

## INVITED REVIEW

# Systematic review of associations between HLA and renal function

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## Abstract

**Introduction:** Kidney dysfunction is a highly significant disease, both in the United Kingdom and globally. Many previous studies have reported associations between human leukocyte antigens (HLA) and renal function; this systematic review attempts to identify, summarize and appraise all published studies of these associations.

**Methods:** A literature search was performed using Medline, Embase and Cochrane Central Register of Controlled Trials to identify papers whose keywords included each of the following concepts: HLA, renal failure and genetic association. A total of 245 papers were identified and assessed for eligibility; 35 of these were included in the final study.

**Results:** A total of 95 HLA types and 14 three-locus haplotypes were reported to be associated with either increased or decreased renal function. A number of these findings were replicated by independent studies that reported 16 types were protective against renal dysfunction and 15 types were associated with reduced renal function. A total of 20 HLA types were associated with both increased risk of renal disease and decreased risk by independent studies.

**Discussion:** There is very little consensus on which HLA types have a protective or deleterious effect on renal function. Ethnicity may play a role, with HLA types possibly having different effects among different populations, and it is possible that the different primary diseases that lead to ESRD may have different HLA associations. Some of the studies may contain type I and type II errors caused by insufficient sample sizes, cohort selection and statistical methods. Although we have compiled a comprehensive list of published associations between renal function and HLA, in many cases, it is unclear which associations are reliable. Further studies are required to confirm or refute these findings.

## KEYWORDS

chronic, genetic predisposition to disease, genome-wide association study, histocompatibility antigens, HLA antigens, kidney failure, renal insufficiency, systematic review

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## 1 | INTRODUCTION AND AIMS

Chronic kidney disease (CKD) is diagnosed either when a person has glomerular filtration rate (GFR)  $< 60$  ml/min/1.73 m<sup>2</sup> or when they have structural or functional abnormalities of the kidney that could lead to renal failure (The Cochrane Collaboration, 2019). In England, over 1.8 m people are affected and it is estimated that over 40,000 of these people die prematurely each year (NHS, 2012). The cost of treating CKD in England in 2019 was approximately £1.5bn (Health Service Journal, 2020), representing 1% of all NHS expenditure. Lower kidney function is associated with decreased quality of life and increased risks of mortality, stroke, myocardial infarction, infection and hospital admission (Go et al., 2004; NHS, 2012; Tonelli et al., 2006; Weiner et al., 2004).

According to the Global Burden of Disease 2015 Study (Mortality & Causes of Death, 2016), 1.2 million people worldwide died due to CKD in 2015 (an increase of 32% on 2005). CKD is now 17th in the list of diseases which cause the most 'years of lost life' (having been 21st in 2005 and 25th in 1990). Understanding the causes of kidney dysfunction could have important applications in terms of diagnosis and treatment of one of the most globally significant diseases.

CKD has a high heritability index (30–75%) (Canadas-Garre et al., 2019), with over 100 genomic regions reported to contribute towards it (Xu et al., 2018). Many previous studies have identified human leukocyte antigen (HLA) types that are associated with increased risk of end-stage renal disease (ESRD), which is when renal replacement therapy (such as dialysis or transplantation) becomes necessary. Other HLA associations indicate a protective effect. Most of these studies focus on subjects from specific ethnic cohorts or particular geographical regions, and HLA associations reported may be contradictory due to variation in disease prevalence and population stratification.

This study performed a systematic search of existing literature. The aim was to identify, summarize and appraise all previous studies which have attempted to find associations between HLA type and renal function. The HLA region was selected for analysis because it is closely linked to many disorders of the kidney (Robson et al., 2018). This suggests that it may have an impact on kidney function.

## 2 | METHODS

This literature review investigates HLA genotypes associated with renal function in global populations. It was defined in terms of the PICO framework, a process which advises clear definitions of the participants, intervention, comparison and outcome that are to be studied (Huang et al., 2006). The participants (i.e. the subjects to be included) were global populations aged 18 years and over. The interventions (the independent variable) were HLA class I and II types. The comparisons (controls) were subjects without renal disease. The outcome (the dependent variable) was renal function (either increased or decreased). As of 19 September 2019 there is no review protocol for studies of HLA and renal function (as per a search of PROSPERO), though there

is one for studies of HLA mismatches and kidney transplant outcomes (Shi et al., 2017).

A literature search was carried out on 30 November 2018 and updated on 17 February 2021 using Medline, Embase and Cochrane Central Register of Controlled Trials on the Ovid platform. These databases are a comprehensive and relevant source of papers and reviews which date back to 1946, 1974 and 2005 respectively. Only primary studies which had been published as full, peer-reviewed papers (rather than abstracts only) were considered. This helped to ensure that only high-quality, reliable evidence was used. Papers were also required to be written in the English language, to guarantee comprehension by the researchers. Their database thesaurus (or 'index') terms were required to include words or phrases associated with the following concepts: HLA, renal failure and genetic association. Medline scope notes were checked and all terms associated with key terms within the MeSH thesaurus tree were examined.

We originally intended to consider only papers investigating subjects of white ethnicity, as this most closely reflected the subjects of a research project that we were planning at the time and have since conducted (Lowe et al., 2021). However, ultimately any ethnicity was included as ethnicity was not reliably indexed in the databases searched, and filtering using this criterion would have lost relevant studies. Medline, for example, had 62,789 results for the search term 'European Continental Ancestry Group' (the index term for the word 'Caucasian'). If the term had been properly indexed, the number of papers identified would have been much higher. The search criterion for white ethnicity was therefore not used. For similar reasons, the review initially intended to consider only subjects of middle-age or older, but age was ultimately not selected as a search term because requiring the index terms 'aged' or 'middle-aged' reduced the yield of publications by approximately 75%. As a result of excluding the concepts of ethnicity and age from the search, papers were identified which related to participants with a wide range of ethnic origins and ages. The observations contained within these papers, therefore, cannot necessarily be applied directly to the middle-aged white population as had originally been intended. A number of more sensitive searches were attempted, using broader search terms. For example, the search term 'haplotypes' was added to the genetic association concept and to the HLA concept. However, the additional papers highlighted through this strategy were not relevant to the research question, so the term was released.

A total of 242 papers were identified through the database search, but an earlier scoping exercise had revealed three additional publications which were not included in the database search (Davood et al., 2008; Mosaad et al., 2014; Nassar et al., 2015), possibly due to their selected keywords. The keywords of two papers did not include the concept of genetic association (Mosaad et al., 2014; Nassar et al., 2015). The keywords of the third paper suggested that this publication should have been captured by the search (Davood et al., 2008); possible explanations for this omission are that either the keywords were not indexed correctly or the journal (Research Journal of Biological Sciences) was not included in the databases searched. All three papers were included, giving a total of 245 publications selected. Of

**TABLE 1** Primary reason for exclusion after screening of titles and abstracts

Reason for exclusion	Number of results excluded
Not related to kidneys	42
Investigating transplantation but not kidney failure	38
Not related to HLA class I and II	33
Only tangentially related to kidney failure	16
Case study	14
Study of children	6
New HLA allele discovery	4
Not an article	2

these 245 papers, 32 were duplicates of the same publication found in different databases, leaving 213 unique papers for screening. The titles and abstracts of these 213 papers were read to assess their relevance to the research question. A total of 155 were deemed irrelevant to the research question and were removed. The primary reason for each exclusion is documented in Table 1. After this initial screening exercise, 58 papers remained for consideration.

In 17 cases, no full text version of the paper was available, either because the reference related to a conference poster or abstract which had not been published as a paper or because the full text was inaccessible. The University of Manchester library was consulted for help in obtaining these papers, but was unsuccessful. This left 41 full text papers for assessment. A further six publications were removed after the full text articles were assessed, either because the paper was not related to HLA class I or II ( $n = 3$ ), the paper did not measure renal failure subjects against healthy controls ( $n = 2$ ), or because the paper was not a primary study ( $n = 1$ ). Thirty-five articles, therefore, were deemed relevant to the research question. Figure 1 summarizes the entire process of exclusion following a strategy adapted from Moher et al. (2009), which outlines the process for completing a systematic review.

The 35 papers were analysed and the results extracted from tables in the Section 3 and prose in the Section 4. No contact with original researchers was made to verify their data or request further information such as funding sources. Each paper was also subject to an assessment using the Critical Appraisal Skills Programme to ensure it was of sufficient quality to be included (Critical Appraisal Skills Programme, 2018). The search was carried out by a single researcher with consultation and advice from two librarians. All screening and assessments of eligibility were performed independently by two researchers who discussed any discrepancies until consensus was reached. Extraction of data from the papers was performed by a single researcher. Different studies used different methods to determine whether HLA types were associated with renal function. The principal summary measures were odds ratio, relative risk and hazard ratio.

### 3 | RESULTS

Associations between HLA and renal function were identified in 30 of the 35 papers. In all, there were a total of 181 associations reported,

relating to 58 different HLA class I types, 37 class II types and 14 three-locus haplotypes. None of the 14 findings which related to a haplotype was independently replicated, but 31 of the findings relating to a single HLA type were replicated. There were 20 types which were found to be associated with increased risk of kidney disease by at least one study, but protective against kidney disease by at least one other.

Sixteen HLA types (HLA-A\*24, A\*26, A\*29, A\*30, A\*32, B\*07, B\*40, B\*44, C\*02, DRB1\*03, DRB1\*04, DRB1\*08, DRB1\*11, DRB1\*13, DQA1\*03 and DQB1\*06) were found to be protective against ESRD by multiple studies (though nine of these were also found to be associated with increased risk of ESRD by at least one other study: A\*24, B\*07, B\*40, C\*02, DRB1\*03, DRB1\*04, DRB1\*11, DRB1\*13 and DQA1\*03). In total, 38 class I types, 24 class II types and 8 haplotypes were found to be protective against ESRD, though 11 of the class I types and 9 of the class II types were in conflict and also associated with ESRD. Similarly, 15 HLA types (HLA-A\*11, B\*08, B\*15, B\*18, B\*49, B\*50, B\*51, B\*53, B\*55, C\*01, DRB1\*03, DRB1\*04, DRB1\*11, DRB1\*12 and DQB1\*02) were associated with ESRD in at least two studies. However, seven of these were protective against ESRD according to a different study (HLA-A\*11, B\*08, B\*50, DRB1\*03, DRB1\*04, DRB1\*11 and DRB1\*12). In total, 31 HLA class I types, 22 class II types and 6 haplotypes were found to be associated with renal dysfunction (though, as mentioned above, 11 of the class I types and 9 of the class II types were also found to be protective against ESRD by different studies).

Many of the findings were directly refuted by other studies. There does not appear to be a consensus around which HLA types have a protective effect and which incur additional risk of ESRD; of the 95 HLA types with a reported association, 20 had the finding refuted by at least one other independent study (21%). Only 10 HLA associations were reported in three or more studies (HLA-A\*11, B\*07, B\*08, B\*53, DRB1\*03, DRB1\*04, DRB1\*08, DRB1\*11, DQB1\*02 and DQB1\*06), and 6 of these were refuted by another study (the exceptions being HLA-B\*53, DRB1\*08, DQB1\*02 and DQB1\*06). Table 2 shows all reported associations between HLA and renal function (some associations with increased incidence of renal dysfunction, and some with decreased incidence). The table illustrates that there are a large number of HLA types which may have an effect on renal failure. The subjects' primary diseases are noted in the table (where possible) to allow for comparison of associations based on the underlying cause of renal dysfunction. There are a number of abbreviations in Table 2; these are expanded below the table. Five of the papers did not report any significant associations. These are listed in Table 3.

### 4 | DISCUSSION

The 35 papers identified 95 HLA types and 14 HLA haplotypes which were associated with renal function. Some of these types appear to confer protection from renal failure, while others appear to confer susceptibility to renal failure. Indeed, 20 HLA types were found to have a protective effect in at least one study but a hazardous effect in at least one other. Only 10 of the associations were replicated by three or more independent studies. This suggests that there may be type I and type II

**TABLE 2** All HLA types and three-locus haplotypes found to be associated with renal function

HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
HLA-A	A*01	Karahan et al. (2009)	Protective against CGN, HTN nephrosclerosis	Turkish	3230 (587 ESRD patients, 2643 controls), Primary diseases: unknown 27%; CGN 23%; HTN nephrosclerosis 17%; PKD 9%; pyelonephritis 9%; VUR nephropathy 4%; diabetic nephropathy 4%; amyloidosis 3%; urologic abnormalities 2%; other 3%
	A*02	Lowe et al. (2021)	Reduced eGFR, increased ESRD	British	401,307 (with a range of kidney function, eGFR calculated for each)
	A*02	Karahan et al. (2009)	Protective against CGN, HTN nephrosclerosis	Turkish	See above
	A*03	Karahan et al. (2009)	Protective against CGN, HTN nephrosclerosis	Turkish	See above
	A*09	Lowe et al. (2021)	Reduced eGFR	British	See above
	A*09	Rivera et al. (2012)	Protective against ESRD	Venezuelan	390 (188 ESRD patients, 202 controls). Majority post-streptococcal or other glomerulonephritis origin
	A*11	Davood et al. (2008)	Associated with ESRD	Azerbaijani	77 (26 ESRD patients awaiting transplantation, primary disease not specified, 51 controls)
		Hernandez-Rivera et al. (2019)	Associated with ESRD	Mexican	3326 (1965 ESRD patients awaiting transplantation, primary disease not specified, 1361 potential kidney donors)
		Pan et al. (2019)	Associated with ESRD	Chinese	2083 (499 ESRD patients awaiting transplantation, 1584 controls). Primary diseases: unknown 63%; glomerulonephritis 13%; HTN nephropathy 8%; diabetic nephropathy 6%; interstitial nephritis 5%; PKD 2%; HSPN 2%; obstructive nephropathy 1%; autoimmune diseases 1%
		Karahan et al. (2009)	Protective against ESRD, CGN, HTN nephrosclerosis	Turkish	See above
	A*23	Karahan et al. (2009)	Protective against ESRD, CGN, HTN nephrosclerosis	Turkish	See above
	A*24	Cao et al. (2014)	Associated with ESRD	Cantonese	8285 (4541 ESRD patients awaiting transplantation, 3744 controls). Primary disease: 57% not specified; 43% glomerulonephritis
		Karahan et al. (2009)	Protective against ESRD, CGN, HTN nephrosclerosis	Turkish	See above
		Uygun et al. (2015)	Protective against ESRD	Turkish	677 (144 highly PRA positive ESRD patients, primary disease not specified, 533 controls)
	A*25:01	Lowe et al. (2021)	Increased eGFR	British	See above
	A*26	Hamdi et al. (2014)	Protective against ESRD	Saudi Arabian	455 (350 ESRD patients, primary disease not specified, 105 controls)

(Continues)

TABLE 2 (Continued)

HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
		Karahan et al. (2009)	Protective against ESRD, CGN, HTN nephrosclerosis	Turkish	See above
A*28		Mosaad et al. (2014)	Protective against ESRD	Kuwaiti	525 (334 ESRD patients, primary disease not specified, 191 controls)
A*29		Karahan et al. (2009)	Protective against ESRD	Turkish	See above
A*30		Lowe et al. (2021)	Increased eGFR	British	See above
		Karahan et al. (2009)	Protective against ESRD, CGN, HTN nephrosclerosis	Turkish	See above
A*31:01		Nassar et al. (2017)	Protective against ESRD	Yemeni	381 (187 CRF patients on haemodialysis, primary disease not specified, 194 controls)
A*32		Pan et al. (2019)	Associated with ESRD	Chinese	See above
		Lowe et al. (2021)	Increased eGFR	British	See above
		Karahan et al. (2009)	Protective against ESRD, CGN, HTN nephrosclerosis	Turkish	See above
A*33		Davood et al. (2008)	Associated with ESRD	Azerbaijani	See above
A*66		Karahan et al. (2009)	Protective against ESRD	Turkish	See above
A*68		Karahan et al. (2009)	Protective against ESRD, CGN, HTN nephrosclerosis	Turkish	See above
A*69		Karahan et al. (2009)	Protective against ESRD	Turkish	See above
A*78		Crispim et al. (2008)	Associated with ESRD	Sao Paulo (Brazil)	265 (105 ESRD patients awaiting transplantation, 160 controls). Primary diseases: undetermined 33%; HTN 25%; diabetes 10%; renal cystic disease 8%; Berger disease 5%; glomerulosclerosis 5%; lupus 4%; other 11%
HLA-B	Bw*4	Prakash et al. (2013)	Associated with ESRD	North Indian	1024 (512 ESRD patients, primary disease not specified, 512 controls)
	B*07	Doxiadis et al. (2001)	Protective against IgA nephropathy	European	2831 (1620 IgA nephropathy patients awaiting kidney transplant, 1211 controls)
		Lowe et al. (2021)	Reduced eGFR	British	See above
		Hieu et al. (2019)	Protective against ESRD	Vietnamese	383 (196 ESRD patients, 187 controls). Primary diseases: CGN 76%; HTN 10%; diabetes 6%; PKD 4%; other 4%
	B*08	Karahan et al. (2009)	Protective against ESRD	Turkish	See above
		Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
		Lowe et al. (2021)	Reduced eGFR, increased ESRD, increased CKD	British	See above

(Continues)

TABLE 2 (Continued)

HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
		Hernandez-Rivera et al. (2019)	Associated with ESRD	Mexican	See above
		Mosaad et al. (2014)	Associated with ESRD	Kuwaiti	See above
B*12		Rivera et al. (2012)	Protective against ESRD	Venezuelan	See above
B*14		Crispim et al. (2008)	Protective against ESRD	Sao Paulo (Brazil)	See above
B*14:01		Lowe et al. (2021)	Increased eGFR	British	See above
B*14:02		Lowe et al. (2021)	Increased eGFR	British	See above
B*15		Hamdi et al. (2014)	Associated with ESRD	Saudi Arabian	See above
		Pan et al. (2019)	Associated with ESRD	Chinese	See above
B*17		Rivera et al. (2012)	Protective against ESRD	Venezuelan	See above
B*18		Hamdi et al. (2014)	Associated with ESRD	Saudi Arabian	See above
		Hernandez-Rivera et al. (2019)	Associated with ESRD	Mexican	See above
B*35		Doxiadis et al. (2001)	Associated with IgA nephropathy	European	See above
B*38		Rivera et al. (2012)	Associated with ESRD	Venezuelan	See above
B*39		Hamdi et al. (2014)	Protective against ESRD	Saudi Arabian	See above
		Pan et al. (2019)	Associated with ESRD	Chinese	See above
B*40		Cao et al. (2014)	Associated with ESRD	Cantonese	See above
		Noureen et al. (2020)	Protective against ESRD	Pakistani	1169 (497 ESRD patients, primary disease not specified, 672 controls)
B*42		Rivera et al. (2012)	Protective against ESRD	Venezuelan	See above
		Yamakawa et al. (2014)	Associated with ESRD	Brazilian	183 ESRD patients on haemodialysis, primary disease not specified, multiple control groups used
B*44		Yamakawa et al. (2014)	Protective against ESRD	Brazilian	See above
		Lowe et al. (2021)	Increased eGFR	British	See above
B*45		Yamakawa et al. (2014)	Associated with ESRD	Brazilian	See above
B*48		Rivera et al. (2012)	Protective against ESRD	Venezuelan	See above
B*49		Hamdi et al. (2014)	Associated with ESRD	Saudi Arabian	See above
		Davood et al. (2008)	Associated with ESRD	Azerbaijani	See above

(Continues)

TABLE 2 (Continued)

HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
B*50		Hamdi et al. (2014)	Protective against ESRD	Saudi Arabian	See above
		Noureen et al. (2020)	Associated with ESRD	Pakistani	See above
		Uygun et al. (2015)	Associated with ESRD	Turkish	See above
B*51		Rivera et al. (2012)	Associated with ESRD	Venezuelan	See above
		Yamakawa et al. (2014)	Associated with ESRD	Brazilian	See above
B*52		Hernandez-Rivera et al. (2019)	Protective against ESRD	Mexican	See above
B*53		Rivera et al. (2012)	Associated with ESRD	Venezuelan	See above
		Hernandez-Rivera et al. (2019)	Associated with ESRD	Mexican	See above
		Lowe et al. (2020)	Reduced eGFR	Black African	3038 subjects (with a range of kidney function, eGFR calculated for each)
B*54		Cao et al. (2014)	Associated with ESRD	Cantonese	See above
B*55		Cao et al. (2014)	Associated with ESRD	Cantonese	See above
		Pan et al. (2019)	Associated with ESRD	Chinese	See above
B*57		Karahan et al. (2009)	Protective against ESRD	Turkish	See above
B*58		Karahan et al. (2009)	Associated with ESRD. Protective against amyloidosis	Turkish	See above
B*62		Rivera et al. (2012)	Associated with ESRD	Venezuelan	See above
C*01		Fejzić et al. (2017)	Associated with ESRD	Bosnian	245 (186 ESRD patients, primary disease not specified, 59 controls)
		Prakash et al. (2013)	Associated with ESRD	North Indian	See above
C*02		Prakash et al. (2013)	Associated with ESRD	North Indian	See above
		Lowe et al. (2021)	Increased eGFR	British	See above
		Almogren et al. (2012)	Protective against ESRD	Saudi Arabian	295 (235 ESRD patients awaiting transplantation, 60 controls). Primary diseases: diabetic nephropathy 74%; CGN 16%; 11% HTN
C*03		Nassar et al. (2015)	Protective against hypertensive ESRD	Yemeni	100 (50 HTN ESRD patients, 50 controls)
C*04:01		Lowe et al. (2020)	Reduced eGFR	Black African	See above
C*05:01		Lowe et al. (2021)	Increased eGFR	British	See above

(Continues)

TABLE 2 (Continued)

HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
	C*06:02	Pan et al. (2019)	Protective against ESRD	Chinese	See above
	C*07:01	Lowe et al. (2021)	Reduced eGFR, increased CKD	British	See above
	C*07:02	Pan et al. (2019)	Protective against ESRD	Chinese	See above
	C*08:02	Lowe et al. (2021)	Reduced eGFR	British	See above
	C*12:03	Lowe et al. (2021)	Increased eGFR	British	See above
	C*16:01	Lowe et al. (2021)	Increased eGFR	British	See above
HLA-DR	DRB1*01	Uygun et al. (2015)	Protective against ESRD	Turkish	See above
	DRB1*02	Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
	DRB1*03	Dai et al. (2015)	Associated with ESRD	Taiwanese	331 (141 ESRD patients, 331 controls). Primary diseases: unknown 63%; diabetes 21%; IgA nephropathy 6%; PKD 3%; other 6%
		Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
		Hamdi et al. (2014)	Associated with ESRD	Saudi Arabian	See above
		Karahan et al. (2009)	Associated with diabetic nephropathy	Turkish	See above
		Pan et al. (2019)	Associated with ESRD	Chinese	See above
		Lowe et al. (2020)	Increased eGFR	Black African	See above
		Lowe et al. (2020)	Reduced eGFR	Indian	5475 subjects (with a range of kidney function, eGFR calculated for each)
		Lowe et al. (2021)	Reduced eGFR, increased ESRD, increased CKD	British	See above
		Yamakawa et al. (2014)	Associated with ESRD	Brazilian	See above
DRB1*04		Chang et al. (2012)	Associated with treatment failure and decreased renal survival	Chinese	152 patients with AAV, no controls
		Cao et al. (2014)	Associated with ESRD	Cantonese	See above
		Perez-Luque et al. (2000)	Protective against ESRD	Mexican	240 (139 patients with combinations of diabetes and ESRD, 101 controls)
		Lowe et al. (2021)	Increased eGFR	British	See above

(Continues)



TABLE 2 (Continued)

HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
		Lowe et al. (2020)	Increased eGFR and protective against CKD	Irish	12,191 subjects (with a range of kidney function, eGFR calculated for each)
		Pan et al. (2019)	Associated with ESRD (DRB1*04:03, 04:04 and 04:05)	Chinese	See above
		Hernandez-Rivera et al. (2019)	Associated with ESRD	Mexican	See above
		Gencik et al. (1999)	Associated with WG	Bavaria (Germany)	102 patients with AASV, size of control group not specified
DRB1*05		Doxiadis et al. (2001)	Associated with IgA nephropathy	European	See above
DRB1*07:01		Lowe et al. (2021)	Increased eGFR	British	See above
DRB1*08		Dai et al. (2015)	Protective against ESRD	Taiwanese	See above
		Hernandez-Rivera et al. (2019)	Protective against ESRD	Mexican	See above
		Nassar et al. (2015)	Protective against hypertensive ESRD	Yemeni	See above
DRB1*09		Hernandez-Rivera et al. (2019)	Protective against ESRD	Mexican	See above
DRB1*10		Liu et al. (2007)	Associated with renal failure	Dalian Han, China	101 (20 patients with renal failure, primary disease not specified, 81 controls)
		Hieu et al. (2019)	Protective against ESRD	Vietnamese	See above
DRB1*11		Crispim et al. (2008)	Associated with ESRD	Sao Paulo (Brazil)	See above
		Dai et al. (2015)	Associated with ESRD	Taiwanese	See above
		Pan et al. (2019)	Associated with ESRD	Chinese	See above
		Hernandez-Rivera et al. (2019)	Associated with ESRD	Mexican	See above
		Karahan et al. (2009)	Protective against ESRD	Turkish	See above
		Mosaad et al. (2014)	Protective against ESRD	Kuwaiti	See above
DRB1*12		Shao et al. (2018)	Associated with ESRD	Dalian Han, China	14,692 (163 ESRD patients, 14,529 controls), Primary disease: CGN 76%; HTN nephrosclerosis 15%; diabetic nephropathy 4%; other 4%
		Pan et al. (2019)	Associated with ESRD	Chinese	See above

(Continues)

TABLE 2 (Continued)

HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
DRB1*13		Noureen et al. (2020)	Protective against ESRD	Pakistani	See above
		Gencik et al. (1999)	Protective against AASV	Bavaria (Germany)	See above
DRB1*15:01		Noureen et al. (2020)	Protective against ESRD	Pakistani	See above
		Gerhardsson et al. (2015)	Associated with ESRD	Swedish	110 (16 patients with HAPLN, 94 patients with LN)
DRB1*15:02		Pan et al. (2019)	Protective against ESRD	Chinese	See above
		Lowe et al. (2021)	Increased eGFR	British	See above
DRB1*16		Perez-Luque et al. (2000)	Associated with ESRD	Mexican	See above
		Hernandez-Rivera et al. (2019)	Protective against ESRD	Mexican	See above
DRB1*17		Hernandez-Rivera et al. (2019)	Associated with ESRD	Mexican	See above
DRB3*01:01		Lowe et al. (2021)	Reduced eGFR	British	See above
	DRB3 - no gene	Lowe et al. (2021)	Reduced eGFR, increased CKD	British	See above
DRB4*01:01		Lowe et al. (2021)	Increased eGFR	British	See above
	DRB4*01:03	Lowe et al. (2021)	Increased eGFR	British	See above
HLA-DP	DRB4 - no gene	Lowe et al. (2021)	Increased eGFR	British	See above
	DPA1*01:03	Lowe et al. (2020)	Increased eGFR	Black African	See above
DPB1*02:01		Lowe et al. (2020)	Reduced eGFR	Black African	See above
	DPB1*02:02	Lowe et al. (2020)	Reduced eGFR	Black African	See above
DPB1*04:02		Chang et al. (2012)	Associated with increased mortality	Chinese	See above
HLA-DQ	DQA1*02:01	Lowe et al. (2021)	Increased eGFR	British	See above
	DQA1*03	Lowe et al. (2021)	Increased eGFR	British	See above
DQA1*04		Noureen et al. (2020)	Protective against ESRD	Pakistani	See above
		Hernandez-Rivera et al. (2019)	Protective against ESRD	Mexican	See above
DQA1*05:01		Hernandez-Rivera et al. (2019)	Protective against ESRD	Mexican	See above
		Lowe et al. (2021)	Reduced eGFR, increased CKD	British	See above
DQA1*06		Noureen et al. (2020)	Protective against ESRD	Pakistani	See above

(Continues)

TABLE 2 (Continued)

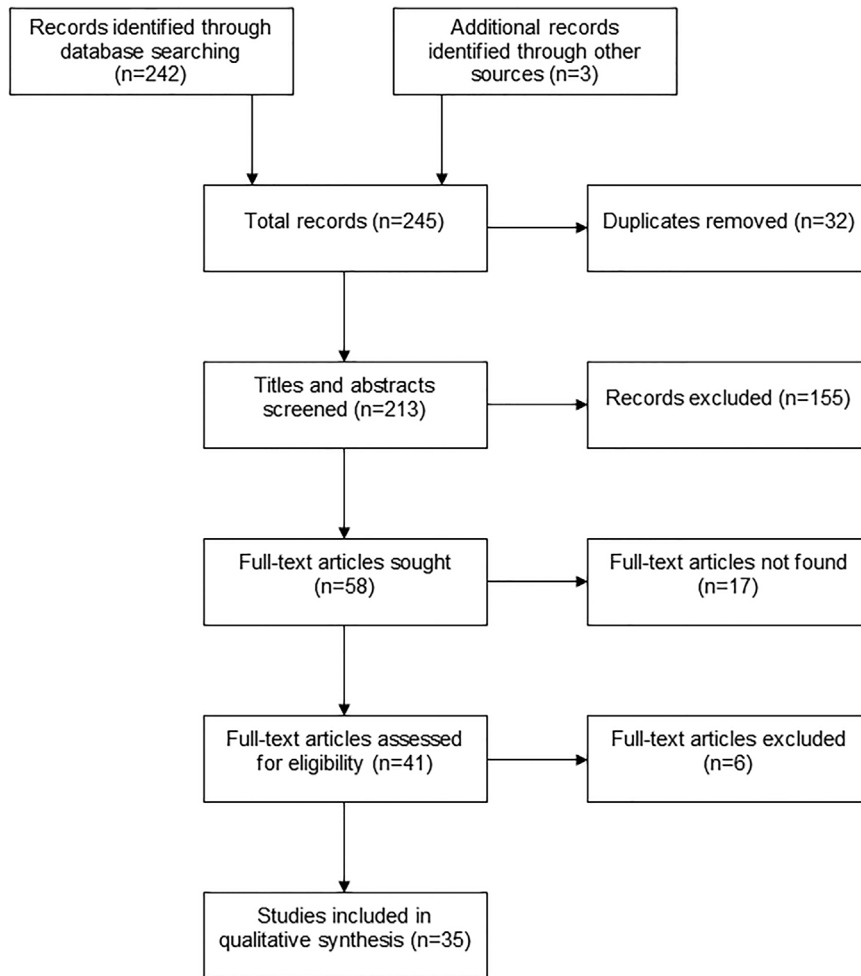
HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
	DQB1*02	Liu et al. (2007)	Associated with renal failure	Dalian Han, China	See above
		Pan et al. (2019)	Associated with ESRD	Chinese	See above
		Lowe et al. (2021)	Reduced eGFR, increased ESRD, increased CKD	British	See above
		Lowe et al. (2020)	Reduced eGFR	Indian	See above
	DQB1*03:01	Pan et al. (2019)	Associated with ESRD	Chinese	See above
	DQB1*03:02	Lowe et al. (2021)	Increased eGFR	British	See above
		Pan et al. (2019)	Associated with ESRD	Chinese	See above
	DQB1*03:08	Almogren et al. (2012)	Associated with ESRD	Saudi Arabian	See above
	DQB1*04:01	Pan et al. (2019)	Associated with ESRD	Chinese	See above
	DQB1*05:01	Perez-Luque et al. (2000)	Associated with ESRD	Mexican	See above
	DQB1*06	Lowe et al. (2021)	Increased eGFR (DQB1*06:01)	British	See above
		Noureen et al. (2020)	Protective against ESRD	Pakistani	See above
		Pan et al. (2019)	Protective against ESRD (DQB1*06:02 and 06:09)	Chinese	See above
		Gencik et al. (1999)	Protective against AASV (DQB1*06:03)	Bavaria (Germany)	See above
		Lowe et al. (2021)	Increased eGFR (DQB1*06:09)	British	See above
Haplotypes	A*01-B*8-DR*03	Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
	A*01-B*15-DR*04	Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
	A*02-B*05-DR*05	Doxiadis et al. (2001)	Associated with IgA nephropathy	European	See above
	A*02-B*07-DR*02	Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
	A*02-B*40-DRB1*09	Shao et al. (2018)	Associated with ESRD	Dalian Han, China	See above
	A*02-B*40-DRB1*12	Shao et al. (2018)	Associated with ESRD	Dalian Han, China	See above
	A*02-B*44-DRB1*07	Chowdhry et al. (2016)	Protective against ESRD	Indian	339 (148 ESRD patients, primary disease not specified, 191 controls)

(Continues)

TABLE 2 (Continued)

HLA Locus	HLA type or haplotype	Study	Effect	Population	Number of subjects
	A*03-B*07-DR*02	Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
	A*09-B*12-DR*07	Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
	A*10-B*18-DR*2	Doxiadis et al. (2001)	Protective against IgA nephropathy	European	See above
	A*11-B*27-DRB1*04	Cao et al. (2014)	Associated with ESRD	Cantonese	See above
	A*24-B*15-DRB1*12	Shao et al. (2018)	Associated with ESRD	Dalian Han, China	See above
	A*33-B*44-DRB1*07	Chowdhry et al. (2016)	Protective against ESRD	Indian	See above
	DRB1*03:01-DQA1*05:01-DQB1*02:01	Levine et al. (2020)	Associated with PMG	European	6588 (146 PMG patients, 6442 controls)

Antineutrophil cytoplasmic antibodies-associated systemic vasculitis (AASV); antineutrophil cytoplasmic antibodies-associated vasculitis (AAV); chronic glomerulonephritis (CGN); chronic renal failure (CRF); histopathological antiphospholipid-associated nephropathy (HA-PLN); hypertensive (HTN); Henoch-Schönlein purpura nephritis (HSPN); immunoglobulin A (IgA); polycystic kidney disease (PKD); primary membranoproliferative glomerulonephritis (PMG); panel reactive antibody (PRA); vesicoureteral reflux (VUR); Wegener's granulomatosis (WG).



**FIGURE 1** Process of including and excluding papers

**TABLE 3** Studies which reported no significant associations between HLA type and renal function

Study	No associations reported between	Population	Number of subjects
Demaine et al. (1982)	HLA and ESRD	Caucasian	275 (163 ESRD patients, 112 controls). Primary diseases: non-immunological eg PKD, HTN 53%; immunological, e.g. glomerulonephritis 47%
Hanna et al. (2015)	HLA and ESRD	Egyptian	94 (50 ESRD patients, 44 controls). Primary diseases: diabetic nephropathy 26%; HTN nephrosclerosis 22%; PKD 10%; lupus 8%; unknown 34%
Regueiro and Arnaiz-Villena (1984)	HLA and CKD	Spanish	216 (20 CKD patients, 196 controls). Primary diseases: 15% glomerulonephritis 15%; lupus 5%; uropathy 5%; unknown 75%
Zachary et al. (1996)	HLA and ESRD	USA	38,582 (20,069 ESRD patients, primary diseases not specified, 18,513 controls)
Spriewald et al. (2005)	HLA and WG	German	123 (32 WG patients, 91 controls)

errors in the findings: true HLA associations with renal function may be more likely to have been replicated in independent cohorts.

Generally, the studies in this review included a group of subjects with ESRD or some other criteria of kidney dysfunction who were compared with a control group of healthy subjects. The subjects were HLA typed by a particular method (such as PCR-SSO or PCR-SSP typing) and the frequencies of the HLA specificities in the different groups compared. HLA specificities which were found significantly more commonly in the disease group were said to confer risk of susceptibility to the disease (or be 'associated' with the disease), while those which were more commonly found in the healthy group were said to confer protection from the disease.

The majority of these studies focused on a specific ethnicity or nationality. HLA allele and haplotype frequencies vary considerably between groups of people of different ethnicities. An allele that confers a risk of (or protection from) ESRD in one population may not have the same effect for people of another population; this may explain some of the discrepant findings from different studies. Each of these studies' findings can only be applied to the ethnic population used in the study. However, such an association may be a good indicator of the same association in other groups. It is important, then, to investigate as many different cohorts of patients as possible, as results do not appear to be universal. There is also often an environmental component to disease onset, which may vary between ethnic groups. Due to the difficulty of comparing HLA associations among different ethnic groups, it was not possible to perform a meta-analysis based on the papers identified by this literature search. Similarly, there are many different primary diseases or underlying causes of CKD (NHS, 2019), and these may each have different HLA associations (or no HLA associations at all), as well as having different frequencies in different ethnic populations (Stratton et al., 2000). This could explain the contradictory associations reported: an allele could possibly lead to increased chance of one underlying disease but decreased chance of another. Depending on the composition of each study's cohort, the cumulative effect of these differences (ethnicity, primary disease, allele frequency and environmental factors) may be responsible for some of the contradictory and discrepant findings. Some of the studies in this review clarified which primary disease they were investigating; where available, the primary diseases can be seen in Table 2. Some studies focused on a particular underlying cause of renal dysfunction, while others provided the proportions of each primary disease but analysed all subjects together in a heterogeneous group, and still others did not mention the cause of renal failure. For this reason, comparing associations based on primary disease is difficult.

One problem with these studies is that the sample sizes are often small, which may lead to insufficient power to detect the true genetic effect size. For example, Liu et al. (2007) included only 20 patients and 81 controls, and other studies such as Regueiro and Arnaiz-Villena (1984), Davood et al. (2008) and Spriewald et al. (2005) all used study groups of  $\leq 32$  patients. The largest case-control study was performed by Zachary et al. (1996), who used a cohort of 20,069 ESRD patients and 18,513 controls. However, this study did not report any significant associations between HLA and ESRD. Although the paper reported the

frequencies of HLA types in both the patient and control groups, it did not investigate whether there were significant differences between the two groups. It is possible that there were significant associations but they were not explicitly mentioned in the paper.

A criticism of some studies is the selection of the case and control groups. For example, in the studies by Nassar et al. (2015) and Hamdi et al. (2014), the control groups of healthy patients were made up of kidney transplantation donors; many of these may have been relatives of people with ESRD (some of whom may even have been included in the case group). The hereditary nature of HLA types means that the HLA haplotypes of living kidney donors may not be representative of a typical group of healthy people from their respective populations; they may have been genetically more similar to the subjects with ESRD. Some studies mentioned that their control group was made up of unrelated people, so this criticism does not apply.

A further drawback of a proportion of these studies is their statistical methodologies. It is not clear in a number of papers whether the researchers applied a correction for multiple tests. As each study tests a large number of HLA alleles for association with ESRD, using a value of  $p < .05$  to indicate significance is likely to lead to a number of apparently significant associations which are simply due to chance. To resolve this, an adjusted  $p$  value should be calculated to correct for multiple tests. Cao et al. (2014) and Mosaad et al. (2014), for example, mentioned that they used the Bonferroni formula to achieve this correction, and only reported corrected  $p$  values as significant. Many studies, though, did not clarify whether they adjusted the significance levels to accommodate multiple testing. A final criticism of these studies is that they often treat renal function as a categorical variable, with subjects classed as either healthy or unhealthy depending on their GFR. In reality, there is a wide range of levels of renal function; future studies should be advised to use continuous measures such as GFR or estimated GFR (eGFR) if possible in order to obtain a more precise measurement of the subjects' kidney functions. Although categorizations based on continuous data have useful clinical applications (e.g. for diagnosis), they lead to reduced statistical power and increased risk of type I errors when used for research (Altman & Royston, 2006). For this reason, the practice is 'rarely defensible and often ... misleading' (MacCallum et al., 2002) and 'unnecessary for statistical analysis' (Naggara et al., 2011). A strength of these studies is that the HLA genotyping methods used are generally very accurate. Subjects were commonly typed by PCR-SSO (Fejzic et al., 2017; Perez-Luque et al., 2000) or PCR-SSP (Cao et al., 2014; Nassar et al., 2015) methods, though some used less accurate serological methods or imputation.

A limitation of the systematic review process is that some of the process was carried out by a single researcher, so the methods were not independently validated. Additionally, only full articles were considered so it is possible that some relevant findings (such as abstracts and posters from conferences) were omitted due to not having been peer-reviewed. Initially there were an additional two concepts which were intended to be included in the review but were ultimately dropped; originally, the review intended to consider only studies of white subjects of middle age or older. Age is related to kidney function (Weinstein & Anderson, 2010) and it is known that genetic associations with

renal function vary according to age. Removing the concept of age increased the sensitivity of the search but reduced the specificity. It is possible also that there is reporting bias, which would mean that studies which did not find any associations between HLA and renal function were less likely to be published. However, five of the studies included in this review reported no associations, so it appears that a lack of findings is not a complete contraindication to publication.

## 5 | CONCLUSION

This paper has performed a systematic review of previous literature investigating associations between HLA type and renal function. A total of 245 papers were considered from a wide range of sources, and 35 were considered relevant. These papers revealed a large number of associations between renal function and HLA types. The findings strongly suggest that there is a link between HLA type and renal function, though the exact nature of this link is unclear. There is very little consensus on which HLA types are protective, or which confer risk of ESRD. Ethnicity appears to have a role in whether particular genes are associated with renal function, and the underlying cause of renal failure may complicate this further. Further research is required to confirm or refute the associations found so far, and possibly to reveal novel associations.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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