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Review

Back to base pairs: What is the genetic risk for red bloodcell alloimmunization?

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ABSTRACT

Red blood cell (RBC) alloimmunization is a serious complication of blood transfusions, challenging selection of compatible units for future transfusions. Genetic characteristics may be associated with the risk of RBC alloimmunization and may therefore serve to identify high-risk patients. The aim of this systematic review was to summarize the available evidence on genetic risk factors for RBC alloimmunization. Electronic databases were searched up to April 2020 for studies (Search terms included transfusion, alloimmunization and genetic). A total of 2581 alloimmunized cases and 26,558 controls were derived from 24 studies. The alleles that were most frequently studied and that demonstrated significant associations in a meta-analysis with alloimmunization to the Duffy[a] antigen were *HLA-DRB1*04* (Odds Ratio 7.80 (95%CI 4.57–13.33)), *HLA-DRB1*15* (OR 3.76 (95%CI 2.14–6.59)), and *HLA-DRB1*03* (OR 0.12 (95%CI 0.05–0.29)). Furthermore, significant associations with anti-K formation was found for the alleles *HLA-DRB1*10* (OR 2.64 (95%CI 1.41–4.95)), *HLA*DRB1*11* (OR 2.11, (95% CI 1.34–3.32)), and *HLA-DRB1*13* (OR 1.71 (95%CI 1.26–2.33)). Overall, the available evidence was of moderate to low quality, hampering interpretation of reported results. There is an urgent need for high quality evidence on genetic risk factors for RBC alloimmunization.

1. Introduction

Blood transfusions are an important and lifesaving treatment modality for several diseases such as myelodysplastic syndrome, hematological malignancies, sickle cell disease (SCD) and β-thalassemia among others [1–3]. A serious hazard of blood transfusions is the development of antibodies directed towards antigens on the donor red blood cells (RBCs). The development of these antibodies complicates the selection of compatible units for future transfusions and may cause life-threatening delays in the administration of RBC units to critically ill patients. Moreover, RBC alloimmunization increases the risk for potentially lethal delayed hemolytic transfusion reactions in subsequent transfusions [4–6].

Antigen mismatch between donor and recipient is the basis for antibody formation, as the recipient recognizes those antigens as non-self and thereby an immune response might be elicited. Consequently, complete antigenic matching would theoretically eliminate all cases of RBC alloimmunization. However, this would lead to complex logistical and financial challenges [7,8]. Therefore, extended matching should be reserved for patients at highest risk to form antibodies. Extended matching for the most immunogenic antigens, RhCcEe and K, has reduced RBC alloimmunization rates in myelodysplastic syndrome and SCD to some extent, but does not completely abrogate antibody formation [9,10].

Several risk factors that predispose for RBC alloimmunization have previously been identified. In general, longstanding infection and

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inflammation have been associated with an increased risk for RBC antibody formation [11,12]. In mice, inflammation has been demonstrated to be a key trigger for RBC alloimmunization [13–15]. Interestingly, infection with gram-negative bacteria leads to a decreased risk of RBC alloimmunization, potentially via LPS signaling, which has been supported by mouse models [11,16]. Moreover, a transfusion in the absence of inflammation seems to have an immunosuppressive effect on a subsequent transfusion [13,17]. Other risk factors that have been identified are the immunogenicity of an antigen, number of transfusions and antigenic differences between donors and recipients [10,12,18,19]. Despite these identified risk factors, in daily practice it remains a great challenge to identify patients at high risk to form antibodies.

Interestingly, it appears that only a subgroup of patients is at a particular high risk to form antibodies (responders), even against less immunogenic antigens, while the majority of patients does not form antibodies, despite multiple transfusions (nonresponders) [6,10]. It has been suggested that responders may represent a genetically distinct group, as currently known clinical risk factors fail to accurately predict RBC alloimmunization [20].

A number of studies addressed the influence of genetic polymorphisms on RBC alloimmunization. Variants of HLA-class II, especially at the DR locus, have been associated with RBC alloimmunization (e.g. *HLA-DRB1*04, HLA-DRB1*10 and HLA-DRB1*15*) [21,22]. This is not unexpected, as most blood group antigens are caused by single amino acid changes, and different HLA molecules have different affinities for the peptides carrying the antigen specific T cell epitope [23]. Furthermore, antibody responses are influenced by the balance between activating and regulatory costimulatory signals to T and B cells. Single nucleotide polymorphisms (SNPs) in these pathways may also contribute to the risk of alloimmunization upon transfusion. SNPs in genes such as *IL-1β* (involved in inflammation and T cell dependent immunization processes [24]), *CD81* (lies in close proximity of Hbβ gene and is directly associated with CD19 receptor function on B cells [25,26]*)* and *FC-gamma-receptor* (regulating immune activation by binding of Fc portion of IgG [27]) have previously been associated with RBC alloimmunization, and support this hypothesis [26–28].

Over the last years, several studies have addressed genetic markers for alloimmunization. Identification of these genetic markers may help to increase our understanding of the pathophysiological mechanism of antibody formation and may improve identification of patients at high risk for alloimmunization. This may provide a basis for new treatment strategies that potentially lead to a safer and more cost-effective transfusion therapy for all patients. However, a clear overview of all available evidence has never been made. The objective of this review was to systematically review the available evidence on genetic risk factors for RBC alloimmunization.

2. Methods

We performed this review following the PRISMA guidelines. The study protocol was published on PROSPERO (CRD42018100040).

2.1. Search strategy

We identified relevant articles from the electronic databases Embase (Ovid Embase Classic and Embase 1947 to present), MEDLINE (Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to present) and the Cochrane library. Terms included in the search were transfusion, alloimmunization and genetic (see Supplemental Table 1 for full search term). In addition, references of selected articles were searched for relevant publications. To limit potential bias, there was no restriction on language, publication year, or publication status. The search was last updated in April 2020.

2.2. Study selection

Studies were included in the review if the following criteria were met: a) primary study that explored associations between genetic polymorphisms and RBC transfusion related alloimmunization; b) study was conducted in human population; c) cohort existed of at least 50 patient; d) full text was available. Titles and abstracts of articles were screened for relevance by three independent reviewers (each article by two reviewers; JG, SM and IO) and selected for full text assessment. Disagreement was resolved by discussion between the two reviewers, if needed with input of a third reviewer.

2.3. Outcomes of this review

The primary outcome of this study was RBC alloimmunization. Besides overall occurrence of alloimmunization, we examined alloimmunization to specific RBC antigens, as described in the included studies (e.g. anti-D, anti-C, anti-Fy^a etc.).

2.4. Data extraction

Titles and abstracts of studies retrieved using the search strategy and studies retrieved from references by the included papers were screened according to the inclusion criteria outlined above. The Rayyan application was used during this process [29]. Full text of the selected studies was retrieved and independently assessed for eligibility by two review authors (JG, SM and IO). Any disagreement was resolved through discussion with a third reviewer.

A standardized data-extraction form was developed to extract data from the included studies for evidence synthesis. Extracted information included study setting, study population, participant demographics and baseline characteristics; details of case and control conditions; study methodology, defined outcomes. Data were independently extracted by three reviewers (JG, SM and IO) and any discrepancies were resolved through discussion.

2.5. Quality assessment

Three authors (JG, SM and IO) assessed risk of bias independently. A validated tool to assess quality of genetic association studies (Q-genie tool) was used to perform quality assessment [30]. This tool is composed of 11 items covering the following categories, all scored from 1 (poor) to 7 (excellent): rationale for study, selection and definition of outcome of interest, selection and comparability of comparison groups, technical classification of the exposure, non-technical classification of the exposure, other source of bias, sample size and power, a priori planning of analysis, statistical methods and control for confounding, testing of assumptions and inferences for genetic analysis, and appropriateness of inferences drawn from results. A total score was calculated, with scores $\leq$35 indicating low quality, $>$35 and $\leq$ 45 moderate quality and $>$ 45 high quality.

2.6. Data synthesis and analysis

Selected studies were classified based on the tested genetic determinant: 1) HLA variants and 2) other genetic non-HLA variants. Statistically significant associations between genetic variants and alloimmunization, reported by the included studies, were visually summarized in forest plots. Associations of HLA variants with alloimmunization are presented, classified by antibody specificity, whereas non-HLA variants are sorted by author. When studies included both a negative control group (patients that received transfusions and did not form antibodies) and healthy controls, we reported the associations of the comparison with the healthy controls. Hereby we aimed to optimize the validity of the results, as negative control groups were selected based on different combinations of selection criteria, hampering the

comparability of results between studies. Moreover, negative controls are more likely to depart from Hardy Weinberg equilibrium, as they might be enriched for protective genes from alloimmunization.

Odds ratios are reported with corresponding 95% confidence intervals. When the original article did not present a measure of association between the tested polymorphism and alloimmunization, odds ratios with 95% confidence intervals were calculated when appropriate, assuming an additive risk model for non-HLA SNPs. For HLA polymorphisms, a dichotomous model was used (allele present or allele absent), as this model was used by all included studies. R studio version 3.5.1 (2018), package 'rmeta' was used for visualization of results by use of forest plots.

A random effects meta-analysis was performed for polymorphisms reported by a minimum of three studies, and only if 1) patients groups were of same ethnic background and 2) similar control group was used (all studies used healthy controls or all studies used non-alloimmunized controls despite transfusion). Study heterogeneity was assessed using the Cochran Q and the I^2statistics. The Cochrane software program Review Manager (RevMan) (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform meta-analysis.

3. Results

3.1. Selection of articles

The online search identified 3295 unique records for title/abstract screening, of which 65 were selected for full text screening (Fig. 1). Forty-one articles were excluded and 24 studies were included in this review. Of these 24 studies, seven also included patients with antibodies due to pregnancy. We decided not to exclude these articles, as the majority of patients was still immunized by RBC transfusion and also during pregnancy, women may be immunized by RBCs transfusion.

3.2. Study characteristics

A summary overview of the study characteristics and risk of bias of the 24 included studies, encompassing 2581 cases and 26,558 controls is depicted in Table 1. The number of unique cases and controls included in this systematic review is most likely to be close to respectively 2348 and 26,147, as a small number of studies were conducted with patients derived from the same hospital. The studies were published between 2006 and 2020. All studies were case-control studies. Five studies were conducted in North America [28,31–33], four studies in Latin America [21,34–36], ten studies in Europe [26,27,37–42] and five in Asia [43–46]. The number of participants per study ranged from 75 to 22,675. The majority of the studies were performed in patients with SCD [26–28,31–33,35,36,47,48], three studies were performed in patients with thalassemia [45,46,49], three studies included patients with multiple diseases [21,34,44], and eight studies did not report the disease of the included patients [37–43,50]. Seven studies included not only cases that were alloimmunized by RBC transfusion, but also by pregnancy [21,38–42,50]. The total percentage of patients potentially immunized by pregnancy was 27%, although not all studies recorded the distribution. The primary endpoint of studies in patients with SCD and thalassemia was any RBC alloimmunization. Other studies only included patients with specific antibodies: Anti-Di^a [21], anti-K [38,40], anti-Mi^a [43], anti-E [44], anti-Fy^a [37,40,50], anti-Jk^a [41]. Two studies included patients with different antibodies, though analyzed all antibodies separately, or in clusters [39,42]. Blood was the most used

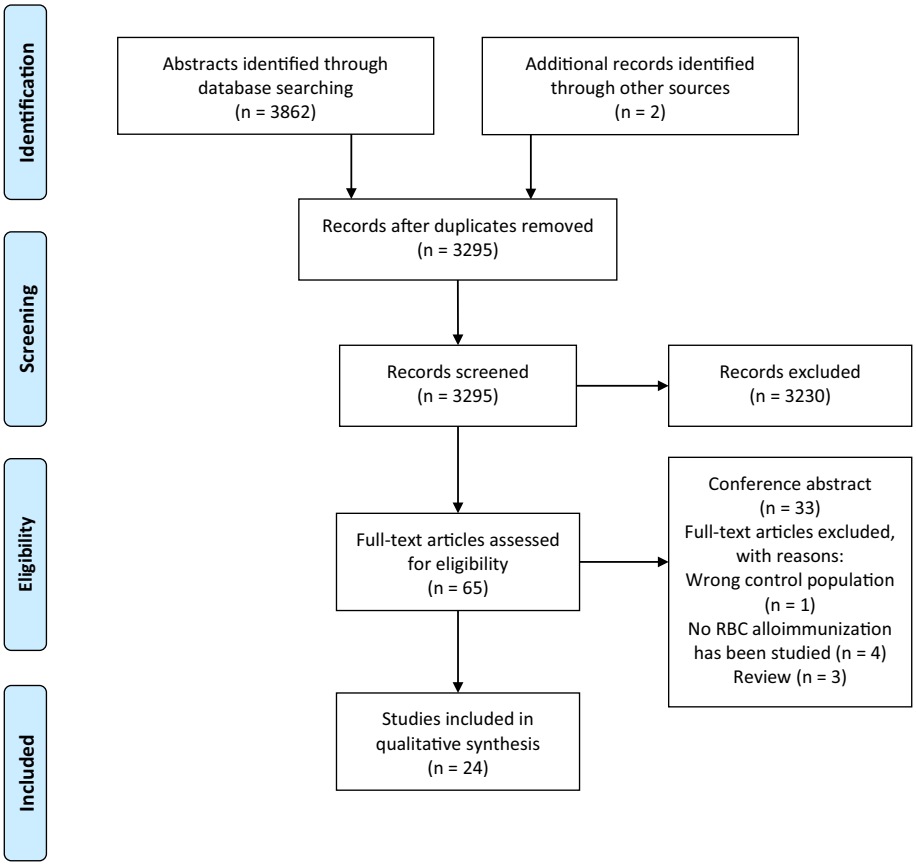

Fig. 1. PRISMA flow diagram. Flowchart of included publications. Our searches identified 3188 unique records for title/abstract screening, of which 65 were included for full-text screening. Hereafter, 41 studies were excluded for various reasons. Four studies did not have RBC alloimmunization as outcome, one study included a wrong control population, and three studies were reviews.

Table 1
Description of included studies.

Study: Author (year)	Geographic location/ ethnic group (s)	Aim:	Study design, number of participants	Number of participants, (age (years))			Gender: Male %			Disease type(s) studied	Tested antibodies	DNA source	Genotype method	Antibody detection method	Quality score (Q-genie tool)
				Cases	Controls	Healthy controls	Cases	Controls	Healthy controls						
Baleotti, 2014	Brazil	To evaluate the immunogenic features of Di[a] alloimmunization	CC, 1047	24, Med = 49, range 30–92 N by pregnancy: NR	15, Med = 30, range 11–53	1008, NR	54%	40%	NR	Chronic renal disease, surgery, hereditary or deficiency anemia, and cancer.	Di[a]	EDTA whole blood	PCR -SSOP	NR	31, Poor
Chiaroni 2006	France	To determine the contribution of genetic variation in HLA-DRB1 to the selective response to K antigen	CC, 254	54, NR N by pregnancy: NR		200, NR	26%		NR	NR	K	NR	PCR-SSOP	LISS antiglobulin test, column agglutination technology	33, Poor
Chu, 2008	Taiwan/ 100% Taiwanese	To investigate whether specific DRB1 alleles are associated with anti-Mi[a] production in the Taiwanese population	CC, 287	68, M = 61,5 ±16		219, M = 38 +/− 11,4	35%		52%	NR	Mi[a]	NR	PCR with cycle sequencing ready reaction kit	(1) Manual polybrene method, (2) commercial RBC panel	40, Moderate
Darvishi, 2018	Iran	To determine the relationship of HLA-DRB1*15:03, HLA-DRB1*11 and HLA-DRB1*09:01 with alloimmunization in Iranian thalassemia patients.	CC, 264	59, NR	259, NR		NR	NR		Thalassemia	Gen	Buffy coat from EDTA tube	PCR-SSP	Tube method with 3 cell panel	31, Poor
Ebrahimi, 2020	Iran	To determine the association of HLA-DRB1*15 and HLA-DRB1*01 with alloimmunization in Iranian thalassemia patients	CC, 106	54, NR	52, NR		52%	40%		Thalassemia	Rh and K	Buffy coat from EDTA tube	PCR-SSP	Tube method with 3 cell panel	35, Poor
Ebrahimi, 2020	Iran	To study the relationship of HLA-DRB1*11 and *13 with alloimmunization in Iranian thalassemia patients	CC, 106	54, NR	52, NR		NR	NR		Thalassemia	Rh and K	Buffy coat from EDTA tube	PCR-SSP	Tube method with 3 cell panel	35, Poor
Hanchard, 2014	USA	To identify large effect susceptibility loci for alloimmunization in patients with SCD	CC, 94	48, NR	44, NR		NR	NR		SCD	Gen	Leukocyte buffy coats or whole blood	HumanOmni1-Quad BeadChips	Lo-Ion and AHG phase using polyspecific antiglobulin reagent	37, Moderate

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Table 1 (*continued*)

Study: Author (year)	Geographic location/ ethnic group (s)	Aim:	Study design, number of participants	Number of participants, (age (years))			Gender: Male %			Disease type(s) studied	Tested antibodies	DNA source	Genotype method	Antibody detection method	Quality score (Q-genie tool)
				Cases	Controls	Healthy controls	Cases	Controls	Healthy controls						
Hoppe, 2009	USA	To determine whether similar HLA allelic associations with alloimmunization exist in patients with SCD who underwent transfusion	CC, 159	59, M = 15.2, range 5–45	100, M = 14.4, range 4–47		48%	50%		SCD	Gen	NR	PCR-SSOP	Gel and antiglobulin techniques	40, Moderate
Lin, 2018	Taiwan	To investigate the association between SNPs in IL-6 promotor and anti-E production	CC, 149	54, Med = 67, range 29–91	45, Med = 79, range 17–95	45, Med = 32.5, range 20–58	43%	78%	58%	Vit B12 deficiency, MDS, myelofibrosis, AML, CML, uremia, solid tumors, acute anemia	Rh-E	Blood samples	PCR- RFLP	manual polybrene test or standard tube methods in 3 phases: immediate spin, 37° C, and anti-IgG	43 Moderate
Maluskova, 2017	Czech Republic	To identify the association of HLA-class II alleles with anti-C, -Cw, −c, −E, −e.	CC, 605	230, NR N by pregnancy: 35		375, mean 30.1, range 19–40	29%		63%	NR	Mult	Blood samples	(1) PCR-SSOP Luminex (2) PCR - SSP	LISS antiglobulin test, column agglutination technology	37, Moderate
Meinderts, 2017	The Netherlands and France	To evaluate the association between genetic variation of FCGR and RBC alloimmunization in SCD.	CC, 272	142, NR	130		NR	NR		SCD	Gen	Whole blood	MLPA	(1) 3-cell panel (2) column agglutination methods	53, Good
Meinderts, 2019	Netherlands and France	To evaluate the association of genes in TLR pathways with alloimmunization in SCD	CC, 275	145, Med = 33, IQR 27–44	130, Med = 31, IQR 25–39		37%	51%		SCD	Gen	Whole blood	Targeted custom AmpliSeq panel	(1) 3-cell panel (2) column agglutination methods	46, Good
Noizat Pirenne, 2006	France, Caucasian	To determine the HLA-DRB1 restriction in anti-Fy^a and -K	CC, 443	59, NR N by pregnancy: NR		384, NR	NR		NR	NR	Fy^a / K	NR	Reverse dot-blot hybridization, PCR-SSP	Gel test, indirect antiglobulin test, anti-IgG, with untreated RBCs.	43, Moderate
Oliviera, 2017	Brazil	To evaluate if polymorphisms in CTLA-4 gene that affect protein expression are associated with RBC alloimmunization.	CC, 387	SCD: 72, M = 30 ±13.1 Non SCD = 126, M = 52 ±17.9	SCD: 62, M = 27 ±16.7 Non-SCD: 127, M = 41 ±61.3		SCD: 39%, Non-SCD: 35%	SCD: 29%, Non-SCD: 57%		SCD, oncological diseases, benign hematological diseases	Gen	EDTA whole blood	PCR-RFLP	LISS antiglobulin test	50, Good
Picard, 2009	France, Southern European	To assess the effect of HLA-DRB1 polymorphisms on Fya immunization in a southern	CC, 267	67, NR		200, NR	34%		NR	NR	Fy^a	NR	(1) PCR-SSOP (2) PCR-SSP	Gel test technique (biovue)	31, Poor

(*continued on next page*)

Table 1 (*continued*)

Study: Author (year)	Geographic location/ ethnic group (s)	Aim:	Study design, number of participants	Number of participants, (age (years))			Gender: Male %			Disease type(s) studied	Tested antibodies	DNA source	Genotype method	Antibody detection method	Quality score (Q-genie tool)
				Cases	Controls	Healthy controls	Cases	Controls	Healthy controls						
		European population.													
Raos, 2019	Croatia/ 100% Caucasian	To investigate HLA-DR and HLA-DQ polymorphisms in Croatian patients alloimmunized against Fy[a]	CC, 280	70, NR N by pregnancy: 2	45, NR	165, range 20–40	NR		NR	NR	Fy[a]	NR	PCR-SSOP Luminex	Column agglutination indirect antiglobulin test.	41, Moderate
Reviron, 2005	France	To search for initial evidence of an association between HLA-DRB1 alleles and Jka immunization.	CC, 220	20, NR N by pregnancy: 4		200, NR	35%		NR	NR	Jk[a]	NR	PCR-SSOP	LISS antiglobulin test, column agglutination technology	31, Poor
Rodrigues, 2017	Brazil	To investigate whether RBC alloimmunization is associated with the HLA type of individuals	CC, 172	44, Med = 32, range 10–63	128 Med = 38, range 2–83		37%	48%		SCD	Gen	EDTA whole blood	PCR-SSOP	NR	38, Moderate
Schonewille, 2014	The Netherlands	To evaluate the presence of the MHC Class II locus-DRB1 as restriction antigens for alloimmunization	CC, 22675	941, NR N by pregnancy: 305		21,734, NR	21%		NR	NR	Mult	Blood samples	PCR-SSOP or reverse SSOP	LISS antiglobulin test, PEG antiglobulin tube method	38, Moderate
Sippert, 2017	Brazil	To search for genetic markers in HLA and cytokine genes that make SCD patients susceptible for RBC alloimmunization.	CC, 459	37, Med =36, range 4–68	94, Med = 34, range 2–70	288, Med =33, range 18–63	40%	28%	43%	SCD	Gen	Peripheral blood	(1) PCR- RFLP (2) Taqman genotyping assay	Serologic and molecular testing	42, Moderate
Tatari-Calderone, 2009	USA	To determine the association of the rs660 and HbS allele and/or development of RBC-specific antibodies in patients with SCD.	CC, 127	28, Med = 14, range 8–21	55, Med = 14, range 3–22	44, NR	57%	55%	NR	SCD	Gen	Peripheral blood	PCR-RFLP	NR	39, Moderate
Tatari-Calderone, 2013	France/ 85% Sub-Saharan Africa, 17% French West Indies	To determine associations of genes in the neighborhood of Hb-beta gene with alloimmunization	CC, 75	35, M = 35.1 ±114	40, M = 30.9 ±8.7		40%	43%		SCD	Gen	Peripheral blood	TaqMan allelic discrimination assay	NR	44, Moderate
Tatari-Calderone, 2016	USA	To examine the distribution of HLA-DRB1 and HLA-DQB1 alleles in SCD patient with and	CC, 204	83, M = 17.2 ±4.6	116, M = 15.9 ±5.5		54%	53%		SCD	Gen	NR	PCR-SSOP Luminex	NR	29, Poor

(*continued on next page*)

Table 1 (*continued*)

Study: Author (year)	Geographic location/ ethnic group (s)	Aim:	Study design, number of participants	Number of participants, (age (years))			Gender: Male %			Disease type(s) studied	Tested antibodies	DNA source	Genotype method	Antibody detection method	Quality score (Q-genie tool)
				Cases	Controls	Healthy controls	Cases	Controls	Healthy controls						
		without RBC alloantibodies													
Williams, 2018	USA	To identify loci with moderate effects on alloimmunization risk in SCD	CC, 288 (replication cohort 130)	154, 139 > 18 years, (replication cohort 62, 62 > 18 years)	134, 117 > 18 years (replication cohort 68, 68 > 18 years)		43%	49%		SCD	Gen	NR	IlluminaOmni2.5 BeadChip	NR	47, Good

CC = Case-Control study, NR = not recorded, Med = Median, IQR = interquartile range, M = Mean +/− SD, SCD = Sickle cell disease, MDS = myelodysplastic syndrome, AML = acute myeloid leukemia, CML = chronic myeloid leukemia, gen = alloimmunization in general, mult = multiple antibodies, PCR- SSOP = polymerase chain reaction with sequence specific oligonucleotide probes, PCR-SSP = polymerase chain reaction with sequence specific primers, PCR-RFLP = polymerase chain reaction with restriction fragment length polymorphism, MLPA = Multiplex ligation-dependent probe amplification.

specimen for genotyping ($n = 15$, 21, 26–28, 31, 34–36, 39, 42, 44–47, 49), while nine studies did not report the origin of the specimen used for genotyping [32,33,37,38,40,41,43,48,50]. Half the studies used healthy controls from the same ethnicity as control population ($n = 12$) [21,28,36–44,50], whereas 17 studies included a population that had been transfused but did not form antibodies [21,26–28,31–36,44–49]. For further presentation of our results, we have divided the results in two main genetic determinant groups that we identified in the included articles: HLA variants (16 studies [21,32,33,35–43,45,46,49,50]) and non-HLA genetic variants (9 studies [26–28,31,34,36,44,47,48]). For HLA typing, the most commonly used genotyping assay was the polymerase chain reaction (PCR) with sequence specific oligonucleotide probes ($n = 10$), or with sequence specific primers ($n = 5$). For non-HLA genotyping, the most frequently used method was PCR-restriction fragment length polymorphism ($n = 4$).

3.3. Quality of included studies

Results of the quality assessment are shown in Fig. 2. The overall quality of the included studies, assessed by the Q-genie tool, was moderate (13 out of 24). Four studies were of high quality, while the quality was ranked as poor for six studies. The studies scored relatively low on the domain sample size and power, as almost none of the included studies had performed a power analysis to determine the required sample size or effect size. Most studies scored low on the non-technical classification of the exposure (Blinding/genotyping performed simultaneously or in batches), as this was not described at all by most studies. Furthermore, selective reporting of positive results was a problem in many studies.

3.4. Alloimmunization and genotype

3.4.1. HLA-variants

The majority of the studies addressing HLA variant reported on HLA-DRB1 alleles. Sixteen different alleles were studied (*01-*16). A minority of the studies reported on other HLA alleles such as HLA-A or HLA-DQB1 variants. As HLA polymorphisms are associated with the presentation of specific antigens, most studies investigated the association of an HLA allele with alloimmunization to a specific blood group antigen. Most studied antibodies were anti-Fy^a [37,40,42,50], anti-K [38,40,42]. Other antibodies that were studied were anti-D [39,42], anti-C [39,42], anti-c [39,42], anti-E [39,42], anti-e [39], anti-Cw [39], anti-Jk^a [41,42], anti-S [42], anti-M [39], anti-Di^a [21] and anti-Mi^a [43]. Seven studies reported on associations of HLA polymorphisms with alloimmunization in general [32,33,35,36,45,46,49]. In Supplemental Table 3 we provide an overview of extracted data of tested polymorphisms.

Most associations of HLA variants with a specific antibody were tested in only one study, a small number of polymorphisms was tested in multiple studies. Five studies were eligible for meta-analysis. (Fig. 3). All these studies were conducted in Caucasian recipients [37,38,40,42,50]. All separate associations that have been described by the original articles are summarized in Fig. 4. Interestingly, the *HLA-DRB1*04* allele was strongly associated with an increased risk of anti-Fy^a formation in four different studies (Picard et al. OR 4.2, 95%CI 2.65–6.65 [37], Noizat-Pirenne et al. OR 12.9, 95%CI 8.01–20.76 [40], and Schonewille et al. OR 7.9, 95%CI 4.2–15, Raos et al. OR 10.5, 95%CI 5.5–20). All four studies fulfilled the selection criteria for meta-analysis of this polymorphism, which resulted in an overall odds ratio of 7.80 (95%CI 4.57–13.33, $p < 10e^{-5}$), although there was substantial heterogeneity across studies. The study by Rodrigues et al. could not be included in the meta-analysis based on a different ethnic population (SCD patients), although this study also reported a statistically non-significant increased prevalence of *HLA-DRB1*04* in anti-Fy^a patients (3 out of 3) compared with antibody negative controls (21 out of 169). *HLA-DRB1*15* was more prevalent in patients with anti-Fy^a as well, compared with controls in three of the studies that tested this association (Picard et al. OR 4.3, 95%CI 2.6–7.12, Schonewille et al. OR 3.2, 95%CI 1.2–5.5, and Raos et al. OR 8.0, 95% CI 4.2–15.1), while Noizat-Pirenne et al. reported a statistically non-significant increased risk (OR 1.72, 95%CI 0.87–3.41). All four studies were included in the meta-analysis, which showed an overall increased risk for alloimmunization with an OR of 3.76 (95%CI 2.14–6.59, $p < 10e^{-5}$). Lastly, *HLA-DRB1*03* was associated with a decreased risk of alloimmunization with an OR of 0.12 (95%CI 0.05–0.29, $p < 10e^{-5}$), as this variant was rare in cases, while being more prevalent in controls.

Four studies have studied the association of HLA polymorphisms with anti-K formation. In these studies, three potential interesting associations were identified by meta-analysis. *HLA-DRB1*10* was associated with anti-K formation in a meta-analysis of three studies (OR 2.64, 95%CI 1.41–4.95, $p = 0.002$), although the prevalence of this polymorphism was fairly low (1–6%).

*HLA-DRB1*11* was associated with increased pooled odds of anti-K formation (OR 2.11, 95%CI 1.34–3.32, $p = 0.001$), while in the separate studies, only Chiaroni et al. (OR 3.5, 95%CI 1.9–6.5) reported a statistically significant association. Furthermore, *HLA-DRB1*13* was

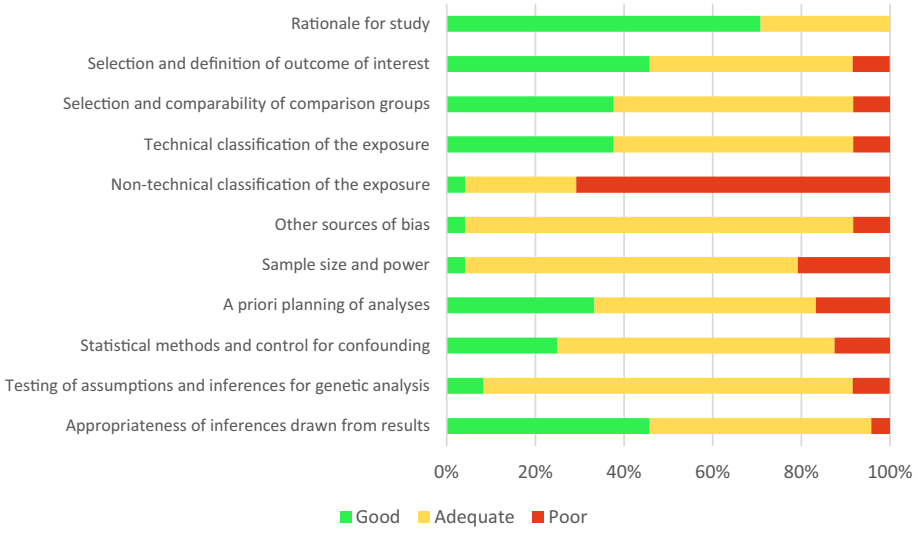
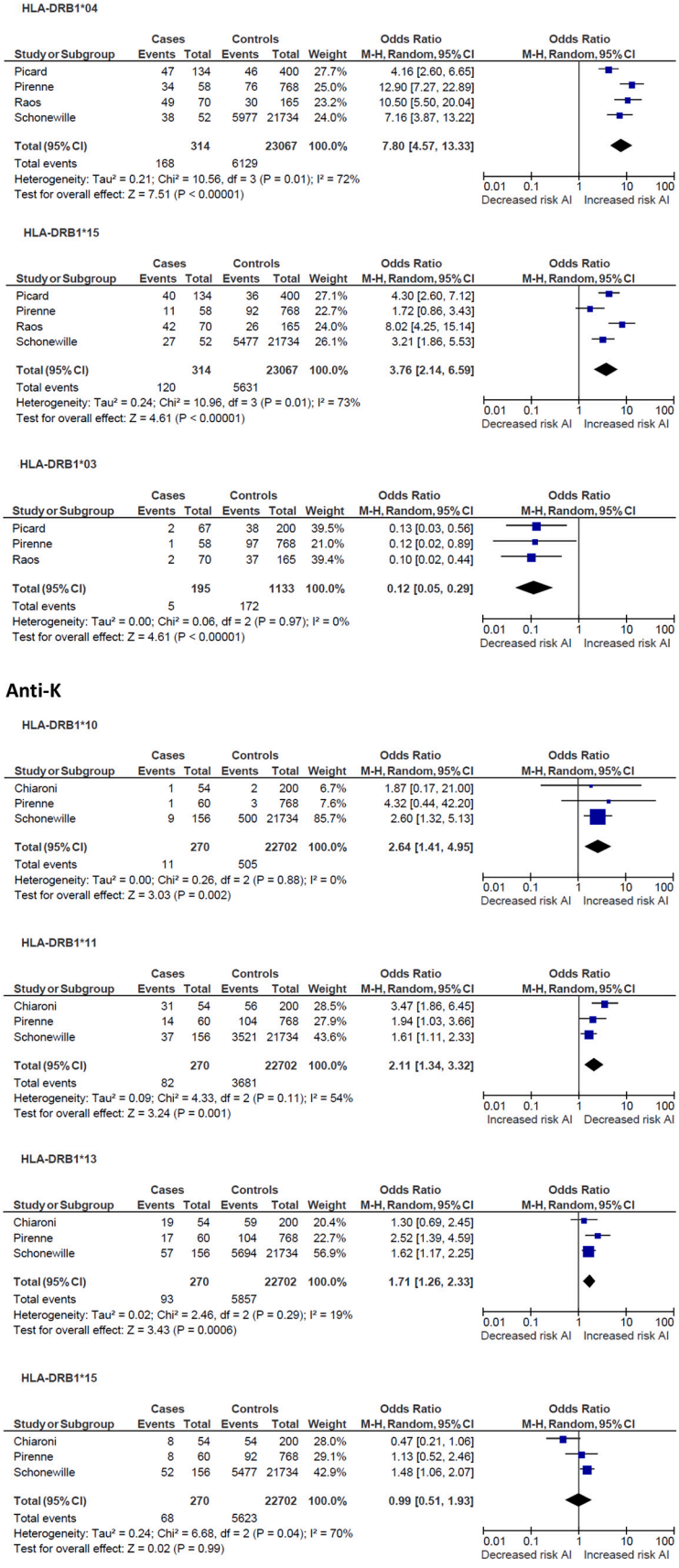


Fig. 2. Quality of included studies. For a detailed overview of the quality appraisal, see Supplemental Table 2.

Anti-Fy[a]



Anti-K

Fig. 3. Forest plots of meta-analysis of HLA-polymorphisms. Analysis is sorted on antibody specificity. AI = RBC alloimmunization.

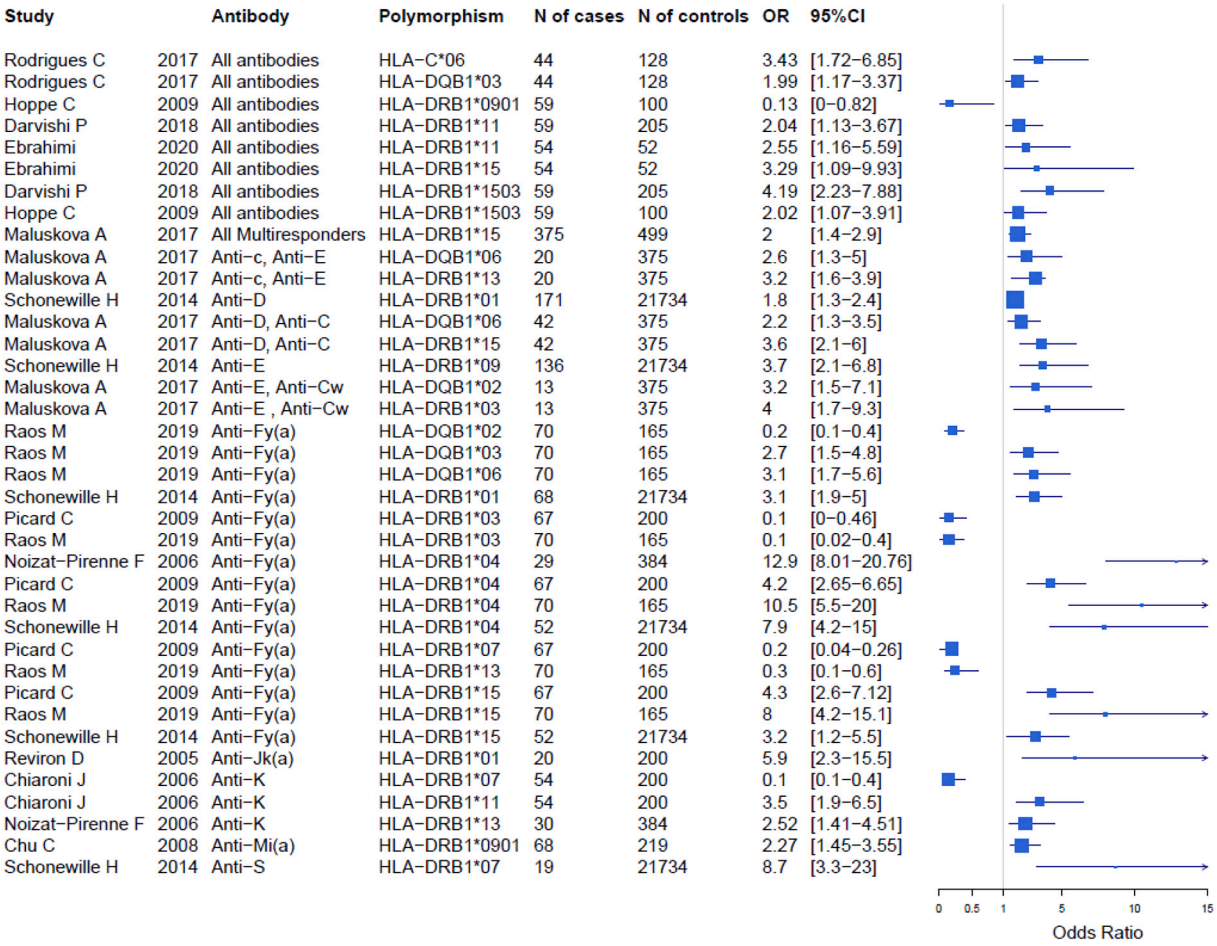


Fig. 4. Forest plot of HLA polymorphisms that have been reported to be significantly associated with antibody formation. Associations are sorted on antibody specificity. *: Negative controls instead of healthy controls as control group.

more prevalent in patients with anti-K antibodies (OR 1.71, 95%CI 1.26–2.33, p = 0.0006). Last, *HLA-DRB1*15* was not associated with alloimmunization with a pooled odds of anti-K formation (0.99, 95%CI 0.51–1.93). A sensitivity analysis excluding studies with both RBC transfusion- and pregnancy-induced alloimmunization could not be performed, as almost all studies from the meta-analysis would then be excluded.

Another polymorphism that has less frequently been studied, *HLA-DRB1*01*, was associated with an increased risk of anti-Jk^a formation in two studies: Reviron et al. (OR 5.9, 95%CI 2.3–15.5) and Schonewille et al. (OR 3.1, 95%CI 1.9–5.0). Most other polymorphisms have either only been described by one study, or were not significantly associated with alloimmunization.

3.4.2. Non-HLA variants

Ten studies investigated polymorphisms other than HLA variants. Only a few polymorphisms were tested by more than one study. All statistically significant associations are summarized in Fig. 5. The majority of the studies was performed in patients with SCD and had a targeted SNP approach. One genome-wide association study (GWAS) and one pilot GWAS have been performed [31,48]. Most studies reported on the association of a polymorphism with alloimmunization, irrespective of antigen specificity. The selected SNPs were mostly involved in immune signaling pathways: Interleukins (IL), Fc-gamma-receptor 2 *(*FCGR2*)*, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and tumor necrosis factor (TNF) among others.

The FCGR2C.non-classical open reading frame *(FCGR2C.nc-ORF)*

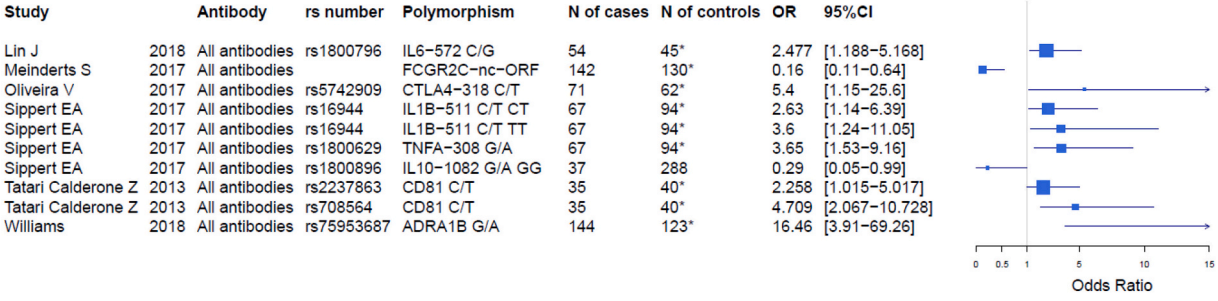


Fig. 5. Forest plot of non-HLA polymorphisms that have been reported to be significantly associated with antibody formation. Associations are sorted on author. *: Negative controls instead of healthy controls as control group.

polymorphism, was associated with lower odds of alloimmunization in a SCD cohort (OR 0.26, 95%CI 0.11–0.64). Interestingly, this association was stronger when excluding the more immunogenic RBC antigens Rh-DCcEe and K from the analysis (OR 0.19 95%CI 0.06–0.59). These results could however not be replicated in a GWAS [48]. This GWAS found only one SNP on chromosome 5 that was significantly associated with alloimmunization (rs75853687). This SNP is located near the adrenoceptor-a 1B (*ADRA1B) gene.*

Oliveira et al. found an association of rs5742909 in cytotoxic T-lymphocyte-associated protein 4 (*CTLA-4-318C/T)* with alloimmunization in SCD (OR 5.4, 95%CI 1.15–25.6). However, this association was not found in a population of non-SCD in the same study [34]. Other cytokine and immune signaling genes that were significantly associated with alloimmunization were rs16944 in *IL-1β-511C/T* (OR 2.63, 95%CI 1.14–6.39), rs1800629 in *TNFα-308G/A* (OR 3.65, 95%CI 1.53–9.16), rs1800896 in *IL-10-1082G/A* (OR 0.29, 95%CI 0.05–0.99) by Sippert et al. [36], rs1800796 in *IL-6-572C/G* (OR 2.77 95%CI 1.21–6.34) by Lin et al. [44], and two polymorphisms rs2237863 and rs708564 in *CD81* (OR 8.44, 95%CI 2.11–33.72 and 10.7, 95%CI 3.29–35.98) by Tatari-Calderon et al. [26] However, Meinderts et al. and Williams et al. [47,48] could not confirm any of these associations.

4. Discussion

To our knowledge, this is the first systematic review that examines the associations of genetic polymorphisms and RBC alloimmunization. We included 24 studies in our review, examining mostly HLA and cytokine polymorphisms. Non-HLA polymorphisms were mostly studied for their association with any alloimmunization, irrespective of antigen specificity, whereas associations of HLA variants were generally studied for alloimmunization to a specific antigen.

As antigen presentation by HLA is influenced by the affinity of the HLA molecule for the peptides carrying the antigen specific T cell epitope, certain HLA variants will either enhance or impair presentation of specific peptides of processed RBC antigens on antigen presenting cells (APCs) [23]. Hereby, HLA polymorphisms are most likely strongly involved in immunization processes [51]. Various studies have demonstrated the effect of specific HLA polymorphisms on diseases such as ankylosing spondylitis [52], systematic juvenile idiopathic arthritis [53], systemic lupus erythematosus [54], and acquired idiopathic thrombotic thrombocytopenic purpura [55]. This supports the findings of studies that demonstrated consistent associations of certain HLA-DRB1 alleles with alloimmunization to specific RBC antigens. Among others, *HLA-DRB1*04* and *HLA-DRB1*15* allele frequencies were consistently raised in anti-Fy^a responders compared to healthy controls. Interestingly, Noizat-Pirenne et al. showed that a Fy^a derived anchor sequence was predicted to bind exclusively to the *HLA-DRB1*04* allele, making it a possible restriction molecule for anti-Fy^a formation [40]. Furthermore, Gunasekera et al. showed that a unique Kell peptide-binding register (W179-S187) is restricted to HLA-DRB1*11:01, which may contribute to the *HLA-DRB1*11* restricted immunogenicity associated with the K antigen. For *HLA-DRB1*10* and **13* this effect could not be shown in this study. For other associations between alloimmunization and HLA polymorphisms, e.g. anti-Fya formation and *HLA-DRB1*15*, the underlying molecular mechanism has not been shown [37].

The results of this systematic review support the pathophysiological concept that it is unlikely for a specific HLA polymorphism to influence any alloimmunization, as HLA polymorphisms are likely to have different effects on different antigens. Although some HLA alleles, such as *HLA-DRB1*15*, might be more promiscuous in RBC antigen presentation, this effect cannot be generalized to any alloimmunization [32,45,49,56]. It should therefore be stressed that studies examining HLA associations should focus on specific antibodies rather than examining any alloimmunization.

The association between alloimmunization and genetic variation beyond HLA polymorphisms has not been studied as extensively as HLA polymorphisms. Most studied genetic variants were polymorphisms in cytokine genes and other immunomodulatory pathways. Associations in *FCGR2.nc-ORF, CD81, CTLA-4, IL-1β, TNFa, IL-6 and lL-10* have all only been described to be associated with alloimmunization in single studies, albeit without other studies being able to confirm these findings [48,57]. This may indicate false positive results, although the failure to replicate the findings could also be explained by the differences in ancestry and disease groups between studies. Moreover, the included studies had mostly small sample sizes and used different inclusion criteria, which complicates the interpretation of the results [58]. For most of the above-mentioned polymorphisms, the stimulating or inhibitory effect on alloimmunization and clinical significance is not known. However, it has been shown that the *rs1800629 (TNFα-308 G/A)* polymorphism leads to increased transcription of TNFα, which is known to promote the inflammatory status and thereby increase alloimmunization risk. Of interest, this polymorphisms has been associated with several other autoimmune diseases [59,60]. As the evidence on the effect of non-HLA polymorphisms on alloimmunization risk remains scarce, further conformation in other cohorts is required.

One major difference between the included studies was the selection of the control group. Population stratification is one of the most important types of bias in genetic research and is minimized when controls and cases are matched for ethnicity [61,62]. The included studies in this systematic review all matched the control group to the cases for ethnicity, although there were some other notable differences. Across studies, there was a wide variety in ethnic backgrounds of the included patients, possibly leading to a heterogeneity among studies in the proportion of antigenic mismatch between donors and patients. As the antigenic mismatch influences alloimmunization risk, this might have differential influence on the effect estimate of the tested polymorphism in some studies [63,64]. Furthermore, some studies selected controls from healthy donors and thereby did not select on any other phenotype. Conversely, some studies, especially the ones that included SCD and thalassemia patients, selected controls from the same disease population that did not form antibodies despite previous exposure to RBC transfusions. However, the minimal number of transfusions in controls differed between studies from two units up to 20 units. It has been described that the number of transfusions in history is a strong predictor of alloimmunization risk. [18,63] Hereby, the comparability of studies that included control groups with a difference alloimmunization risk is impaired, as controls with higher transfusion exposure are more likely to be real negative controls compared to controls with a transfusion exposure of two units [65]. Consequently, the above mentioned factors hamper the comparison and aggregation of reported results in this systematic review [62].

A number of other limitations of this systematic review need to be considered. First, the total number of included studies was relatively low and heterogeneous in inclusion criteria, ethnicity and diseases of the included patients, precluding quantitative meta-analysis. Ethnicity highly influences results of genetic studies, due to differences in ancestry based allele frequencies [62]. Only for some HLA polymorphisms could meta-analysis be performed. Second, the methodological quality of the included studies was generally suboptimal, hampering the validity of the results. Third, some of the included studies did not exclusively include patients with RBC transfusion related alloimmunization, but also included a group (max 32% of patients) with pregnancy-induced alloimmunization. As far as we know there is no evidence demonstrating a different immunological mechanism for the immunization process in pregnancy-induced alloimmunization compared to RBC transfusion-induced alloimmunization. In fact, mouse studies have shown that the immunological response to the KEL2 antigen administered via RBC transfusion or a pregnancy route is comparable. Moreover in human, previous RBC transfusions are the strongest risk factor for pregnancy-induced RBC alloimmunization. [66,67]

5. Conclusion and future directions

This systematic review has summarized the available evidence on genetic markers for alloimmunization after RBC transfusion. Until now, not many adequately powered studies investigating this important issue have been performed. Still, some HLA polymorphisms have consistently been associated with antibody formation to either the Fy^a or K antigen, although the molecular basis for these associations has not been elucidated yet. These variants may aid in the identification of patients at risk for antibody formation to specific antigens. To gain more insight in the complex interaction between genetic variation and RBC alloimmunization, future epidemiological studies should investigate larger and well-defined cohorts. After confirmation of the associations in confirmatory cohorts, mechanistic studies may further validate these findings before they can be used in clinical practice as preventive screening tool for patients receiving multiple transfusions.

Practice points

- RBC alloimmunization is a serious complication of blood transfusions, challenging selection of compatible units for future transfusions.
- Personalized transfusion medicine requires a robust assessment of alloimmunization risk, including genetic and clinical markers.
- HLA-DRB1 polymorphisms are important markers for alloimmunization to specific antigens, such as Fy^a and K.

Research agenda

- Large international collaborative studies are needed to increase understanding of the influence of genetic polymorphisms on alloimmunization risk
- Determining the effect of HLA polymorphisms on alloimmunization to distinct antigens.
- Development of prediction models for alloimmunization risk.
- Increase understanding of the pathophysiological mechanism of alloimmunization

Disclosures

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Author contributions

JG, JGvdB and KF designed the study. JG, IO, SM screened the abstracts, and acquired the data. All authors contributed to the formal analysis and interpretation of the data. JG wrote the original draft, all authors contributed to the writing – review & editing of the final manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2020.100794.

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