84).

RHD alleles

The earliest reports of anti-D in D positive patients have been associated with variant D phenotypes. The DVI phenotype and *RHD**06 (*RHD*DVI*) alleles have been responsible for many anti-D alloimmunizations with severe consequences

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(7,21-23). This has given rise to recommendations for reagent selection, adopted by many countries, so that *RHD*06* carriers are typed as D negative and are managed as such (24,25). Patients with the DFR phenotype, attributed to *RHD*17* (*RHD*DFR*) alleles, have also made allo-anti-D (26-28). Many *RHD* alleles, listed in *Table 1*, have since been associated with anti-D formation in carriers of these alleles, in the absence of conventional *RHD*01*.

A few common *RHD* alleles have a somewhat controversial status regarding anti-D formation risk, such as *RHD*10.01* (*RHD*DAU0*) (29,37,41,58,63,76,79,104,105), *RHD*09.03* (*RHD*weak D type 4.0*) and *RHD*09.04* (*RHD*weak D type 4.1*) (76,79,106-108). Both auto- and allo-anti-D have been reported in carriers. Several studies in populations with a high prevalence for these alleles have reported no anti-D in carriers, with the inherent limits of retrospective studies (50,109,110). None of the allo-anti-D descriptions were able to demonstrate that the anti-D could not be auto-absorbed on the carrier's own RBCs (104,111). Nevertheless, the incidence of presumed allo-anti-D is very low compared to the alleles' prevalence. Erythrogene (13) reports *RHD*09.03* as being present in 1.21% in Africa, and reports a very high prevalence for *RHD**10.01 in all populations assessed (Africa: 37.75%; America: 12.54%; East Asia: 8.83%; Europe: 4.47%; South Asia: 12.68%).

Many rare *RHD* alleles, not listed in *Table 1*, have been associated with anti-D formation at least once in published articles, including *RHD*02* (*RHD*DII*) (112,113), *RHD*19* (*RHD*DHMi*) (7,21,114), *RHD*27* (*RHD*DDE*) (7,21), *RHD*33* (*RHD*DWI*) (115), *RHD*38* (*RHD*DNT*) (7,21), *RHD*39* (*RHD*307C*) (80), *RHD**47 (*RHD*DMI*) (7,21,54), *RHD*50* (*RHD*1060A*) (116), *RHD*weak D type 57* (*RHD*01W.57*) (73), *RHD*710T* {provisional name: [7] *RHD*01W.155*} (55). Some have been associated with anti-D formation in abstract form, including: *RHD*03.02* (*RHD*DIIIb Caucasian*) (117), *RHD*03.08* (*RHD*DIII type 8*) (118), *RHD*24* (*RHD*DNAK*) (119), *RHD*48* (*RHD*DNS*) (120), *RHD*01*W.33 (*RHD*weak D type 33*) (121,122), as well as several alleles not yet listed by ISBT: *RHD*95A* (123), *RHD*325G* (124), *RHD*470G* (125), *RHD*455C,968A* (118), *RHD*1048C* (65).

A few cases of allo-anti-D have been reported in abstract form for *RHD*01W.1* (*RHD*weak D type 1*) (126), *RHD*01W.2* (*RHD*weak D type 2*) (127) and *RHD*01W.3* (*RHD*weak D type 3*) (128,129), but these reports are extremely rare compared to the number of carriers and the consensus is that these alleles should be considered to produce normal D antigen (104).

As underlined recently (130), the alleles *RHD*01W.33* and *RHD*01W.45* have quite a high prevalence: in America (0.14%) for the former, and in America and Europe (0.29% and 0.20%, respectively) for the latter (13). Very rare anti-D have been reported in carriers of these alleles (69,121,122), which may reveal a very low anti-D formation risk, perhaps comparable to that of *RHD*01W.1*, *RHD*01W.2* and *RHD*01W.3*. The paucity of anti-D reports may also be biased by the genotyping strategies in place and by the difficulty to present or publish case reports for such data.

Next to *RHD*01W.1*, *RHD*01W.2*, and *RHD*01W.3*, the most important *RHD* allele for which no allo-anti-D has ever been reported despite a large number of carriers is *RHD*01EL.01* (*RHD*1227A*). Erythrogene reports *RHD*01EL.01* with: America 0.29%, East Asia 0.69% and Europe 0.10%. Erythrogene also reports *RHD*01EL.36*, which differs from the first by c.1073+152C>A only (a genetic variation reported in all populations and also found with other genetic variants) (13) with: Africa 1.13%, America 0.14%, East Asia 0.20%, Europe 0.60%, South Asia 1.94%. Several studies support the absence of anti-D formation risk in carriers of this allele (131-133), but others urge caution and recommend waiting for the results of an ongoing prospective study on the matter (134).

Table 2 lists other *RHD* alleles frequently reported in immunohematology studies, reported in a large number of carriers, or associated with a prevalence in Erythrogene (13), and for which no anti-D has been reported. In the absence of prospective studies following Ab formation in a large number of carriers, it may be premature to definitely rule out any anti-D formation risk in these alleles. This is particularly true for alleles which tend to type as D negative, as carriers are less likely to be exposed to D positive RBC units (see *Table 2*), and molecular analysis is less likely to be performed in an apparently D negative patient with anti-D.

Some *RHD* alleles produce low prevalence Ag which may be responsible for Ab formation in an individual exposed to the Ag. *Table 3* lists reports of such alloimmunization, including many with severe hemolytic consequences in pregnancy.

RBCs carrying variants in the Rh system can also induce Ab formation in recipients negative for the corresponding Ag. There are comparatively few reports, mainly of D variants with a DEL (226) or very weak D phenotype (any variant with a stronger reactivity is of course capable of inducing Ab formation in carriers). Cases of primary alloimmunization, including *RHD*01EL.01* (227,228), *RHD*01W.1* (229), *RHD*01W.67* (230) and cases of anti-D reactivation, including *RHD*01EL.01* (231), *RHD*01W.26* (81) have been reported.

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Table 1 *RHD* alleles associated with anti-D formation in carriers of these alleles, according to the current literature

Common name, ISBT numerical (name based on nucleotide changes)	References of the anti-D	Prevalence (Erythrogene) (13)	Reports† (RHeference) (8)
*RHD*DIIIa, RHD*03.01 (RHD*186T,410T,455C,602G,667G,819A)*	(29-31)	Africa: 0.76%	(29-35)
*RHD*DIIIc, RHD*03.03 (RHD*361A,380C,383G,455C)*	(7,21,36)	–	(36-38)
*RHD*DIII type 4, RHD*03.04 (RHD*186T,410T,455C)*	(7,37)	Africa: 0.76%; America: 0.14%	(21,37-40)
*RHD*DIVa, RHD*04.01 (RHD*186T,410T,455C,1048C)*	(7,16,21,29,41)	Africa: 1.06%; America: 0.29%	(21,29,33,34,42)
*RHD*DV type 2, RHD*05.02 (RHD*D-CE(5)-D)*	(7,21)	–	(43-46)
*RHD*DV type 7, RHD*05.07 (RHD*D-CE(5:667-5:787)-D)*	(7,21)	–	(47,48)
*RHD*DVII, RHD*07.01 (RHD*329C)*	(7,21,49)	Europe: 0.30%; South Asia: 0.10%	(37,48-53)
*RHD*DFV, RHD*08.01 (RHD*667G)*	(40)	Africa: 0.08%	(19,34,40,53-57)
*RHD*DAU3, RHD*10.03 (RHD*835A,1136T)*	(7,21,29,55,58,59)	Africa: 3.03%; America: 0.72%; Europe: 0.10%	(29,32-34,40,42,58-60)
*RHD*DAU4, RHD*10.04 (RHD*697A,1136T)*	(7,21,29,61)	–	(58,59,62)
*RHD*DAU5, RHD*10.05 (RHD*667G,697C,1136T)*	(29,62-64)	Africa: 0.83%	(32-34,40,42,53,62)
*RHD*DOL1, RHD*12.01 (RHD*509C,667G)*	(7,21,54,65)	–	(50,65-67)
*RHD*DOL2, RHD*12.02 (RHD*509C,667G,1132G)*	(65)	–	(34,38,65,67,68)
*RHD*DNB, RHD*25 (RHD*1063A)*	(7,21,69-71)	America: 0.14%; Europe: 0.20%	(53,66,68,69,72)
*RHD*DFL, RHD*28 (RHD*494G)*	(7,21,54)	–	(54,73,74)
*RHD*DWN, RHD*49 (RHD*1053T,1057_1061delinsTGGAA)*	(7,21)	–	(75)
*RHD*DAR,* with or without additional silent mutations *RHD*09.01 (.00, .01, .02, .03) (RHD*602G,667G,1025C +/– c.744T, c. 957A)*	(7,21,37,49,76,77)	–	(34,37,38,40,44,49,55,77,78)
*RHD*partial weak D type 11, RHD*11 (RHD*885T)*	(7,54,79)	–	(37,44,48,53,72,74,78,80-91)
*RHD*partial weak D type 15, RHD*15 (RHD*845A)*	(7,37,76,79)	East Asia: 0.10%	(37,43-45,56,72,80,87,89,92-95)
*RHD*partial weak D type 21, RHD*21 (RHD*938T)*	(18)	–	(48,66)
*RHD*weak D type 41, RHD*01W.41 (RHD*1193T)*	(96)	–	
*RHD*weak D type 42, RHD*01W.42 (RHD*1226T)*	(69)	–	(62,66)
*RHD*weak D type 45, RHD*01W.45 (RHD*1195A)*	(69)	America: 0.29%; Europe: 0.20%	(97,98)
*RHD*DEL8, RHD*01EL.8 (RHD*486+1A)*	(99-101)	–	(47,51,81,82,86,87,90,91,101-103)

The *RHD*06 (RHD*DVI)* and *RHD*17 (RHD*DFR)* alleles, *RHD*10.00 (RHD*DAU0), RHD*09.03 (RHD*weak D type 4.0)* and *RHD*09.04 (RHD*weak D type 4.1)* are not listed in this table. See text for commentary of these alleles. †, a complete list of the anti-D reported in the literature for these alleles can be found in the RHeference database (8).

RHCE alleles

Most *RHCE* alleles are responsible for the expression of a pair of RhCE Ag: C (RH2), E (RH3), c (RH4), e (RH5). The *RHCE* alleles associated with Ab formation to the corresponding Ag are listed in *Table 4*.

A few *RHCE* alleles, for which no RH10 or RH20 phenotype, no prevalence in Erythrogene and, more

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Table 2 *RHD* alleles frequently reported and for which no anti-D have been reported in carriers

Common name, ISBT numerical when applicable (name based on nucleotide changes)	Prevalence (Erythrogene) (13)	Reports (RHeference)[†] (8)
*RHD*DIII type 6, RHD*03.06 (RHD*410T,455C,602G,667G,819A)*	America: 0.14%	(39,40,135)
*RHD*DV type 1, RHD*05.01 (RHD*667G,697C)*	–	(34,44,45,56,136,137)[‡]
*RHD*DV type 4, RHD*05.04 (RHD*697C)*	Africa: 0.08%; South Asia: 1.02%	(45,56,136,137)[‡]
*RHD*DAU0.01, RHD*10.00.01 (RHD*579A,1136T)*	Africa: 1.66%	(34,38,49,59)
*RHD*DAU0.02, RHD*10.00.02 (RHD*150C,1136T)*	Africa: 0.08%	(59)
*RHD*DAU6, RHD*10.06 (RHD*998A,1136T)*	Africa: 0.23%	(59,62)
*RHD*DAU14, RHD*10.14 (RHD*201A,203A,1136T)*	Africa: 0.08%	(59,116)
*RHD*667G,1136T*	Africa: 0.08% South Asia: 0.10%	(38)
*RHD*DFW, RHD*18 (RHD*497C)*	–	(54-56)
*RHD*DVL2, RHD*32 (RHD*705_707delGAA)*	–	(85,86,138)[§]
*RHD*DUC2, RHD*37 (RHD*733C)*	America: 0.14%	(53)
*RHD*186T*	Africa: 0.76%; America: 3.89%; East Asia: 11.41%; Europe: 4.47%; South Asia: 1.23%[¶]	(30,67)
*RHD*525T, RHD*59*	Africa: 0.15%; America: 0.14%; East Asia: 0.20%	(52)
*RHD*932C*	Africa: 1.36%; America: 7.35%; East Asia: 11.81%; Europe: 10.34%; South Asia: 0.51%	Never reported in an immunohematology study or abstract
*RHD*weak D 4.3, RHD*09.05 (RHD*602G,667G,819A,872G)*	–	(90,139,140)[§]
*RHD*weak D type 5, RHD*01W.5 (RHD*446A)*	–	(37,44,47,48,51,80,81,88,90,139)[§]
*RHD*weak D type 14, RHD*01W.14 (RHD*544A,594T,602G)*	–	(37,48,72,89)
*RHD*weak D type 18, RHD*01W.18 (RHD*19T)*	–	(43,73,94)
*RHD*weak D type 24, RHD*01W.24 (RHD*1013C)*	–	(45,94)
*RHD*weak D type 25, RHD*01W.25 (RHD*341A)*	East Asia: 0.10%	(43,45,55,56,92)
*RHD*weak D type 28, RHD*01W.28 (RHD*1152C)*	Africa: 0.15%	(141,142)
*RHD*weak D type 38, RHD*01W.38 (RHD*833A)*	–	(27,47,68,73,78,82,85,86,97,98,139,143)[§]
*RHD*weak D type 66, RHD*01W.66 (RHD*916A)*	Africa: 0.08%; Europe: 0.10%	(135)
*RHD*weak D type 93, RHD*01W.93 (RHD*359A)*	–	(51,144,145)
*RHD*weak D type 100, RHD*01W.100 (RHD*787A)*	–	(56,94)
*RHD*DEL1, RHD*01EL.01 (RHD*1227A)*	America: 0.29%; East Asia: 0.69%; Europe: 0.10%[§§]	See text
*RHD*DEL18, RHD*01EL.18 and RHD*01N.50 (RHD*93insT)*	–	(47,74,84,85,103)[§]
*RHD*DEL43, RHD*01EL.43 (RHD*46C)*	–	(51,83,85)[§]
*RHD*DEL11, RHD*01EL.11 (RHD*1252_1253insT)*	–	(47,74,81)[§]

Table 2 (*continued*)

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Table 2 (*continued*)

Common name, ISBT numerical when applicable (name based on nucleotide changes)	Prevalence (Erythrogene) (13)	Reports (RHeference)[†] (8)
*RHD*Ex3dup, RHD*01W.150*[††] *(RHD*327_487-4163dup)*	–	(55,56)
*RHD*Ex10del*	–	(85,146,147)[§]
*RHD*175A, RHD*01W.151*[††]	South Asia: 0.20%	(55)
*RHD*648C, RHD*01W.154*[††]	South Asia: 0.82%	(55,56)
*DBO3, RHD*968A*	East Asia: 0.50%	(148)
*RHD*960A*	–	(56,142,149)

List of *RHD* alleles frequently reported in immunohematology studies, or reported in a large number of carriers in the current literature, but for which no anti-D have been reported in carriers. [†], additional references listing carriers of these alleles can be found in the RHeference database (8). [‡], anti-D have been reported with "DV" phenotype. [§], these alleles have a very low D antigen expression (DEL phenotype or very weak D phenotype) and anti-D formation in carriers may have occurred but not have been differentiated from anti-D in true D negative individuals. [¶], Prevalence for *RHD*186T* may be overestimated, as this genetic variation can be found in many *RHD*03 (RHD*DIII)* alleles combining several point mutations. [††], provisional ISBT name according to the Human RhesusBase (7). [§§], also see text.

Table 3 Low prevalence antigens produced by *RH* alleles

Low prevalence Antigens	Alleles reported to express the antigen	References of antibodies to the Ag
RH8 (C^W)	*RHCE*02.08.01 (RHCE*CeCW)* (150); *RHCE*02.08.02 (RHCE*CeNR)* (151)	(152-154)
RH9 (C^X)	*RHCE*02.09 (RHCE*CeCX)* (150)	(155)
RH10 (V)	See *Table 4* (194,195)	(196)
RH11 (E^W)	*RHCE*cEEW (RHCE*03.01)* (190)	(197,198)
RH20 (VS)	See *Table 4* (194,195)	(199)
RH23 (D^W)	*RHD*05 (.01, .02, .04, .06, and .08) (RHD*DV type 1, 2, 4, 6 and 8)* (136); *RHD*10.05 (RHD*DAU5) (57); RHD*D-cE(5,6)-D* (200)	(201,202)
RH30 (Go^a)	*RHD*04.01 (RHD*DIVa)* (21); *RHD*1048C* (123); *RHD*712A,1048C* (203)	(204,205)
RH32	*RHCE*CeRN (RHCE*02.10.01)* (206); *RHD*14.01* and *.02* (*RHD*DBT-1* and *2*) (207)	(208,209)
RH36 (Be^a)	*RHCE*01.14 (RHCE*ceBE)* (210)	(210-212)
RH40 (Tar)	*RHD*07.01 (RHD*DVII)* (213); *RHD*07.02 (RHD*DVII type 2)* (214)	(215)
RH45 (Riv)	Haplotype associating *RHD*04.01* (*RHD*DIVa*) and *RHCE*DIVa(C)*– (216)	(217)
RH48 (JAL)	*RHCE*01.20.07 (RHCE*ceJAL)* (173); *RHCE*01.21 (.01* and *.02)* (218); *RHCE*02.01 (RHCE*CeMA* or *RHCE*CeJAL)* (173,218)	(173,219,220)
RH49 (STEM)	*RHCE*01.08 (RHCE*ceBI), RHCE*01.09 (RHCE*ceSM)* (175)	(221)
RH54 (DAK)	*RHCE*CeRN (RHCE*02.10.01)* (67,222); *RHD*12.02 (RHD*DOL2)* (175); *RHD*03.01 (RHD*DIIIa)* (including with c.150C), *RHD*03.07 (RHD*DIII type 7)*, and *RHD*186T* (30,39,67)	(223)
RH55 (LOCR)	*RHCE*01.15 (RHCE*ceLOCR)* (224)	(225)

As all alleles have not been tested for all low prevalence antigens, the allele list for each antigen may not be comprehensive.

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Table 4 *RHCE* alleles associated with antibody formation to the corresponding antigen(s), RH10 (V) and RH20 (VS) phenotypes

Name based on nucleotide substitutions (ISBT numerical, common name)	Reference of antibodies to the antigens listed	Prevalence (Erythrogene) (13)	RH10, RH20 phenotypes
*RHCE*ce48C (RHCE*01.01)*	See text	See text	RH:–10,–20, (67,156)
*RHCE*ce48C,1025T (RHCE*01.02.01, RHCE*ceTI)*	Heterozygous: RH4, RH5 (157)	Africa: 2.27%; America: 0.43%	–
*RHCE*ce1025T (RHCE*01.03)*	–	Africa: 0.30%	RH:–10,–20, (31)
*RHCE*ce48C,712G,733G,787G,800A,916G (RHCE*01.04.01, RHCE*ceAR)*	Homozygous: RH18, RH19 (19,158); Heterozygous, compound heterozygote: RH4, RH5 (19,158-160)	–	RH:–10,–20, (77,161)
*RHCE*ce48C,712G,787G,800A (RHCE*01.05.01, RHCE*ceEK)*	Homozygous: RH18, RH19 (19); compound heterozygote: RH5 (19,41,65)	–	RH:–10, (162)
*RHCE*ce254G (RHCE*01.06.01, RHCE*ceAG)*	Homozygous: RH5, RH59 (163); heterozygous: RH5 (163)	Africa: 5.60%; America: 0.72%	–
*RHCE*ce48C,667T (RHCE*01.07.01, RHCE*ceMO)*	Homozygous: RH5, RH19, RH31, RH61 (105,158); heterozygous, compound heterozygote: RH5 (19,41,164)	Africa: 1.44%; America: 0.43%; East Asia: 0.20%; Europe: 0.10%	RH:–10,–20, (19,105,165)
*RHCE*ce667T (RHCE*01.07.02, RHCE*ceMO.02)*	–	Africa: 0.08%	–
*RHCE*48C,712G,818T,1132G (RHCE*01.08, RHCE*ceBI)*	Homozygous: RH18, RH19 (19,65,158); heterozygous, compound heterozygote: RH5 (19,41,65,67,158)	Africa: 0.08%	RH:–10,–20, (67)
*RHCE*48C,712G,818T (RHCE*01.09,RHCE*ceSM)*		–	RH:–10,–20, (67)
*RHCE*ce687_689delAAG (RHCE*01.13,RHCE*ceBP)*	Compound heterozygote: RH31, RH34 (166)	–	–
*RHCE*ce286A (RHCE*01.15, RHCE*ceLOCR)*	Heterozygous: RH26 (167)	–	–
*RHCE*48C,1170T, 1193A (RHCE*ce48C-D(9)-ce, RHCE*01.16)*	Homozygous: RH5 (168)	East Asia: 0.60%; South Asia: 0.10%	–
*RHCE*ce733G (RHCE*01.20.01)*	Compound heterozygote (29,31), see text	Africa: 15.28%; America: 2.31%; Europe: 0.30%	RH:10,20, (31,161)
*RHCE*ce48C,733G (RHCE*01.20.02)*	Compound heterozygote (29,31), see text	–	RH:10,20, (31,161)
*RHCE*ce48C,733G,1006T (RHCE*01.20.03 RHCE*ceS)*	Homozygous: RH2, RH31, RH34 (19,30,31,158,169); Heterozygous: RH4[†], RH5, RH31 (31,41,158,169,170)	–	RH:–10,20, (31,35,67,161)
*RHCE*ce48C,733G,1025T (RHCE*01.20.04.01, RHCE*ceTI type 2)*	–	Africa: 0.08%; Europe: 0.20%	RH:10,20, (31,161)
*RHCE*ce733G,1006T (RHCE*01.20.05)*	–	Africa: 0.08%	RH:20, (161)
*RHCE*ce48C,697G,733G (RHCE*01.20.06, RHCE*ceCF)*	Homozygous: RH4, RH5, RH58 (171); heterozygous: RH4, RH5 (49,171)	Africa: 0.08%	RH:10,20, (161,171,172)
*RHCE*ce340T,733G (RHCE*01.20.07, RHCE*ceJAL)*	Homozygous: RH57 (173); heterozygous: RH4 (174), RH5, (19)	–	Variable: very weak or negative for RH10 and RH20 (67,161,173,175)

Table 4 (*continued*)

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Table 4 (*continued*)

Name based on nucleotide substitutions (ISBT numerical, common name)	Reference of antibodies to the antigens listed	Prevalence (Erythrogene) (13)	RH10, RH20 phenotypes
*RHCE*ce48C,733G,941C (RHCE*01.20.09)*	Heterozygous: RH31 (176)	Africa: 2.57%; America: 0.14%	RH:10,20, (176,177)
*RHCE*ce-D(5)-ce (RHCE*01.22, RHCE*ceHAR)*	RH1 (178), RH5 (179)	–	–
*RHCE*ce114C (RHCE*01.41, RHCE*ceWA)*	Homozygous: RH62 (5,180)	–	–
*RHCE*505C,509G,514T*‡ *(RHCE*ceMNL)*	Heterozygous: RH5 (181)	–	
*RHCE*Ce340T (RHCE*02.01, RHCE*CeMA, RHCE*CeJAL)*	–	–	RH:–10,–20, (173,182)
*RHCE*Ce-D(5)-Ce (RHCE*02.04, RHCE*CeVA)*	–	–	RH:–10,–20, (182)
*RHCE*Ce122G (RHCE*02.08.01, RHCE*CeCW)*	Homozygous: RH51 (183,184); heterozygous: RH2 (41)	§	
*RHCE*Ce122G-D(6-10) (RHCE*02.08.02, RHCE*CeNR)*	Homozygous: RH17-like (151,185)	–	RH:–10,–20, (151)
*RHCE*Ce106A (RHCE*02.09, RHCE*CeCX)*	Homozygous: RH51 (183); heterozygous: RH2 (41)	–	
*RHCE*ce48C,106A,733G*	–	–	RH:20, (140)
*RHCE*Ce-D(4)-Ce (RHCE*02.10.01, RHCE*CeRN)*	Homozygous: RH46 (158,186); Heterozygous: RH2, RH5 (158,187,188); compound heterozygote (19,166)	–	RH:–10,–20, (19,67)
*RHCE*Ce890C (RHCE*02.18)*	Heterozygous: RH31-like (189)	–	–
*RHCE*Ce667T (RHCE*02.22)*	Heterozygous: RH5 (158)	–	–
*RHCE*cE500A (RHCE*03.01)*	Heterozygous: RH3 (190)	–	–
*RHCE*cE697G,712G (RHCE*03.03.01, RHCE*cEFM)*	Heterozygous: RH3 (191)	–	–
*RHCE*cE602C (RHCE*03.04, RHCE*cEIV)*	¶	Africa: 0.15%	–
*RHCE*cE48C (RHCE*03.18)*	–	Africa: 0.76%; America: 1.87%; East Asia: 0.99%. Europe: 0.80%; South Asia: 0.41%	–
*RHCE*cE350_358delCCATGAGTG*†† *(RHCE*03.31, RHCE*cEMI)*	RH17-like (192)	–	–
*RHD*DIIIa-CEVS(4-7)-D (RHD*03N.01) and RHD*D-CEVS(4-7)-D (RHD*01N.06)*	RH2 (31,41,158,187,188)	–	–
*RHCE*CE-D(4-7)-CE*	RH17-like (193)	–	–

†, an antibody to this antigen was only reported in poly-immunized patient(s), requiring differential adsorptions to separate specificities. ‡, nucleotide substitutions were not explicit in the abstract, and were deduced. §, since none of the *RHCE*02* alleles have been associated with a prevalence in Erythrogene (probably because of the sequence identity of *RHD*01* exon 2 and *RHCE*02* exon 2), the numbers listed for *RHCE*ce48C,122G* may in fact apply to *RHCE*02.08.01*: Europe: 0.99%. South Asia: 0.20%. ¶, carriers of *RHCE*03.04* have been receiving RH:3 (E positive) RBC units for many years, with no documented allo-anti-RH3 formation.

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importantly, no Ab report could be found, but are worth mentioning are: *RHCE*02.02* (*RHCE*CeFV*) (232), *RHCE*02.03* (*RHCE*CeJAHK*) (233), *RHCE*02.11* (*RHCE*Ce286A*) (234).

As for *RHD*, a few *RHCE* alleles have a controversial status. Both allo- and auto-anti-e Ab have been reported for *RHCE*01.01* (*RHCE*ce48C*) and *RHCE*01.20* alleles (comprising c.733C>G) (32,60,187). Erythrogene reports *RHCE*01.20.01* in Africa (15.28%), America (2.31%), and Europe (0.30%). The prevalence of *RHCE*01.01* reported by Erythrogene is overestimated, probably because *RHCE*02* alleles could not be recognized. Nevertheless, other sources list the allele as common, particularly in Africans (161).

Some studies with immunization data and the clinical consequences of Ab were performed before molecular typing became standard (235). Unfortunately, molecular typing has not since been published for these samples.

Similarly to what is observed for *RHD* alleles, some *RHCE* alleles produce low prevalence Ag, which may be responsible for Ab formation in an exposed individual (*Table 3*).

Discussion

For only a fraction of *RHD* and *RHCE* reported to-date, Ab to the expressed Ag have been reported. The list presented here may not be comprehensive. Some Ab may have been reported in other languages, or not reported at all. It should be underlined that the data presented in abstract form only have not undergone peer-review. It may be that doubts arose later as to the specificity of the Ab.

In many of the studies referenced in this review, the serology of the Ab is not detailed. Ab to Rh antigens may combine allo- and auto-Ab components and be difficult to interpret. In many cases, it does not serve any practical purpose to perform extensive serology testing once a variant has been identified, except for research purposes, as the findings would have no effect on patient management (e.g., if a patient has anti-D and a D variant, they will receive D negative RBC units regardless). This is particularly true for the more common alleles and for those previously associated with allo-Ab formation. Some studies seem to have found allo-Ab in individuals with apparently normal *RH* alleles (e.g., anti-e in an individual with *RHCE*01*), which interrogates the allo-Ab listed in the same study with Rh variants (could auto-Ab explain some of the findings?). More serology data would often be valuable. It would be valuable to the community if, whenever possible, allo- and auto-Ab were identified and studies could report the analyses performed for this purpose, even when incomplete testing was performed.

The common practice of using the term "partial" Ag as a synonym with "at risk for Ab formation to the corresponding Ag" should continue to be questioned. This leads to considering Ab formation risk as a binary, putting all Rh variants on the same level and limits our ability to adjust policies depending on the variants. The variants discussed here are not all equivalent in terms of Ab formation risk, as mentioned above for several *RHD* alleles. From our experience, *RHD*03.01* (*RHD*DIIIa*), *RHD*10.05* (*RHD*DAU5*), *RHD*04.01* (*RHD*DIVa*) and *RHD*49* (*RHD*DWN*) are among the alleles particularly prone to anti-D formation. This is observed in our setting where carriers are relatively common thanks to the African and Afro-Caribbean heritage of many French people, even if we cannot estimate the prevalence precisely. These variants are not screened by our routine phenotyping methods and carriers are unlikely to receive D negative RBC units or anti-D immunoglobulins to prevent anti-D alloimmunization (which would be the standard patient management when D variants at risk for anti-D are detected in our country because of weakened Ag expression). These variants are regularly detected in D positive individuals after forming anti-D. This observation in our setting may not be as relevant in populations with a different genetic makeup, or with different policies for patient management.

The prevalence listed here is only indicative, as the quality of the 1000 Genomes project data is imperfect (236). Many alleles have no prevalence associated: either the genetic variation(s) are too rare, or the variations could not be phased, especially for hybrid alleles or equivalent (none of the *RHCE*02* alleles has a prevalence, as mentioned in the introduction).

With the expansion of genotyping, an increasing number of genotyping studies revealing the Rh genetic makeup of different populations is being published. When possible, the Ab found in the same population would be worth presenting together with the genotyping data. Authors should make sure to provide serological data, even when incomplete, and present the clinical consequences of the alloimmunization, if any.

Antibodies can cause HDFN or hemolytic transfusion reactions (HTR). The risk is considered to be possible for any Rh allo-antibody, and patients with Ab are usually not re-exposed to the offending Ag to avoid such complications. Therefore, hemolytic consequences of alloimmunization

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have been reported in only a subset of the alleles discussed here and the available data must be interpreted with caution. The most severe HTR, with hyperhemolysis, occur in SCD patients (237). In these patients, the causality of a specific Ab is particularly hard to establish (16,17). HTR with hyperhemolysis can occur in patients with multiple Ab, can be caused by auto-Ab or Ab not usually considered clinically significant, or even occur in the absence of Ab, making the interpretation for a single Ab difficult (32,237-239).

HTR or decreased survival of RBCs have been reported for anti-D associated with partial D, including *RHD*04.01* (*RHD*DIVa*) (32), *RHD*10.04* (*RHD*DAU4*) (29,32,61), *RHD*03.01* (*RHD*DIIIa*) and *RHD*weak partial D 4.2* (*RHD*DAR*) (29), anti-C associated with partial C of *RHD*03N.01* [*RHD*DIIIa-CE(4-7)-D*] (32,188), and anti-c associated with partial c of *RHCE*01.20.07* (*RHCE*ceJAL*) (174), among others (29,32,239,240). Decreased survival of transfused RBC has been reported for anti-e associated with several alleles predicted to be RH:–19 and/or RH:–31 in SCD patients (29,32). Many *RHCE* alleles have been reported as RH:–19 and/or RH:–31 but anti-RH19 and anti-RH31 may sometimes be reported as anti-e or anti-e-like (161). The clinical consequences of anti-RH19 and anti-RH31 may depend on the underlying alleles but it is difficult from the available data to compare them. Further monitoring of anti-RH19 and anti-RH31 Ab formation and potential hemolytic consequences, with molecular data and robust serological workups could shed light on the heterogeneity of these cases to better inform transfusion decisions.

Some *RHCE* alleles can probably be considered at a low risk for Ab formation or severe hemolytic complications: *RHCE*01.01* (*RHCE*ce48C*), *RHCE*01.20.01* (*RHCE*ce733G*) and *RHCE*01.20.02* (*RHCE*ce48C,733G*). Severe hemolytic consequences attributable to these alleles have not been reported in the literature, and many countries do not take prophylactic measures for alloimmunization when transfusing carriers. If the c (RH4) and e (RH5) Ag produced by these alleles were at a risk for severe hemolytic complications, the incidence would remain very low compared to the alleles' prevalence in some populations (29,32).

It is hard to say if the literature over- or under-estimates the clinical consequences of Ab to low prevalence Ag. On the one hand, these Ab may be difficult to detect and characterize. On the other hand, case reports with these Ab may be more likely to be published. A more systematic approach to study these Ab could be helpful (241,242).

A better understanding of which Ab are at the highest risk for hemolytic complications could be a key to improving our inventory management while guaranteeing patient safety. Next-generation sequencing is also expanding the possibilities and revealing unexpected complexity (243,244). Hopefully, data will continue to be reported to guide us. Moving forward, it may become possible to classify the alloimmunization and hemolytic risks associated with more Rh variants and adapt the recommendations for each variant. Such recommendations would take into account the alloimmunization risk associated with a variant, the risk of hemolytic complications, the prevalence of the variant in the population, and the availability of Ag negative RBC units in the population.

Web resources

ISBT RHD allele tables (last update Feb 2018, accessed: Nov 2020)

- http://www.isbtweb.org/fileadmin/user_upload/Working_parties/WP_on_Red_Cell_Immunogenetics_and/RHD_Partial_D_blood_group_alleles_v5.0_180207.pdf
- http://www.isbtweb.org/fileadmin/user_upload/Working_parties/WP_on_Red_Cell_Immunogenetics_and/004_RHD_weak_D_and_Del_alleles_v5.0_180207.pdf
- http://www.isbtweb.org/fileadmin/user_upload/Working_parties/WP_on_Red_Cell_Immunogenetics_and/004_RHD_negative_null_blood_group_alleles_v4.0_180208.pdf

ISBT RHCE allele table (last update July 2019, accessed: Nov 2020)

- http://www.isbtweb.org/fileadmin/user_upload/ISBT004-RHCE-15th_July_2019.pdf

The Human RhesusBase (last update March 2020, accessed: Nov 2020)

- http://www.rhesusbase.info/

Erythrogene (last update Nov 2017, accessed: Nov 2020)

- http://www.erythrogene.com/

Reference Sequence database (RefSeq)

- RHD: https://www.ncbi.nlm.nih.gov/nuccore/171184448 (last update Oct 2020, accessed:

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Nov 2020);
- RHCE: https://www.ncbi.nlm.nih.gov/nuccore/588480537 (last update Oct 2020, accessed: Nov 2020).

RHeference database (last update April 2021, accessed: April 2021)

- https://www.rheference.org/

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References

1. Landsteiner K, Wiener AS. An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood. Proceedings of the Society for Experimental Biology and Medicine 1940;43:223.
2. Landsteiner K, Wiener AS. Studies on an agglutinogen (Rh) in human blood reacting with anti-Rhesus sera and with human isoantibodies. J Exp Med 1941;74:309-20.
3. Chérif-Zahar B, Bloy C, Le Van Kim C, et al. Molecular cloning and protein structure of a human blood group Rh polypeptide. Proc Natl Acad Sci U S A 1990;87:6243-7.
4. Le van Kim C, Mouro I, Chérif-Zahar B, et al. Molecular cloning and primary structure of the human blood group RhD polypeptide. Proc Natl Acad Sci U S A 1992;89:10925-9.
5. Storry JR, Clausen FB, Castilho L, et al. International Society of Blood Transfusion Working Party on Red Cell Immunogenetics and Blood Group Terminology: Report of the Dubai, Copenhagen and Toronto meetings. Vox Sang 2019;114:95-102.
6. Benson DA, Cavanaugh M, Clark K, et al. GenBank. Nucleic Acids Res 2013;41:D36-42.
7. Wagner FF, Flegel WA. The Rhesus Site. Transfus Med Hemother 2014;41:357-63.
8. Floch A, Téletchéa S, Tournamille C, et al. A review of the literature organized into a new database: RHeference. Transfus Med Rev 2021;35:70-7.
9. Chou ST, Westhoff CM. The Rh and RhAG blood group systems. Immunohematology 2010;26:178-86.
10. Pruitt KD, Tatusova T, Maglott DR. NCBI Reference Sequence (RefSeq): a curated non-redundant sequence database of genomes, transcripts and proteins. Nucleic Acids Res 2005;33:D501-4.
11. Garratty G. Do we need to be more concerned about weak D antigens? Transfusion 2005;45:1547-51.

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12. Daniels G. Variants of RhD--current testing and clinical consequences. Br J Haematol 2013;161:461-70.
13. Möller M, Jöud M, Storry JR, et al. Erythrogene: a database for in-depth analysis of the extensive variation in 36 blood group systems in the 1000 Genomes Project. Blood Adv 2016;1:240-9.
14. Silvy M, Tournamille C, Babinet J, et al. Red blood cell immunization in sickle cell disease: evidence of a large responder group and a low rate of anti-Rh linked to partial Rh phenotype. Haematologica 2014;99:e115-7.
15. Tormey CA, Hendrickson JE. Transfusion-related red blood cell alloantibodies: induction and consequences. Blood 2019;133:1821-30.
16. Noizat-Pirenne F, Tournamille C. Relevance of RH variants in transfusion of sickle cell patients. Transfus Clin Biol 2011;18:527-35.
17. Thonier V. Immuno-hematological findings in Delayed Hemolytic Transfusion Reaction (DHTR). Transfus Clin Biol 2019;26:102-8.
18. McGann H, Wenk RE. Alloimmunization to the D antigen by a patient with weak D type 21. Immunohematology 2010;26:27-9.
19. Noizat-Pirenne F, Lee K, Le Pennec PY, et al. Rare RHCE phenotypes in black individuals of Afro-Caribbean origin: identification and transfusion safety. Blood 2002;100:4223-31.
20. Westhoff CM. Blood group genotyping. Blood 2019;133:1814-20.
21. von Zabern I, Wagner FF, Moulds JM, et al. D category IV: a group of clinically relevant and phylogenetically diverse partial D. Transfusion 2013;53:2960-73.
22. Mouro I, Le Van Kim C, Rouillac C, et al. Rearrangements of the blood group RhD gene associated with the DVI category phenotype. Blood 1994;83:1129-35.
23. Ye L, Wang P, Gao H, et al. Partial D phenotypes and genotypes in the Chinese population. Transfusion 2012;52:241-6.
24. Jones J, Scott ML, Voak D. Monoclonal anti-D specificity and Rh D structure: criteria for selection of monoclonal anti-D reagents for routine typing of patients and donors. Transfus Med 1995;5:171-84.
25. Wagner FF, Gassner C, Muller TH, et al. Three molecular structures cause rhesus D category VI phenotypes with distinct immunohematologic features. Blood 1998;91:2157-68.
26. Tippett P, Lomas-Francis C, Wallace M. The Rh antigen D: partial D antigens and associated low incidence antigens. Vox Sang 1996;70:123-31.
27. Ansart-Pirenne H, Asso-Bonnet M, Le Pennec PY, et al. RhD variants in Caucasians: consequences for checking clinically relevant alleles. Transfusion 2004;44:1282-6.
28. Lomas C, Grässmann W, Ford D, et al. FPTT is a low-incidence Rh antigen associated with a "new" partial Rh D phenotype, DFR. Transfusion 1994;34:612-6.
29. Sippert E, Fujita CR, Machado D, et al. Variant RH alleles and Rh immunisation in patients with sickle cell disease. Blood Transfus 2015;13:72-7.
30. Reid ME, Hipsky CH, Velliquette RW, et al. Molecular background of RH in Bastiaan, the RH:-31,-34 index case, and two novel RHD alleles. Immunohematology 2012;28:97-103.
31. Westhoff CM, Vege S, Halter-Hipsky C, et al. DIIIa and DIII Type 5 are encoded by the same allele and are associated with altered RHCE*ce alleles: clinical implications. Transfusion 2010;50:1303-11.
32. Chou ST, Jackson T, Vege S, et al. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. Blood 2013;122:1062-71.
33. Granier T, Beley S, Chiaroni J, et al. A comprehensive survey of both RHD and RHCE allele frequencies in sub-Saharan Africa. Transfusion 2013;53:3009-17.
34. Kappler-Gratias S, Auxerre C, Dubeaux I, et al. Systematic RH genotyping and variant identification in French donors of African origin. Blood Transfus 2014;12 Suppl 1:s264-72.
35. Pham BN, Peyrard T, Juszczak G, et al. Heterogeneous molecular background of the weak C, VS+, hr B-, Hr B-phenotype in black persons. Transfusion 2009;49:495-504.
36. Faas BH, Beckers EA, Simsek S, et al. Involvement of Ser103 of the Rh polypeptides in G epitope formation. Transfusion 1996;36:506-11.
37. Wagner FF, Frohmajer A, Ladewig B, et al. Weak D alleles express distinct phenotypes. Blood 2000;95:2699-708.
38. Reid ME, Halter Hipsky C, Hue-Roye K, et al. Genomic analyses of RH alleles to improve transfusion therapy in patients with sickle cell disease. Blood Cells Mol Dis 2014;52:195-202.
39. Lomas-Francis C, Halter Hipsky C, Velliquette RW, et al. DIII Type 7 is likely the original serologically defined DIIIb. Transfusion 2012;52:39-42.
40. Grootkerk-Tax MGHM, van Wintershoven JD, Ligthart PC, et al. RHD(T201R, F223V) cluster analysis in five different ethnic groups and serologic characterization of a new Ethiopian variant DARE, the DIII type 6, and the RHD(F223V). Transfusion 2006;46:606-15.
41. Westhoff CM. Rh complexities: serology and DNA

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genotyping. Transfusion 2007;47:17S-22S.
42. Touinssi M, Chapel-Fernandes S, Granier T, et al. Molecular analysis of inactive and active RHD alleles in native Congolese cohorts. Transfusion 2009;49:1353-60.
43. Zhang X, Li G, Zhou Z, et al. Molecular and computational analysis of 45 samples with a serologic weak D phenotype detected among 132,479 blood donors in northeast China. J Transl Med 2019;17:393.
44. Koutsouri T, Chaikali A, Giannopoulos A, et al. Frequency distribution of RHD alleles among Greek donors with weak D phenotypes demonstrates a distinct pattern in central European countries. Transfus Med 2019;29:468-70.
45. Ye SH, Wu DZ, Wang MN, et al. A comprehensive investigation of RHD polymorphisms in the Chinese Han population in Xi'an. Blood Transfus 2014;12:396-404.
46. Yan L, Wu J, Zhu F, et al. Molecular basis of D variants in Chinese persons. Transfusion 2007;47:471-7.
47. Stegmann TC, Veldhuisen B, Bijman R, et al. Frequency and characterization of known and novel RHD variant alleles in 37 782 Dutch D-negative pregnant women. Br J Haematol 2016;173:469-79.
48. Müller TH, Wagner FF, Trockenbacher A, et al. PCR screening for common weak D types shows different distributions in three Central European populations. Transfusion 2001;41:45-52.
49. Dezan MR, Ribeiro IH, Oliveira VB, et al. RHD and RHCE genotyping by next-generation sequencing is an effective strategy to identify molecular variants within sickle cell disease patients. Blood Cells Mol Dis 2017;65:8-15.
50. El Housse H, El Wafi M, Ouabdelmoumene Z, et al. Comprehensive phenotypic and molecular investigation of RhD and RhCE variants in Moroccan blood donors. Blood Transfus 2019;17:151-6.
51. Trucco Boggione C, Nogués N, González-Santesteban C, et al. Characterization of RHD locus polymorphism in D negative and D variant donors from Northwestern Argentina. Transfusion 2019;59:3236-42.
52. Haer-Wigman L, Veldhuisen B, Jonkers R, et al. RHD and RHCE variant and zygosity genotyping via multiplex ligation-dependent probe amplification. Transfusion 2013;53:1559-74.
53. Chen Q, Flegel WA. Random survey for RHD alleles among D+ European persons. Transfusion 2005;45:1183-91.
54. Flegel WA, von Zabern I, Doescher A, et al. D variants at the RhD vestibule in the weak D type 4 and Eurasian D clusters. Transfusion 2009;49:1059-69.
55. Fichou Y, Parchure D, Gogri H, et al. Molecular basis of weak D expression in the Indian population and report of a novel, predominant variant RHD allele. Transfusion 2018;58:1540-9.
56. Thongbut J, Raud L, Férec C, et al. Comprehensive Molecular Analysis of Serologically D-Negative and Weak/Partial D Phenotype in Thai Blood Donors. Transfus Med Hemother 2020;47:54-60.
57. Flegel WA, von Zabern I, Doescher A, et al. DCS-1, DCS-2, and DFV share amino acid substitutions at the extracellular RhD protein vestibule. Transfusion 2008;48:25-33.
58. Wagner FF, Ladewig B, Angert KS, et al. The DAU allele cluster of the RHD gene. Blood 2002;100:306-11.
59. Srivastava K, Polin H, Sheldon SL, et al. The DAU cluster: a comparative analysis of 18 RHD alleles, some forming partial D antigens. Transfusion 2016;56:2520-31.
60. Chou ST, Flanagan JM, Vege S, et al. Whole-exome sequencing forRHgenotyping and alloimmunization risk in children with sickle cell anemia. Blood Adv 2017;1:1414-22.
61. Ipe TS, Wilkes JJ, Hartung HD, et al. Severe hemolytic transfusion reaction due to anti-D in a D+ patient with sickle cell disease. J Pediatr Hematol Oncol 2015;37:e135-7.
62. Denomme GA, Wagner FF, Fernandes BJ, et al. Partial D, weak D types, and novel RHD alleles among 33,864 multiethnic patients: implications for anti-D alloimmunization and prevention. Transfusion 2005;45:1554-60.
63. Noizat-Pirenne F. Relevance of blood groups in transfusion of sickle cell disease patients. C R Biol 2013;336:152-8.
64. Duncan JA, Nahirniak S, Onell R, et al. Two cases of the variant RHD*DAU5 allele associated with maternal alloanti-D. Immunohematology 2017;33:60-3.
65. Roussel M, Poupel S, Nataf J, et al. RHD*DOL1 and RHD*DOL2 encode a partial D antigen and are in cis with the rare RHCE*ceBI allele in people of African descent. Transfusion 2013;53:363-72.
66. Clarke G, Hannon J, Berardi P, et al. Resolving variable maternal D typing using serology and genotyping in selected prenatal patients. Transfusion 2016;56:2980-5.
67. Reid ME, Halter Hipsky C, Hue-Roye K, et al. The low-prevalence Rh antigen STEM (RH49) is encoded by two different RHCE*ce818T alleles that are often in cis to RHD*DOL. Transfusion 2013;53:539-44.
68. Arnoni CP, Latini FRM, Muniz JG, et al. How do we identify RHD variants using a practical molecular approach? Transfusion 2014;54:962-9.
69. St-Louis M, Richard M, Côté M, et al. Weak D type 42 cases found in individuals of European descent. Immunohematology 2011;27:20-4.

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70. Wagner FF, Eicher NI, Jørgensen JR, et al. DNB: a partial D with anti-D frequent in Central Europe. Blood 2002;100:2253-6.
71. Quantock KM, Lopez GH, Hyland CA, et al. Anti-D in a mother, hemizygous for the variant RHD*DNB gene, associated with hemolytic disease of the fetus and newborn. Transfusion 2017;57:1938-43.
72. Guzijan G, Jovanovic Srzentic S, Pavlovic Jankovic N, et al. Implementation of Molecular RHD Typing at Two Blood Transfusion Institutes from Southeastern Europe. Transfus Med Hemother 2019;46:114-20.
73. Le Maréchal C, Guerry C, Benech C, et al. Identification of 12 novel RHD alleles in western France by denaturing high-performance liquid chromatography analysis. Transfusion 2007;47:858-63.
74. Flegel WA, von Zabern I, Wagner FF. Six years' experience performing RHD genotyping to confirm D- red blood cell units in Germany for preventing anti-D immunizations. Transfusion 2009;49:465-71.
75. Fichou Y, Le Maréchal C, Bryckaert L, et al. Variant screening of the RHD gene in a large cohort of subjects with D phenotype ambiguity: report of 17 novel rare alleles. Transfusion 2012;52:759-64.
76. Pham BN, Roussel M, Gien D, et al. Molecular analysis of patients with weak D and serologic analysis of those with anti-D (excluding type 1 and type 2). Immunohematology 2013;29:55-62.
77. Hemker MB, Ligthart PC, Berger L, et al. DAR, a new RhD variant involving exons 4, 5, and 7, often in linkage with ceAR, a new Rhce variant frequently found in African blacks. Blood 1999;94:4337-42.
78. Costa S, Martin F, Chiba A, et al. RHD alleles and D antigen density among serologically D- C+ Brazilian blood donors. Transfus Med 2014;24:60-1.
79. Flegel WA. How I manage donors and patients with a weak D phenotype. Curr Opin Hematol 2006;13:476-83.
80. Van Sandt VST, Gassner C, Emonds MP, et al. RHD variants in Flanders, Belgium. Transfusion 2015;55:1411-7.
81. Gassner C, Doescher A, Drnovsek TD, et al. Presence of RHD in serologically D-, C/E+ individuals: a European multicenter study. Transfusion 2005;45:527-38.
82. Perez-Alvarez I, Hayes C, Hailemariam T, et al. RHD genotyping of serologic RhD-negative blood donors in a hospital-based blood donor center. Transfusion 2019;59:2422-8.
83. Trucco Boggione C, Luján Brajovich ME, Tarragó M, et al. Molecular structures identified in serologically D- samples of an admixed population. Transfusion 2014;54:2456-62.
84. Scott SA, Nagl L, Tilley L, et al. The RHD(1227G>A) DEL-associated allele is the most prevalent DEL allele in Australian D- blood donors with C+ and/or E+ phenotypes. Transfusion 2014;54:2931-40.
85. Crottet SL, Henny C, Meyer S, et al. Implementation of a mandatory donor RHD screening in Switzerland. Transfus Apher Sci 2014;50:169-74.
86. Gowland P, Gassner C, Hustinx H, et al. Molecular RHD screening of RhD negative donors can replace standard serological testing for RhD negative donors. Transfus Apher Sci 2014;50:163-8.
87. Orzińska A, Guz K, Polin H, et al. RHD variants in Polish blood donors routinely typed as D-. Transfusion 2013;53:2945-53.
88. Rizzo C, Castiglia L, Arena E, et al. Weak D and partial D: our experience in daily activity. Blood Transfus 2012;10:235-6.
89. Dogic V, Bingulac-Popovic J, Babic I, et al. Distribution of weak D types in the Croatian population. Transfus Med 2011;21:278-9.
90. Polin H, Danzer M, Gaszner W, et al. Identification of RHD alleles with the potential of anti-D immunization among seemingly D- blood donors in Upper Austria. Transfusion 2009;49:676-81.
91. Wagner FF, Frohmajer A, Flegel WA. RHD positive haplotypes in D negative Europeans. BMC Genet 2001;2:10.
92. Ji YL, Luo H, Wen JZ, et al. RHD genotype and zygosity analysis in the Chinese Southern Han D+, D- and D variant donors using the multiplex ligation-dependent probe amplification assay. Vox Sang 2017;112:660-70.
93. Seo MH, Won EJ, Hong YJ, et al. An effective diagnostic strategy for accurate detection of RhD variants including Asian DEL type in apparently RhD-negative blood donors in Korea. Vox Sang 2016;111:425-30.
94. Isa K, Sasaki K, Ogasawara K, et al. Prevalence of RHD alleles in Japanese individuals with weak D phenotype: Identification of 20 new RHD alleles. Vox Sang 2016;111:315-9.
95. Hussein E, Teruya J. Weak D types in the Egyptian population. Am J Clin Pathol 2013;139:806-11.
96. Martinez Badas M, Garcia Sanchez F, Moreno Jimenez G, et al. P-355: Anti-D immunization in a D-positive mother. Vox Sang 2007;93:187.
97. Dezan MR, Guardalini LGO, Pessoa E, et al. Evaluation of the applicability and effectiveness of a molecular strategy for identifying weak D and DEL phenotype

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among D- blood donors of mixed origin exhibiting high frequency of RHD*Ψ. Transfusion 2018;58:317-22.
98. Bub CB, Aravechia MG, Costa TH, et al. RHD alleles among pregnant women with serologic discrepant weak D phenotypes from a multiethnic population and risk of alloimmunization. J Clin Lab Anal 2018;32:e22221.
99. Tsui NBY, Hyland CA, Gardener GJ, et al. Noninvasive fetal RHD genotyping by microfluidics digital PCR using maternal plasma from two alloimmunized women with the variant RHD(IVS3+1G>A) allele. Prenat Diagn 2013;33:1214-6.
100. Gardener GJ, Legler TJ, Hyett JA, et al. Anti-D in pregnant women with the RHD(IVS3+1G>A)-associated DEL phenotype. Transfusion 2012;52:2016-9.
101. Körmöczi GF, Gassner C, Shao CP, et al. A comprehensive analysis of DEL types: partial DEL individuals are prone to anti-D alloimmunization. Transfusion 2005;45:1561-7.
102. Ogasawara K, Suzuki Y, Sasaki K, et al. Molecular basis for D- Japanese: identification of novel DEL and D- alleles. Vox Sang 2015;109:359-65.
103. Christiansen M, Sørensen BS, Grunnet N. RHD positive among C/E+ and D- blood donors in Denmark. Transfusion 2010;50:1460-4.
104. Sandler SG, Flegel WA, Westhoff CM, et al. It's time to phase in RHD genotyping for patients with a serologic weak D phenotype. College of American Pathologists Transfusion Medicine Resource Committee Work Group. Transfusion 2015;55:680-9.
105. Westhoff CM, Vege S, Horn T, et al. RHCE*ceMO is frequently in cis to RHD*DAU0 and encodes a hr(S) -, hr(B) -, RH:-61 phenotype in black persons: clinical significance. Transfusion 2013;53:2983-9.
106. Ouchari M, Chakroun T, Abdelkefi S, et al. Anti-D auto-immunization in a patient with weak D type 4.0. Transfus Clin Biol 2014;21:43-6.
107. Westhoff CM, Nance S, Lomas-Francis C, et al. Experience with RHD*weak D type 4.0 in the USA. Blood Transfus 2019;17:91-3.
108. Flegel WA, Peyrard T, Chiaroni J, et al. A proposal for a rational transfusion strategy in patients of European and North African descent with weak D type 4.0 and 4.1 phenotypes. Blood Transfus 2019;17:89-90.
109. Ouchari M, Jemni-Yaacoub S, Chakroun T, et al. RHD alleles in the Tunisian population. Asian J Transfus Sci 2013;7:119-24.
110. Ouchari M, Srivastava K, Romdhane H, et al. Transfusion strategy for weak D Type 4.0 based on RHD alleles and RH haplotypes in Tunisia. Transfusion 2018;58:306-12.
111. Flegel WA, Denomme GA, Queenan JT, et al. It's time to phase out "serologic weak D phenotype" and resolve D types with RHD genotyping including weak D type 4. Transfusion 2020;60:855-9.
112. Lomas C, McColl K, Tippett P. Further complexities of the Rh antigen D disclosed by testing category DII cells with monoclonal anti-D. Transfus Med 1993;3:67-9.
113. Tippett P, Sanger R. Observations on subdivisions of the Rh antigen D. Vox Sang 1962;7:9-13.
114. Jones J. Identification of two new D variants, DHMi and DHMii using monoclonal anti-D. Vox Sang 1995;69:236-41.
115. Körmöczi GF, Legler TJ, Daniels GL, et al. Molecular and serologic characterization of DWI, a novel "high-grade" partial D. Transfusion 2004;44:575-80.
116. Garcia F, Rodriguez MA, Goldman M, et al. New RHD variant alleles. Transfusion 2015;55:427-9.
117. Thonier VL, Iobagiu C, Duboeuf S, et al. IGT57: Complex Antibody Mixture in a Pregnant Woman Harboring the RHD*DIIIb Variant Allele. Transfusion 2018;58:183A.
118. Tilley L, Mathlouthi R, Needs M, et al. Five Novel RHD Alleles Resulting in D Variant Phenotypes. Transfus Med 2009;19:23.
119. Bruce DG, Poole J, Tilley L, et al. Immune Alloanti-D in a Patient with a Novel RHD Mutation. Transfus Med 2005;15:52.
120. Etheridge W, Tilley L, Poole J, et al. Two Novel D Genes of the Rh Blood Group System Producing D Variant Phenotypes. Transfus Med 2006;16:21.
121. Bruce D, Rounding L, Barnes S, et al. Immune Alloanti-D in a Patient With Weak D Type 33 Genotype. Transfus Med 2011;21:15.
122. Lambert M, Grimsley SP, O'Donghaile D, et al. The second example of alloanti-D in a weak D type 33 individual. Vox Sang 2015;109:252-3.
123. Vege S, Hong H, Burgos A, et al. D typing discrepancies and anti-D production associated with six new RHD alleles. Transfusion 2016;56:17A.
124. Castilho L, Arnoni C, Vendrame T, et al. P-374: From genotyping to the functional and clinical interpretation of variations in blood group genes by 3D-protein structure investigation: two novel variant alleles in the RHD gene. Vox Sang 2019;114:185.
125. Lewis S, Dzialach E, Grimsley SP, et al. PO36: Identification of a novel D variant I157S in a patient with alloanti-D. Transfus Med 2018;28:39.
126. Woo JS, Gikas A, Moayeri M, et al. IGT14-ST4-23: Robust allo-anti-D with subsequent anti-K production

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after transfusion of D-positive RBCs to a patient with weak D type 1. Transfusion 2018;58:42A.
127. Vege S, Fong C, Lomas-Francis C, et al. S91-040B: Weak D Type 2 and Production of Anti-D. Transfusion 2011;51:41A.
128. Nixon C, Ochoa-Garay G, Sweeney J. S74-040A: A Patient with Weak D Type 3 and Anti-D Alloimmunization. Transfusion 2016;56:33A.
129. Castilho L, Delfino dos Santos T, Menegati S, et al. P-392: RHD*weak D type 3 and production of allo-anti-D in a patient with sickle cell disease (SCD). Vox Sang 2019;114:190.
130. Wagner FF. P-376: The RHD allele inventory: lessons from high-throughput genome databases. Vox Sang 2019;114:181.
131. Wang M, Wang BL, Xu W, et al. Anti-D alloimmunisation in pregnant women with DEL phenotype in China. Transfus Med 2015;25:163-9.
132. Wang QP, Dong GT, Wang XD, et al. An investigation of secondary anti-D immunisation among phenotypically RhD-negative individuals in the Chinese population. Blood Transfus 2014;12:238-43.
133. Shao CP, Xu H, Xu Q, et al. Antenatal Rh prophylaxis is unnecessary for "Asia type" DEL women. Transfus Clin Biol 2010;17:260-4.
134. Kim H, Ko DH. Reconsidering RhD positive blood transfusion for Asia type DEL patients. Transfus Apher Sci 2019;58:422.
135. Stabentheiner S, Danzer M, Niklas N, et al. Overcoming methodical limits of standard RHD genotyping by next-generation sequencing. Vox Sang 2011;100:381-8.
136. Omi T, Okuda H, Iwamoto S, et al. Detection of Rh23 in the partial D phenotype associated with the D(Va) category. Transfusion 2000;40:256-8.
137. Omi T, Takahashi J, Tsudo N, et al. The genomic organization of the partial D category DVa: the presence of a new partial D associated with the DVa phenotype. Biochem Biophys Res Commun 1999;254:786-94.
138. Flegel WA, Eicher NI, Doescher A, et al. In-frame triplet deletions in RHD alter the D antigen phenotype. Transfusion 2006;46:2156-61.
139. Mota M, Dezan MR, Valgueiro MC, et al. RHD allelic identification among D-Brazilian blood donors as a routine test using pools of DNA. J Clin Lab Anal 2012;26:104-8.
140. Polin H, Gaszner W, Hackl C, et al. On the trail of anti-CDE to unexpected highlights of the RHD*weak 4.3 allele in the Upper Austrian population. Vox Sang 2012;103:130-6.
141. Fichou Y, Gehannin P, Corre M, et al. Extensive functional analyses of RHD splice site variants: Insights into the potential role of splicing in the physiology of Rh. Transfusion 2015;55:1432-43.
142. Chun S, Yun JW, Park G, Cho D. The synonymous nucleotide substitution RHD 1056C>G alters mRNA splicing associated with serologically weak D phenotype. J Clin Lab Anal 2018;32:e22330.
143. Gaspardi AC, Sippert EA, Araujo Botelho M, et al. RHD variants in blood donors from Southeast Brazil. Transfusion 2015;55:19A.
144. Arnoni CP, Muniz JG, de Paula Vendrame TA, et al. Identification of four novel RHD alleles with altered expression of D in Brazilians. Transfusion 2016;56:1475-6.
145. Trucco Boggione C, Luján Brajovich ME, Gaspardi AC, et al. Weak D antigen expression caused by a novel RHD allele in Argentineans. Transfusion 2016;56:2895-6.
146. Fichou Y, Chen JM, Le Maréchal C, et al. Weak D caused by a founder deletion in the RHD gene. Transfusion 2012;52:2348-55.
147. Srivastava K, Stiles DA, Wagner FF, et al. Two large deletions extending beyond either end of the RHD gene and their red cell phenotypes. J Hum Genet 2018;63:27-35.
148. Wei Q. Random survey for RH allele polymorphism among 50 native Tibetans. Open Access Repositorium der Universität Ulm. Dissertation. 2006. doi: 10.18725/OPARU-747.
149. Ogasawara K, Sasaki K, Isa K, et al. Weak D alleles in Japanese: a c.960G>A silent mutation in exon 7 of the RHD gene that affects D expression. Vox Sang 2016;110:179-84.
150. Mouro I, Colin Y, Sistonen P, et al. Molecular basis of the RhCW (Rh8) and RhCX (Rh9) blood group specificities. Blood 1995;86:1196-201.
151. Westhoff CM, Storry JR, Walker P, et al. A new hybrid RHCE gene (CeNR) is responsible for expression of a novel antigen. Transfusion 2004;44:1047-51.
152. Bowman JM, Pollock J. Maternal CW alloimmunization. Vox Sang 1993;64:226-30.
153. Byers BD, Gordon MC, Higby K. Severe hemolytic disease of the newborn due to anti-Cw. Obstet Gynecol 2005;106:1180-2.
154. May-Wewers J, Kaiser JR, et al. Severe neonatal hemolysis due to a maternal antibody to the low-frequency Rh antigen C(w). Am J Perinatol 2006;23:213-7.
155. Stratton F, Renton PH. Haemolytic disease of the newborn caused by a new Rh antibody, anti-Cx. Br Med J 1954;1:962-5.

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156. Westhoff CM, Silberstein LE, Wylie DE, et al. 16Cys encoded by the RHce gene is associated with altered expression of the e antigen and is frequent in the R0 haplotype. Br J Haematol 2001;113:666-71.
157. Hue-Roye K, Halter Hipsky C, Velliquette RW, et al. RHCE*ce(1025C>T) encodes partial c and e antigens. Transfusion 2010;50:147A.
158. Pham BN, Peyrard T, Juszczak G, et al. Analysis of RhCE variants among 806 individuals in France: considerations for transfusion safety, with emphasis on patients with sickle cell disease. Transfusion 2011;51:1249-60.
159. Peyrard T, Pham BN, Poupel S, et al. Alloanti-c/ce in a c+ceAR/Ce patient suggests that the rare RHCE ceAR allele (ceAR) encodes a partial c antigen. Transfusion 2009;49:2406-11.
160. Hipsky CH, Lomas-Francis C, Fuchisawa A, et al. RHCE*ceAR encodes a partial c (RH4) antigen. Immunohematology 2010;26:57-9.
161. Reid ME, Lomas-Francis C, Olsson ML. The Blood Group Antigen FactsBook. 3rd edition. Academic Press, 2012.
162. Deleers M, Thonier V, Claes V, et al. A Tutsi family harbouring two new RHCE variant alleles and a new haplotype in the Rh blood group system. Vox Sang 2020;115:451-5.
163. Westhoff CM, Vege S, Hipsky CH, et al. RHCE*ceAG (254C>G, Ala85Gly) is prevalent in blacks, encodes a partial ce-phenotype, and is associated with discordant RHD zygosity. Transfusion 2015;55:2624-32.
164. O'Suoji C, Liem RI, Mack AK, et al. Alloimmunization in sickle cell anemia in the era of extended red cell typing. Pediatr Blood Cancer 2013;60:1487-91.
165. Noizat-Pirenne F, Mouro I, Le Pennec PY, et al. Two new alleles of the RHCE gene in Black individuals: the RHce allele ceMO and the RHcE allele cEMI. Br J Haematol 2001;113:672-9.
166. Crowley J, Nickle P, Christensen J, et al. P-494: CERN/CEBP: a rare RHCE compound heterozygote. Vox Sang 2012;103:222-3.
167. Faas BH, Ligthart PC, Lomas-Francis C, et al. Involvement of Gly96 in the formation of the Rh26 epitope. Transfusion 1997;37:1123-30.
168. Lavoie J, Éthier C, St-Louis M. A new RHCE variant allele, RHCE*48C,1170T,1193A. Transfusion 2016;56:1915-7.
169. Pham BN, Peyrard T, Tourret S, et al. Anti-HrB and anti-hrb revisited. Transfusion 2009;49:2400-5.
170. Pham BN, Peyrard T, Juszczak G, et al. Alloanti-c (RH4) revealing that the (C)ce s haplotype encodes a partial c antigen. Transfusion 2009;49:1329-34.
171. Hipsky CH, Lomas-Francis C, Fuchisawa A, et al. RHCE*ceCF encodes partial c and partial e but not CELO, an antigen antithetical to Crawford. Transfusion 2011;51:25-31.
172. Esteban R, Nogues N, Montero R, et al. S02-003: RhD epitope expression in a RHD negative individual: characterization of a novel RHCE variant allele. Transfus Clin Biol 2001;8:8s-9s.
173. Lomas-Francis C, Alcantara D, Westhoff C, et al. JAL (RH48) blood group antigen: serologic observations. Transfusion 2009;49:719-24.
174. Ong J, Walker PS, Schmulbach E, et al. Alloanti-c in a c-positive, JAL-positive patient. Vox Sang 2009;96:240-3.
175. Hue-Roye K, Reid ME, Westhoff CM, et al. Red cells from the original JAL+ proband are also DAK+ and STEM+. Vox Sang 2011;101:61-4.
176. Hue-Roye K, Hipsky CH, Velliquette RW, et al. A novel RHCE*ce 48C, 733G allele with Nucleotide 941C in Exon 7 encodes an altered red blood cell e antigen. Transfusion 2011;51:32-5.
177. Moulds M, Billingsley L, Noumsi T, et al. 4D-S26-04: Allele drop-out as a possible cause for discrepant V genotyping. Vox Sang 2015;109:60.
178. Hazenberg CA, Beckers EA, Overbeeke MA. Hemolytic disease of the newborn caused by alloanti-D from an R0Har r Rh:33 mother. Transfusion 1996;36:478-9.
179. Grimsley S, Bullock T, Search S, et al. SI39: An Individual with the R2R0HAR Phenotype was Positive with Three Monoclonal Anti-e and Produced Alloanti-e. Transfus Med 2014;24:27.
180. Poole J, Grimsley S, Thornton NM, et al. PO70: A novel mutation in RHCE giving rise to the Rh:-51 phenotype and an antibody to a high frequency Rh antigen present on other Rh:-51 cells. Transfus Med 2012;22:56.
181. von Zabern I, Oswald F, Weinstock C. SP293: Allo-Anti-e in a Carrier of a Partial e: The Allele RHCE*ceMNL Encodes for a Novel e Variant. Transfusion 2012;52:164A.
182. Noizat-Pirenne F, Le Pennec PY, Mouro I, et al. Molecular background of D(C)(e) haplotypes within the white population. Transfusion 2002;42:627-33.
183. Sistonen P, Sareneva H, Pirkola A, et al. MAR, a novel high-incidence Rh antigen revealing the existence of an allelic sub-system including Cw (Rh8) and Cx (Rh9) with exceptional distribution in the Finnish population. Vox Sang 1994;66:287-92.

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184. Peyrard T, Nataf J, Poupel S, et al. SP291: CxCx and CwCx Red Blood Cells are Incompatible with MAR-like Antibody Made by a CwCw Patient. Transfusion 2012;52:163A.
185. Daniels GL. An investigation of the immune response of homozygotes for the Rh haplotype --D-- and related haplotypes. Using cells of rare Rh phenotypes. Rev Fr Transfus Immunohematol 1982;25:185-97.
186. Le Pennec PY, Rouger P, Klein MT, et al. A serologic study of red cells and sera from 18 Rh:32,-46 (RN/RN) persons. Transfusion 1989;29:798-802.
187. Floch A, Tournamille C, Chami B, et al. Genotyping in Sickle Cell Disease Patients: The French Strategy. Transfus Med Hemother 2018;45:264-70.
188. Tournamille C, Meunier-Costes N, Costes B, et al. Partial C antigen in sickle cell disease patients: clinical relevance and prevention of alloimmunization. Transfusion 2010;50:13-9.
189. Vege S, Adamy J, Hu Z, et al. S36-020C: Anti-hrB-like Reactivity Identified in a Caucasian Patient: Evidence That RHCE*Ce(890C) Encodes a Partial Phenotype. Transfusion 2014;54:31A.
190. Strobel E, Noizat-Pirenne F, Hofmann S, et al. The molecular basis of the Rhesus antigen Ew. Transfusion 2004;44:407-9.
191. Yamada M, Yamada N, Kon E, et al. SP225: A Partial E III (EFM) Patient with Rare Genotype Expressing Anti-E Antibody after Transfusion of Platelet Concentrates. Transfusion 2014;54:146A.
192. de Haas M, Ligthart PC, Haer L, et al. P-433: A pregnant woman with antibodies against a high-frequency RH antigen. Vox Sang 2012;103:204.
193. Lomas-Francis C, Rodriguez M, Velliquette RW, et al. SP227: A New Hybrid RHCE*CE-D(4-7)-CE in a Patient with Anti-RH17 and the Rare Dc- Phenotype. Transfusion 2014;54:147A.
194. Daniels GL, Faas BH, Green CA, et al. The VS and V blood group polymorphisms in Africans: a serologic and molecular analysis. Transfusion 1998;38:951-8.
195. Faas BH, Beckers EA, Wildoer P, et al. Molecular background of VS and weak C expression in blacks. Transfusion 1997;37:38-44.
196. Giblett ER, Chase J, Motulsky AG. Studies on anti-V, a new potentially dangerous blood group antibody. Bibl Haematol 1958;7:119-22.
197. Greenwalt TJ, Sanger R. The Rh antigen Ew. Br J Haematol 1955;1:52-4.
198. Grobel RK, Cardy JD. Hemolytic disease of the newborn due to anti-EW. A fourth example of the Rh antigen, EW. Transfusion 1971;11:77-8.
199. Behzad O, Lee CL, Smith D. Hemolytic disease of the newborn due to anti-VS. Transfusion 1982;22:83.
200. Lopez GH, McGowan EC, McGrath KA, et al. A D+ blood donor with a novel RHD*D-CE(5-6)-D gene variant exhibits the low-frequency antigen RH23 (D(W)) characteristic of the partial DVa phenotype. Transfusion 2016;56:2322-30.
201. Chown B, Lewis M, Kaita H. A New Rh Antigen and Antibody. Transfusion 1962;2:150-4.
202. Spruell P, Lacey PA, Bradford M, et al. Incidence of hemolytic disease of the newborn due to anti-Dw. Transfusion 1997;37:43S.
203. Aeschlimann J, Vege S, Lomas-Francis C, et al. IGT16-ST4-24: Serological and Molecular Characterization of Three New RHD Alleles. Transfusion 2018;58:44A.
204. Leschek E, Pearlman SA, Boudreaux I, et al. Severe hemolytic disease of the newborn caused by anti-Gonzales antibody. Am J Perinatol 1993;10:362-4.
205. Alter AA, Gelb AG, Lee SL. Hemolytic disease of the newborn caused by a new antibody (anti-Go-a). Bibl Haematol 1964;19:341-3.
206. Reid ME, Sausais L, Zaroulis CG, et al. Two examples of an inseparable antibody that reacts equally well with DW+ and Rh32+ red blood cells. Vox Sang 1998;75:230-3.
207. Wallace M, Lomas-Francis C, Beckers EA, et al. DBT: a partial D phenotype associated with the low-incidence antigen Rh32. Transfus Med 1997;7:233-8.
208. Issitt PD, Gutgsell NS, Martin PA, et al. Hemolytic disease of the newborn caused by anti-Rh32 and demonstration that RN encodes rhi (Ce,Rh7). Transfusion 1991;31:63-6.
209. Orlina AR, Unger PJ, Lacey PA. Anti-Rh32 causing severe hemolytic disease of the newborn. Rev Fr Transfus Immunohematol 1984;27:613-8.
210. Hue-Roye K, O'Shea K, Gillett R, et al. The low prevalence Rh antigen Be(a) (Rh36) is associated with RHCE*ce 662C>G in exon 5, which is predicted to encode Rhce 221Arg. Vox Sang 2010;98:e263-8.
211. Davidsohn I, Stern K, Strauser ER, et al. Be, a new private blood factor. Blood 1953;8:747-54.
212. Stern K, Davidsohn I, Jensen FG, et al. Immunologic studies on the Bea factor. Vox Sang 1958;3:425-34.
213. Rouillac C, Le Van Kim C, Beolet M, et al. Leu110Pro substitution in the RhD polypeptide is responsible for the DVII category blood group phenotype. Am J Hematol

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1995;49:87-8.
214. Faas BH, Beuling EA, Ligthart PC, et al. Partial expression of RHc on the RHD polypeptide. Transfusion 2001;41:1136-42.
215. Levene C, Sela R, Grunberg L, et al. The Rh antigen Tar (Rh40) causing haemolytic disease of the newborn. Clin Lab Haematol 1983;5:303-5.
216. Hipsky CH, Hue-Roye K, Lomas-Francis C, et al. Molecular basis of the rare gene complex, DIVa(C)-, which encodes four low-prevalence antigens in the Rh blood group system. Vox Sang 2012;102:167-70.
217. Delehanty C, Wilkinson S, Issitt P, et al. Riv: a new low incidence Rh antigen. Transfusion 1983;23:410.
218. Schmid P, von Zabern I, Scharberg EA, et al. Specific amino acid substitutions cause distinct expression of JAL (RH48) and JAHK (RH53) antigens in RhCE and not in RhD. Transfusion 2010;50:267-9.
219. Lomas C, Poole J, Salaru N, et al. A low-incidence red cell antigen JAL associated with two unusual Rh gene complexes. Vox Sang 1990;59:39-43.
220. Poole J, Hustinx H, Gerber H, et al. The red cell antigen JAL in the Swiss population: family studies showing that JAL is an Rh antigen (RH48). Vox Sang 1990;59:44-7.
221. Marais I, Moores P, Smart E, et al. STEM, a new low-frequency Rh antigen associated with the e-variant phenotypes hrS-(Rh: -18, -19) and hrB-(Rh: -31, -34). Transfus Med 1993;3:35-41.
222. Reid ME, Storry JR, Sausais L, et al. DAK, a new low-incidence antigen in the Rh blood group system. Transfusion 2003;43:1394-7.
223. Toly-Ndour C, Huguet-Jacquot S, Pernot F, et al. Anticorps anti-privé dans le système RH et maladie hémolytique du nouveau-né?: à propos de 2 cas. Transfus Clin Biol 2017;24:347.
224. Coghlan G, Moulds M, Nylen E, et al. Molecular basis of the LOCR (Rh55) antigen. Transfusion 2006;46:1689-92.
225. Coghlan G, McCreary J, Underwood V, et al. A "new" low-incidence red cell antigen, LOCR, associated with altered expression of Rh antigens. Transfusion 1994;34:492-5.
226. Flegel WA, Wagner FF. DEL. Blood Transfus 2020;18:159-62.
227. Yang HS, Lee MY, Park TS, et al. Primary anti-D alloimmunization induced by "Asian type" RHD (c.1227G>A) DEL red cell transfusion. Ann Lab Med 2015;35:554-6.
228. Kim KH, Kim KE, Woo KS, et al. Primary anti-D immunization by DEL red blood cells. Korean J Lab Med 2009;29:361-5.
229. Mota M, Fonseca NL, Rodrigues A, et al. Anti-D alloimmunization by weak D type 1 red blood cells with a very low antigen density. Vox Sang 2005;88:130-5.
230. Berardi P, Bessette E, Ng M, et al. Weak D type 67 in four related Canadian blood donors. Immunohematology 2015;31:159-62.
231. Yasuda H, Ohto H, Sakuma S, et al. Secondary anti-D immunization by Del red blood cells. Transfusion 2005;45:1581-4.
232. Bugert P, Scharberg EA, Geisen C, et al. RhCE protein variants in Southwestern Germany detected by serologic routine testing. Transfusion 2009;49:1793-802.
233. Scharberg EA, Green C, Daniels GL, et al. Molecular basis of the JAHK (RH53) antigen. Transfusion 2005;45:1314-8.
234. Vrignaud C, Ramelet S, Joffrin C, et al. CP239: RHCE*Ce286A Is a Novel RHCE Allele That Causes a Weak C Expresion and Codes for the Low-Prevalence LOCR (RH55) Antigen. Transfusion 2017;57:156A.
235. Moores P. Rh18 and hrS blood groups and antibodies. Vox Sang 1994;66:225-30.
236. Belsare S, Levy-Sakin M, Mostovoy Y, et al. Evaluating the quality of the 1000 genomes project data. BMC Genomics 2019;20:620.
237. Pirenne F, Yazdanbakhsh K. How I safely transfuse patients with sickle-cell disease and manage delayed hemolytic transfusion reactions. Blood 2018;131:2773-81.
238. Ibanez C, Habibi A, Mekontso-Dessap A, et al. Anti-HI can cause a severe delayed hemolytic transfusion reaction with hyperhemolysis in sickle cell disease patients. Transfusion 2016;56:1828-33.
239. Coleman S, Westhoff CM, Friedman DF, et al. Alloimmunization in patients with sickle cell disease and underrecognition of accompanying delayed hemolytic transfusion reactions. Transfusion 2019;59:2282-91.
240. Walters TK, Lightfoot T. A delayed and acute hemolytic transfusion reaction mediated by anti-c in a patient with variant RH alleles. Immunohematology 2018;34:109-12.
241. Floch A, Gien D, Tournamille C, et al. High immunogenicity of red blood cell antigens restricted to the population of African descent in a cohort of sickle cell disease patients. Transfusion 2018;58:1527-35.
242. Boateng LA, Schonewille H, Ligthart PC, et al. One third of alloantibodies in patients with sickle cell disease transfused with African blood are missed by the standard red blood cell test panel. Haematologica 2021;106:2274-6.

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243. Stef M, Fennell K, Apraiz I, et al. RH genotyping by nonspecific quantitative next-generation sequencing. Transfusion 2020;60:2691-701.

244. Halls JBL, Vege S, Simmons DP, et al. Overcoming the challenges of interpreting complex and uncommon RH alleles from whole genomes. Vox Sang 2020;115:790-801.

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