Maternal red blood cell alloimmunisation Working Party, literature review. RH blood group system: rare specificities

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Abstract:	Abstract in English: This report is part of a series reporting the GRADE review performed by the 2018-2020 French Working Party on maternal red blood cell alloimmunisation. This report focusses on the clinical significance in obstetrics, as published in the scientific literature, of the rare RH antibodies, variants and antigens (i.e. excluding conventional RH1 trough RH8 antigens, RH12, RH22 and RH27, which are discussed in other reports of this series). Extremely severe or severe haemolytic disease of the fetus and the newborn (HDFN), leading to death or requiring transfusions, have been reported for: anti-RH1 (-D) associated with DVI, DBT and DIVb phenotypes, RHD*12.04 (DOL4), RHD*03.03 (DIIIc), RHD*D-CE(2-5)-D RHD*01EL.31 (RHD*148+1T) , anti-RH9 (-CX), anti-RH11 (-EW), anti-RH17 (-Hr0), anti-RH18 (-Hr), anti-RH19 (-hrS), anti-RH23 (-DW), anti-RH29 (“total” Rh) , anti-RH30 (-Goa), anti-RH32, anti-RH34 (-HrB), anti-RH36 (-Bea), anti-RH40 (-Tar), anti-RH46 (-Sec), anti-RH48 (-JAL), anti-RH54 (DAK), and antibodies to high prevalence antigens such as those associated with RHCE*02.08.02 (RHCE*CW-RHD(6-10)), RHCE*03N.01 (RHCE*cEMI) . HDFN of moderate, mild or undetailed severity have been reported for: anti-RH1 associated with DHar, DIIIa and DIVa phenotypes, RHD*01EL.08 (RHD*486+1A), RHD*01EL.44 (RHD*D-CE(4-9)-D), RHD*25 (DNB), anti-RH20 (-VS), anti-RH31 (-hrB), anti-RH37 (-Evans), ani-RH42, anti-RH49 (-STEM), anti-RH51 (-MAR), anti-RH55 (-LOCR), anti-RH58 (-CELO). Positive direct antiglobulin test in the newborn but no clinically significant HDFN has been reported for anti-RH1 (-D) associated with RHD*10.05 (DAU5), RHD*12.02 (DOL2) . Because so many specificities are associated with severe HDFN in the RH system, all RH antibodies should be considered as potentially able to cause HDFN, even if none has been reported yet. Résumé en français : Cet article fait partie d’une série qui restitue les travaux de bibliographie selon la méthodologie GRADE réalisés par le groupe de travail français sur les alloimmunisations anti-érythrocytaires materno-fœtales. Il présente la signification clinique en obstétrique, telle que publiée dans la littérature scientifique, des anticorps, variants et antigènes rares du système RH (à l’exclusion des antigènes RH1 à RH8 normaux, RH12, RH22 et RH27, qui seront abordés dans d’autres rapports). Des maladies hémolytiques du fœtus et du nouveau-né (MHNN) extrêmement sévères ou sévères (responsables de décès, ou nécessitant une ou plusieurs transfusions) ont été décrites pour : anti-RH1 (-D) associé aux phenotypes DVI, DBT and DIVb, à

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Abstract in English:

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Extremely severe or severe haemolytic disease of the fetus and the newborn (HDFN), leading to death or requiring transfusions, have been reported for: anti-RH1 (-D) associated with DVI, DBT and DIVb phenotypes, *RHD*12.04 (DOL4), RHD*03.03 (DIIIc), RHD*D-CE(2-5)-D RHD*01EL.31 (RHD*148+1T)*, anti-RH9 (-C^X), anti-RH11 (-E^W), anti-RH17 (-Hr^0), anti-RH18 (-Hr), anti-RH19 (-hr^S), anti-RH23 (-D^W), anti-RH29 ("total" Rh), anti-RH30 (-Go^a), anti-RH32, anti-RH34 (-Hr^B), anti-RH36 (-Be^a), anti-RH40 (-Tar), anti-RH46 (-Sec), anti-RH48 (-JAL), anti-RH54 (DAK), and antibodies to high prevalence antigens such as those associated with *RHCE*02.08.02 (RHCE*C^W-RHD(6-10)), RHCE*03N.01 (RHCE*cEMI)*.

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has been reported for anti-RH1 (-D) associated with *RHD*10.05 (DAU5), RHD*12.02 (DOL2)*. Because so many specificities are associated with severe HDFN in the RH system, all RH antibodies should be considered as potentially able to cause HDFN, even if none has been reported yet.

Keywords: Maternal alloimmunisation; RH blood group; RH variants; high prevalence antigens; low prevalence antigens

Résumé en français :

Cet article fait partie d'une série qui restitue les travaux de bibliographie selon la méthodologie GRADE réalisés par le groupe de travail français sur les alloimmunisations anti-érythrocytaires materno-fœtales. Il présente la signification clinique en obstétrique, telle que publiée dans la littérature scientifique, des anticorps, variants et antigènes rares du système RH (à l'exclusion des antigènes RH1 à RH8 normaux, RH12, RH22 et RH27, qui seront abordés dans d'autres rapports).

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Des MHNN modérées, peu sévères ou de sévérité non précisée ont été rapportées pour : anti-RH1 associé aux phénotypes DHar, DIIIa et DIVa, *RHD*01EL.08 (RHD*486+1A), RHD*01EL.44 (RHD*D-CE(4-9)-D)*, *RHD*25 (DNB)*, anti-RH20 (-VS), anti-RH31 (-hr^B),

anti-RH37 (-Evans), ani-RH42, anti-RH49 (-STEM), anti-RH51 (-MAR), anti-RH55 (-LOCR), et anti-RH58 (-CELO).

Étant donné les MHNN sévères associées à de nombreuses spécificités RH, tous les anticorps du système RH peuvent être considérés comme potentiellement à risque de MHNN sévère.

Mots clefs : Alloimmunisation materno-fœtale; système de groupe sanguin RH; variants RH; antigènes publics; antigènes privés

Introduction

The large – and constantly increasing – number of known blood group systems, antigens (Ag), and alleles pose a challenge in obstetrics. During pregnancy, a patient may develop an alloantibody to a fetal red blood cell (RBC) antigen. Such an antibody (Ab) may lead to varying degrees of haemolytic disease of the fetus and the newborn (HDFN), ranging from a positive direct antiglobulin test at birth, kernicterus and/or anaemia, to fetal or neonatal death. Kernicterus management may require phototherapy, albumin infusions, immunoglobulin infusions, exchange transfusion therapy. Anaemia management, in the most severe cases, may require intrauterine transfusion therapy. Careful monitoring of pregnancies of women with allo-Ab to RBC antigens is key to a favourable fetal and neonatal outcome. However, excessive procedures are costly, time-consuming, and cause unnecessary stress to the mother-to-be and her fetus, while mobilizing resources which could be allocated otherwise. It is important to adapt the monitoring of pregnancies to the Ab specificity.

Non-specialists, and even transfusion specialists, may have difficulties identifying the clinical significance and HDFN risk of a given Ab. For common, high risk Ab, like anti-RH1 (anti-D) in RH:–1 (D negative) individuals, many studies have been published. However, for the many rare antigens, antibodies and variants of the RH blood group system, data is dispersed in a number of case reports.

The published evidence regarding the clinical significance in obstetrics of the rare antibodies, variants and antigens of the RH blood group system was collected and organized and is presented here. The normal RH1 to RH8, (D, C, E, c, e, f or ce, Ce, C^W), RH12 (G), RH22 (CE) and RH27 (cE) antigens were excluded from the analysis, as they will be discussed in other reports of this series. Of the 55 antigens currently listed by the International Society of Blood Transfusion (ISBT), 44 were evaluated here (Table 1). The variants of the RH1, RH2, RH3, RH4 and RH5 antigens were also evaluated (Table 2).

This review is part of a series reporting the systematic review of the literature performed by the 2018-2020 French Working Party on maternal RBC alloimmunization, based on the GRADE methodology to guide recommendations, with the objective of assessing the obstetrical risk associated with the different antibodies to RBC antigens.

Methodology and biases of the available literature

To assess the obstetrical risk associated with rare RH specificities, 192 studies and abstracts were evaluated. Studies were excluded either because of insufficient typing (e.g. anti-RH1 in a "Du" mother), because patients had not developed antibodies, or because no obstetrical data was included. Medical care has substantially evolved over the past decades and outcomes of earlier reports cannot be transferred to current practice. Nonetheless, as long as the differences in medical care are taken into account, these outcomes can inform current decisions. The indicative article publication date fixed by the Working Party for inclusion in this literature review was 1998, which could be extended for rare specificities (with no limit) when more recent references were not available.

Of the 192 studies evaluated, 64 were included in the literature review (the complete reference list included in the GRADE review of the literature can be found in the Online Supporting Material S1). Twenty-nine of the studies included (45,3%) had been published before 1998.

Fifty-six studies (87,5%) were case reports and eight were observational cohort studies. This repartition is a clear bias: the most severe cases are likely to have been reported, while the mild or asymptomatic cases were not. Moreover, important elements are often absent. Maternal antibody titres and titre evolution during pregnancy are too sparse to determine critical antibody titres and thresholds. The (in)compatibility of the neonates is not always clear, as neonate RBC phenotypes are not systematically determined. ABO antibodies are not explicitly excluded in most publications. Finally, the severity of HDFN is not always evaluable, as haemoglobin and bilirubin levels are not consistently reported, and some patients are lost to follow-up. Because of all these biases, this review presents a measured interpretation of the available data and remains cautious in its recommendations, based on the very low certainty of the evidence.

Moreover, because the Ab discussed here are particularly rare, the present report references several additional cases which were not included in the GRADE literature review but may be of interest to readers. Most of these additional cases have been reported in abstract form only, with the same biases as exposed above. It should be noted that these reports in abstracts may never have become full-length articles because doubts arose as to the specificity or the imputability of the antibodies in the HDFN. For each antigen, the references listed here are to one or more of the most severe HDFN cases reported. Recent, well-documented, peer-reviewed reports would be a welcome addition to the scientific literature.

The most severe haemolytic disease of the fetus and the newborn

HDFN were considered extremely severe if fetal or neonatal deaths, or in utero transfusions had been reported. The antigens for which such HDFN have been reported are listed in Table 1, and the alleles in Table 2. HDFN were considered severe if neonatal transfusions or exchange transfusions were reported but no extremely severe HDFN (Table 1, Table 2).

A large number of pregnancies complicated by anti-RH17 Ab in RH:–17 individuals (D– – or RH:1,–2,–3,–4,–5 phenotype) have been reported and continue to be regularly reported. Fatal HDN occurred in several primiparous RH:–17 women with no history of blood transfusions. [4,51] In many reports, the fetus/neonate could be saved by intrauterine transfusions or early neonatal transfusions. Securing compatible blood for the fetus or the neonate is a major issue in anti-RH17 immunized pregnancies, and most difficult when the mother's rare phenotype and the Ab were discovered at delivery or towards the end of the pregnancy. This underlines the importance of phenotyping expectant mothers early during the pregnancy and screening for Ab, especially during the 3rd trimester. For the fetus/neonate's transfusion, the blood donor was most often the mother (sometimes regardless of ABO blood group)[52] or a close relative. Rarely, the least incompatible blood available was successfully transfused.[53] Nonetheless, it is certainly best to be prepared and resort to truly compatible blood when possible. Reports of anti-RH29 in RH:–29 individuals (RH_{null} or RH:–1,–2,–3,–4,–5 phenotype) are rarer, but have the potential to be as dangerous as anti-RH17. Similarly, anti-RH29 have been observed in primiparous women,[54] and securing compatible blood is an even bigger issue.

Many low prevalence antigens are associated with severe HDFN, and the rare RH phenotypes found in individuals of African descent (RH:–18, RH:–34, RH:–46). The RH18 and RH19 antigens have heterogeneous molecular backgrounds,[55] and the HDFN reports for Ab to these Ag unfortunately did not include molecular typing.[6,7] The report of severe HDFN associated with anti-RH34 was not analysed on the molecular level either.[7]

Severe or extremely severe HDFN have been reported for several D phenotypes and a few of the known *RHD* alleles.[56] This is due in part to the importance of the RH1 antigen in transfusion medicine and obstetrics. Moreover, RHCE variants are more readily characterized by defining new RH antigens (absent from carriers of the corresponding *RHCE* alleles) than D variants, to enhance communication.[26] E.g., the RH26, RH46 and RH58 antigens are absent

from *RHCE*01.15 (RHCE*ceLOCR),*[57] *RHCE*02.10.01 (RHCE*CeRN)*[58] and *RHCE*01.20.06 (RHCE*ceCF)*[26] homozygotes, respectively. Another explanation is that cross-matches between different antibodies and RBC, and rare reagent exchanges are much less common nowadays than in earlier works. Alleles are now often simply described as producing "partial" antigens or not, which is a practical approach, adapted for daily practice, but limits our ability to compare phenotypes.

Absence of severe haemolytic disease of the fetus and the newborn

HDFN were considered moderate if phototherapy, albumin or immunoglobulin infusions were reported, but no transfusions or deaths (Table 1, Table 2). HDFN were considered mild if biological stigma (a slight anaemia or slight elevation in bilirubin levels) were observed but none of the above-mentioned therapies were necessary (Table 1, Table 2). For some antigens, pregnancies, but no HDFN, have been reported in the literature in individuals with Ab to the Ag. These Ag are: RH41, the high prevalence antigens RH26 (c-like), RH57 (CEST), RH59 (CEAG), RH61 (CEVF), and the low prevalence antigens: RH10 (V), RH28 (hrH), RH33 (formerly known as R0Har), RH35, RH43 (Crawford), RH53 (JAHK), RH60 (PARG).

The risk of severe HDFN cannot be ruled out for these specificities. Nonetheless, for some of these antigens, incompatible situations are probably not exceptional and it seems reasonable to infer that the risk is lower for these antigens than for those for which HDFN has been reported to date. The RH20 and RH10 antigens are prevalent in many populations of African descent.[1,59] The *RHCE*01.06.01 (RHCE*254G)* allele, responsible for the RH:–59 phenotype when homozygous,[60] has a prevalence of about 5% in French patients with sickle cell disease.[61] The *RHCE*01.07.01 (RHCE*ce48C,667T)* allele, responsible for the RH:–61 phenotype when homozygous,[62] is a frequent cause of weakened RH5 (e) phenotype. This allele is currently identified in about half the French individuals with RH:3,w5 phenotype (E+,

weakened e),[63] and a number of homozygous individuals have also been detected, only rarely presenting with anti-RH5 Ab.

Many variant *RHD* and *RHCE* alleles have been associated with Ab formation[56] but no HDFN has been reported to date. A few *RHD* and *RHCE* alleles, for which no HDFN has been reported despite a relatively high prevalence, are listed in Table 3 and Table 4, respectively. The risk is certainly lower for these alleles than for the alleles listed in Table 2.

Finally, for some antigens, no reports could be found of pregnancies in patients with an Ab to the Ag. Among these Ag, RH21 (C^G), and the high prevalence antigens: RH39, RH44 (Nou), RH47 (Dav), are probably not very relevant to obstetrical patient management: because of the way they were initially defined,[1] it is unlikely that an alloimmunization specific to these Ag could occur. The low prevalence antigens for which no pregnancy report could be found were: RH50 (FPTT), RH52 (BARC), RH56 (CENR). The risk of severe HDFN cannot be ruled out for these low prevalence antigens, as they may not have been detected or identified for lack of appropriate reagents.

Concluding remarks and recommendations

It is easier to demonstrate that there is a risk for severe HDFN for a specificity, than to prove that there is none. HDFN have been reported for almost all RH antigens, with severe or extremely severe cases for many. Most authors consider an Ab to any RH antigen to be potentially at risk for severe HDFN,[1,68–70] perhaps in connection with unpublished observations, and for some Ag and alleles, because haemolytic transfusion reactions have been reported.[71,72] Since antibody formation is a prerequisite for haemolytic complications of alloimmunisation, it is important to monitor which RH variants are at risk for antibody formation.[56]

HDFN associated with the RH specificities listed here remain extremely rare. Some may be less infrequent as appears to-date, similarly to anti-RH17, which is more frequent in Japanese individuals, with a high number of cases (over 50) initially reported in Japanese.[4] Some phenotypes or alleles may be frequent in populations not yet or not well represented in the scientific literature. Interestingly, haemolytic transfusion reactions and HDFN case reports caused by anti-RH17 continue to be reported each year in the literature. The fact that the risk is well documented risk for this specificity does not seem to limit reporting. This can be explained in part by the prevalence of D – – phenotype (lacking all RHCE antigens) and by the relative simplicity to characterize anti-RH17. However, this is also a modest argument to support that some of the more common RH Ag and alleles for which HDFN has never been reported may not be at risk for HDFN at all, because one could expect that moderate or more severe HDFN at least would have been reported.

The position on the Rh proteins of the antigens and alleles associated with the most severe HDFN, when these are encoded by a single substitution, should be noted. In many, the substitution alters a residue in one of the two largest extracellular loops of the Rh proteins (Figure 1). Thus, any variant affecting these loops should be considered at a very high risk for severe HDFN, even if none has yet been observed. The absence of HDFN associated with residue 38, is most likely explained by the very recent description of the corresponding antigen (p.L38P on RhCE abolishes the RH62 (CEWA) antigen expression) and by the rarity of the change.[73]

Because of the very low certainty levels and the limited data available, we recommend that patient management (Ab screening and quantification frequencies, threshold to initiate Doppler ultrasound surveillance…) should follow the recommendations for the more common RH antigens, with a few specificities. For the rare phenotypes lacking a high prevalence antigen, we recommend following the upcoming guidelines of our working party for D negative (RH:–

1) patients, with an increased vigilance and anticipation of potential transfusion requirements, to secure compatible blood ahead of a potential emergency. For other RH Ab and Ag, we recommend following the upcoming guidelines of our working party for the conventional RHCE antigens. More data is clearly necessary to establish more specific guidelines in the future. Consequently, we recommend always identifying RH antibodies responsible for HDFN, including Ab to low prevalence antigens, and genotyping mothers who develop Ab to an Ag they seemingly carry (i.e. a potential partial RH Ag). Only by reporting these findings and additional detailed case reports, will it be possible to improve our management of rare RH alloimmunisations.

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Web resources

Grade methodology https://www.gradeworkinggroup.org/

The Human RhesusBase http://www.rhesusbase.info/

Protter http://wlab.ethz.ch/protter/start/

RHeference https://www.rheference.org/

International Society of Blood Transfusion website http://www.isbtweb.org/

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Tables

Table 1

Obstetrical significance of the antigens of the RH blood group system (excluding RH1 to RH8, RH12, RH22 and RH27).

Antigen	Ag prevalence [1]	HDFN severity
RH9 (C^X)	Low	Severe[2]
RH11 (E^W)	Low	Severe[3]
RH17 (Hr_0)	High	Extremely severe[4,5]
RH18 (Hr or Hr^S)†	High	Extremely severe[6] but no molecular typing
RH19 (hr^S)†	High	Severe[7]
RH20 (VS)	Low	Mild[8]
RH23 (D^W)	Low	Severe[9]
RH29 (formerly known as "Total Rh")	High	Extremely severe (although the imputability of the Ab in the outcome is unclear)[10] or severe[11]
RH30 (Go^a)	Low	Severe[12]
RH31 (hr^B)†	High	Mild[13] but no molecular typing
RH32 (formerly known as R^N)	Low	Severe[14]
RH34 (Hr^B)	High	Severe[7] (no molecular typing)
RH36 (Be^a)	Low	Severe[15]
RH37 (Evans)	Low	HDFN reported, severity unknown[16]
RH40 (Tar)	Low	Severe[17]
RH42	Low	Mild[18]‡
RH45 (Riv)	Low	Positive DAT[19] (but associated with an anti-RH30)
RH46 (Sec)	High	Severe[20]
RH48 (JAL)	Low	Severe[21]
RH49 (STEM)	Low	Moderate[22]
RH51 (MAR)†	High	HDFN reported, severity unknown[23]
RH54 (DAK)	Low	Severe[24]
RH55 (LOCR)	Low	Mild[25]‡
RH58 (CELO)	High	Moderate[26]

Reference(s) are to the most severe cases associated with the specificity. HDFN levels: Extremely severe (HDFN leading to fetal or neonatal death), severe (HDFN required neonatal transfusions or exchange transfusions), moderate (HDFN required phototherapy), mild (HDFN required surveillance but did not require any specific therapy), positive DAT (with no other signs). For clarity, the Ag for which no HDFN has been reported are not included in this table (see text). † This antigen presents with heterogeneous molecular background. ‡ Severity reported as such by authors but not detailed.

Table 2

Obstetrical significance of the variants of the RH1, RH2, RH3, RH4 and RH5 antigens.

Ab and Allele	HDFN severity
With No molecular typing:	
- Anti-D associated with a DVI phenotype†	Extremely severe[27]
- Anti-D associated with a DBT phenotype	Severe[28]
- Anti-D associated with a "DHar" phenotype	Moderate[29]
- Anti-D associated with DIVa phenotype	Mild[30]
- Anti-D associated with DIVb phenotype	Severe[31]
- Antibody to a high prevalence Ag, associated with an RH:1,–2, –3,4,–5 (Dc–) phenotype, no molecular typing	Extremely severe[32]
With molecular typing:	
- Anti-D associated with *RHD*01EL.31 (RHD*148+1T)*	Extremely severe[33]
- Anti-D associated with *RHD*25 (RHD*DNB)*	Moderate[34,35]
- Anti-D associated with *RHD*12.04 (RHD*DOL4)*	Severe[36]
- Anti-D associated with *RHD*03.01 (RHD*DIIIa)*	Severity unknown [37]
- Anti-D associated with *RHD*03.03 (RHD*DIIIc)*	Severe[38]
- Anti-D associated with *RHD*01EL.08 (RHD*486+1A)*	Moderate[39]
- Anti-D associated *with RHD*05* (*RHD*DV)*, partly characterized	Moderate[34]
- Anti-D associated with *RHD*10.05 (RHD*DAU5)*	Positive DAT[40]
- Anti-D associated with *RHD*12.02 (RHD*DOL2)*	Positive DAT[41]
- Anti-D associated with *RHD*D-CE(2-5)-D*	Moderate or severe[42]
- Anti-D associated with *RHD*01EL.44 (RHD*D-CE(4-9)-D)*	Moderate[43]
- Antibody to a high prevalence Ag, associated with *RHCE*02.08.02 (RHCE*CW-RHD(6-10))*	Severe[44]‡
- Antibody to a high prevalence Ag, associated with homozygous *RHCE*03N.01 = RHCE*cEMI*	Severe[45]§
- Antibody to a high prevalence Ag, associated with *DIVa2 - DIV(C)*– haplotype	Extremely severe according to some references.[46] The original reference makes no mention of HDFN.[47]
- Antibody to a high prevalence Ag associated in several patients with a Dc- phenotype and no molecular typing	Extremely severe[32,48–50]

See Table 1 legend for the definitions of the severity grades. † In many countries, RH1 typing reagents are now selected to detect DVI individuals as RH:–1 (D negative), except for blood donors. ‡ Severity reported as such by authors but not detailed. § This allele is listed despite being a null allele in the ISBT nomenclature because the patient was reported in the abstract to have a weak c (RH4) phenotype and RH3 (E) was detected by adsorption-elution with anti-RH3.

Table 3

Some *RHD* alleles commonly found in immunohematology and immunogenomics publications[64,65] for which no HDFN has been reported, despite references to pregnancy follow-ups.

Allele	**Prevalence according to Erythrogene[67]**	**Number of published carriers[64,65]**
*RHD*1136T (RHD*DAU0)* †	Africa: 37.75%. America: 12.54%. East Asia: 8.83%. Europe: 4.47%. South Asia: 12.68%.	>150
*RHD*602G,667G,1025C (RHD*DAR1)*, with or without additional silent mutations †	-	>150
*RHD*602G,667G,819A (RHD*weak D type 4.0)* †	Africa: 1.21%. Europe: 0.10%.	>150
*RHD*1227A (RHD*DEL1)* ‡	Africa: 1.13%. America: 0.14%. East Asia: 0.20%. Europe: 0.60%. South Asia: 1.94%	>150
*RHD*93dupT (RHD*01N.50* and *RHD*01EL.18)* §	-	50 - 150
*RHD*809G (RHD*weak D type 1)*	Africa: 0.08%. Europe: 0.20%	>150
*RHD*1154C (RHD*weak D type 2)*	-	>150
*RHD*8G (RHD*weak D type 3)*	America: 0.29%. Europe: 0.10%	>150
*RHD*446A (RHD*weak D type 5)*	-	50 - 150
*RHD*885T (RHD*partial weak D type 11)*†, §	-	>150
*RHD*845A (RHD*partial weak D type 15)*†, §	East Asia: 0.10%	>150
*RHD*833A (RHD*weak D type 38)*	-	>150

† Anti-RH1 have been reported[56] ‡ Some authors consider that the risk of anti-RH1 alloimmunisation has not been ruled out yet for this allele.[66] § These alleles have a very low RH1 antigen expression (DEL phenotype or very weak D phenotype), and alloimmunization and/or HDFN may have occurred but not been differentiated from anti-RH1 in truly RH:–1 (D negative) individuals.

Table 4

Some relatively common *RHCE* alleles according to Erythrogene,[67] for which no HDFN has been reported.

Allele	**Prevalence according to Erythrogene[67]**
*RHCE*ce48C (RHCE*01.01)*	Africa: 35.25%. America: 51.59%. East Asia: 73.81%. Europe: 44.63%. South Asia: 67.48%. †
*RHCE*ce733G (RHCE*ceVS.01)*	Africa: 15.28%. America: 2.31%. Europe: 0.30%.
*RHCE*ce48C,733G (RHCE*ceVS.02)*	Africa: 2.87%.
*RHCE*ce48C,733G, 941C (RHCE*ceVS.09)*	Africa: 2.57%. America: 0.14%.
*RHCE*ce48C,1025T* *RHCE*ce1025T* *RHCE*ce48C,733G,1025T* *(RHCE*ceTI* alleles)	Africa: 2.27%. America: 0.43% Africa: 0.30%. Africa: 0.08%. Europe: 0.20%.
*RHCE*cE602C (RHCE*cEIV)* ‡	Africa: 0.15%.

† Prevalence is probably overestimated in some populations because of the *RHCE*02 (RHCE*Ce)* allele. ‡ No anti-E has ever been reported in a carrier of this allele.[56]

Figure 1 Legend

Position on the Rh proteins of the antigens and alleles discussed here with a single or main substitution, represented on an RhD protein with Protter. Transemembrane (TM) domains are positioned as recently described through 3D modelling.[74] Residues 36, 41, 110, 114, 167, 221, 233, 350, 355, in red, have been associated with severe or extremely severe HDFN reports. Residues 3, 38, 85, 96, 122, 149, 201, 223, 245, 270, 278, 282, 295, 314, 342, 379 and 385, in blue, have not been associated with severe HDFN. The position of loop 2 could maybe be adjusted, since no severe HDFN has been reported for residue 96 (despite being extracellular with the current TM domain positions), but has been reported for residue 114 (despite being in a TM domain).