The Genetic Variants of HLA-DRB1 Alleles and the Chance of Developing Rheumatoid Arthritis: Systematic Review and meta-analysis

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Abstract

Rheumatoid arthritis (RA) is more common in those who have special human leukocyte antigen (HLA) genetic types. One of the most important genetic risk factors for RA lies in HLA-DRB1 locus. The purpose of this meta-analysis was to figure out which HLA-DRB1 allele frequencies are associated with a risk of RA per allele and phenotype group. The statistics data was calculated using RevMan version 5.4.1. This meta-analysis includes nine articles involving 3004 RA patients and 2384 healthy controls. In the allele group, three HLA-DRB1 alleles; HLA-DRB1*10 (OR = 1.88, 95%CI = 1.25-2.83, $p = 0.002$), HLA-DRB1*04 (OR = 2.38, 95%CI = 1.73-3.29, $p < 0.00001$), and HLA-DRB1*01 frequencies were shown to be considerably higher in RA patients compared to controls, potentially increasing the chance of disease development. Four HLA-DRB1 alleles among the included studies (*03, *07, *11, *13, and *14) which was observed that these are more prevalent in healthy persons than in RA patients, and may contribute as a protective factor against disease onset. Only the DRB1*04 subtypes DRB1*0401 (OR = 1.37, 95 percent CI = 1.05-1.79, $p = 0.02$) and DRB1*0404 (OR = 1.73, 95% CI = 1.19-12.53, $p = 0.004$) show a significant association with the risk of RA in our pooled effect. Moreover, the findings demonstrated a significant relationship between HLA-DRB1 and the risk of disease in various ethnic groups.

Introduction

The most frequent type of autoimmune arthritis is rheumatoid arthritis (RA). It is caused by the immune system attacking healthy body tissue, means that when the body's defense mechanism is not functioning properly [1]. Although the disease affects people of all ethnic groups around the world, its prevalence varies by race, ranging from 0.1 percent in native Africans [2] to 5% in Pima Indians [3]. However, it is unknown what causes this diseases, Nevertheless, major histocompatibility complex (MHC), also known as Human leukocyte antigen (HLA) in human, is one of the most important genetic variables in RA. One of the genetic loci linked to RA variations is the MHC class II regions. The most important genetic risk factor for the onset of RA is found in the MHC class II region [4, 5].

RA has been linked to more than 30 risk alleles. The HLA-DRB1 gene in the MHC II region is the gene most strongly linked to RA, which is thought to account for up to one-third of the genetic risk to RA [6]. Most individuals with RA have preferred HLA-DRB1 alleles with a shared epitope [7, 8]. Amino acid sequences in the DR β chain at locations 70 to 74 were retained in RA-associated DRB1 alleles as either QRRAA, or RRRAA, which is the shared epitope (SE) [7]. The SE-RA link appears to be complicated and variable among populations [9]. Differences in clinical and laboratory markers between DR4 + and DR4- patients in RA patients have been questioned [10]. Meanwhile, research also suggests that the SE's principal function is linked to disease severity than susceptibility [11].

Diverse populations have various HLA-DRB1 risk alleles. Some meta-analyses have been undertaken in specific ethnic groupings of the population. In Asian populations, a meta-analysis of the association

between the HLA-DRB1 allele and rheumatoid arthritis susceptibility was conducted [12]. It was also done in Latin American [13] and in Caucasian [14]. However, no meta-analysis has been reported in multi-ethnic groups with the most up-to-date information.

In this study all reports relating to the risk of HLA-DRB1 alleles with RA were considered. This meta-analysis aggregated all data from different ethnic groups to produce a more general and comprehensive results. To our knowledge, this is the only study that takes into account multi-ethnic groups data to infer new insights between the HLA-DRB1 allele and the chance of developing RA.

Methods

Search strategy and Study selection

We used the search terms "HLA-DRB1" or "HLA-DRB1 allele" AND "Associated polymorphism" AND "Rheumatoid arthritis" to explore for studies published before June 2021 in the Google Scholar, PubMed, and Springer databases. The following criteria were used to determine which should be included: 1) case-control (RA patients vs healthy) studies; 2) if sufficient data for each allele was given; and 3) NOS featured studies that were of high quality; 4) conventional molecular techniques were applied. Meta-analysis studies and non-original papers were not included in the study.

Quality assessment and data extraction

The first author's last name, publication year, study area, sample size, gender frequency, average age, and HLA-typing method were all obtained from each study. The Newcastle-Ottawa Scale (NOS) [15] was used to assess the quality of these investigations, with articles scoring more than five out of a possible eight being considered high-quality and included in this meta-analysis (Supplementary)

Risk of bias assessment

The funnel plots were used to reveal the distribution of odds ratios (ORs) from separate studies in relation to their respective standard error (SE). The regression test proposed by Egger et al.[16] was used to analyze publication bias statistically. In addition, for a sensitivity test, we compared trim and fill [17] estimates from fixed-effect (FE) and random-effect (RE) model.

Analysis

All statistical analysis was performed with Review Manager 5.4.1. The Mantel-Haenszel technique was used to analyze the effect of HLA-DRB1 alleles in RA. We used odds ratio (OR) and 95 percent confidence interval (CI) to measure the effect of HLA-DRB1 alleles in RA. The forest plot was also shown, along with an explanation of the total pooled P-value. The diamond at the bottom of the forest plot represents the outcome of combining and averaging all of the individual studies. The horizontal points of the diamond are the 95 % CI and they can be interpreted the same way as any of the other individual studies on the plot.

I^2 was used to assess statistical heterogeneity between the included studies. The I^2 value varies from 0 to 100% ($I^2 = 0-25\%$, no/low heterogeneity; $I^2 = 25-50\%$, moderate heterogeneity; $I^2 = 50-75\%$, substantial/high heterogeneity; $I^2 = 75-100\%$, extreme heterogeneity) [18]. For $I^2 \leq 50\%$, a fixed-effect (FE) model was utilized otherwise a random-effect model was used since $I^2 > 50\%$ appeared to be that did not happen by chance. GraphPad Prism 9 (<https://www.graphpad.com/>) was also used to do simple statistical tests and combine scientific graphing, which served as a cross-check.

Results

Characteristics of included studies

This meta-analysis contained nine reports published between 2011 and 2019. The initial database search yielded 232 articles based on PRISMA 2020 checklist (<http://www.prisma-statement.org/>), as shown in Fig. 1. The final included papers were chosen after filtering 148 duplicated studies, 61 content-based article screenings, and 14 non-eligible research.

Table 1 shows the characteristics of the included studies. There were 3004 cases and 2384 controls in total, with a case-to-control ratio of 1.26. In all groups, the average age was 46 years old, with females accounting for 3823 and males accounting for 960, with the exception of one study [5] that did not provide gender frequency.

Association between HLA-DRB1 alleles and RA

In this meta-analysis, a forest plot showing the correlation between HLA-DRB1 allele and the chance of RA is presented in Fig. 2. Table 2 shows the relationship between the HLA-DRB1 allele and the risk of RA; Fig. 3 popped up the general frequency of the cases and control.

The pooled HLA-DRB1*03 allele was found to be significantly lower among RA patients (OR = 0.72, 95%CI = 0.61–0.85, $p < 0.00001$), and the fixed-effect model applied for low-heterogeneity.

The total effect of HLA-DRB1*04 reveals that those who carry this allele are 2.38 times more likely to develop RA (OR = 2.38, 95%CI = 1.73–3.29, $p < 0.00001$) and the random-effect model was utilized in the included studies because of high-heterogeneity ($I^2 = 85\%$).

The proportion of HLA-DRB1*07 allele was 78% less among RA patients, as per HLA-DRB1*07 pooled data (OR = 0.78, 95%CI = 0.65–0.92, $p = 0.005$). In addition, in the given interval, the overall likelihood of having RA was 63 percent lower in HLA-DRB1*11 allele (OR = 0.63, 95%CI = 0.47–0.85, $p = 0.003$). The fixed-effect model (low heterogeneity, $I^2 = 0\%$) was used for the first allele, followed by the random-effect model (high heterogeneity, $I^2 = 68\%$) for the second allele.

Because of the moderate-heterogeneity ($I^2 = 54\%$) in the HLA-DRB1*10 allele, the random-effect model was employed for meta-analysis. According to the overall data, the allele is associated with a

significantly increased risk of RA. (OR = 1.88, 95%CI = 1.25–2.83, $p = 0.002$).

Both allele frequencies of HLA-DRB1*13 (OR = 0.57, 95%CI = 0.46–0.72, $p < 0.00001$) and HLA-DRB1*14 (OR = 0.80, 95%CI = 0.67–0.96, $p = 0.02$) were shown to have a significantly decreased chance of developing RA than the control group. The Random-effect model (moderate-heterogeneity, $I^2 = 51\%$) and the fixed-effect model (low-heterogeneity, $I^2 = 26\%$) were applied respectively.

We discovered no relationship between a few HLA-DRB1 alleles and the chance of developing RA in our pooled effect analysis. In a random-effect model, HLA-DRB1*08 (OR = 0.71, 95%CI = 0.47–1.07, $p = 0.10$) and HLA-DRB1*09 (OR = 1.42, 95%CI = 0.68–2.96, $p = 0.34$) revealed no correlation with the risk of RA. Likewise no association with the risk of RA was found in a fixed-effect model, HLA-DRB1*12 (OR = 0.86, 95%CI = 0.69–1.06, $p = 0.15$) and HLA-DRB1*15 (OR = 0.90, 95%CI = 0.79–1.01, $p = 0.08$).

Because two studies from South Africa [19] and Japan [20] had no HLA-DRB1*16 allele frequency, only seven studies were included in the analysis and there is no link between the alleles and the risk of RA on the total outcome.

Subgroup analysis

We further assessed at each phenotypic group separately to see if there was a specific link between HLA-DRB1 and the risk of getting RA at an individual level (Table 3). Among the subtypes; Only DRB1*0401 (OR = 1.37, 95%CI = 1.05–1.79, $p = 0.02$) and DRB1*0404 (OR = 1.73, 95%CI = 1.19–12.53, $p = 0.004$) of the DRB1*04 subtypes indicate a significant association with the diseases RA in six studies.

Nonetheless, the DRB1*0403 (OR = 0.36, 95%CI = 0.19–0.68, $p = 0.002$), and DRB1*0407 (OR = 0.32, 95%CI = 0.10–1.04, $p = 0.05$) subgroups with high-heterogeneity showed a decreased risk of developing RA. In a Random-effect model, the genotype groups DRB1*0101 (OR = 1.55, 95%CI = 0.58–4.17, $p = 0.38$) and DRB1*0102 (OR = 0.99, 95%CI = 0.37–2.66, $p = 0.98$) show no association with RA, unlike the allele group DRB1*01.

The relationship between HLADRB1 and RA appeared to be somewhat symmetric in a funnel plot. Furthermore, the findings of Egger's test indicate that there was no bias ($p > .05$).

Discussion

Meta-analyses can assist in determining statistical significance across studies that appear to have contradictory results. The statistical significance established when multiple researches are considered at once is significantly higher than when one study is considered alone [21]. Some of the benefits of meta-analysis include a pooled estimate of impact, an objective assessment of evidence, and the ability to explain heterogeneity between research results [22].

This meta-analysis found three HLA-DRB1 alleles (*01, *04, and *10) which have been shown to be predisposing for RA. The controls, on the other hand, are favored by four HLA-DRB1 alleles (*03, *07, *11,

*13, and *14) which were shown to be significantly lower in RA patients than in controls allele group, potentially decreasing the risk of disease development. However, no association was observed across five HLA-DRB1 alleles (*08, *09, *12, *15, and *16).

Despite the fact that there is no significant link ($P = 0.006$), the forest plot HLA-DRB1*01 has showed that is more likely to develop RA than controls. This may be because of the longer confidence interval on individual studies. Closer to our findings, two studies from Syria ($OR = 2.29$, $95\%CI = 1.11-4.75$, $P = 0.022$) [14] and Turkey ($OR = 1.99$, $95\%CI = 1.19-3.33$, $P = 0.04$) [6] both found a robust link of RA in the allele group. HLA-DRB1*01 has also been linked to the risk of RA in areas of northeastern Spain [23] and India [24].

Our findings on the DRB1*0401 genotype group demonstrate a predisposition to RA, which is consistent with research in European populations [16] that reveal DRB1*0401 is one of the most important genetic risk factors for RA. Also the prevalence of DRB1*0401 is significantly higher in RA patients, according to a report in the Chinese population [25]. In contrast to research DRB104:05 is negatively related with RA in Japanese people [20], however our pooled findings reveal no connection at all with this subgroup across included studies.

Interestingly, unlike many other research, HLA-DRB1*14 was found to be protective in our pooled effects. There are research that do not complement our findings of alleles include: The HLA-DRB1*14 ($OR = 2.74$) allele and RA are linked in a study of a mixed Peruvian population ($n = 65$) [26]. Similarly, according to another research the HLA-DRB1*14 allele has demonstrated a tendency to be associated with RA was observed in Yakima Indians, a Native American tribe[27].

The HLA-DRB1*09 alleles, which are found to be a predisposing factor on RA patients of Malaysia [28], are not observed in our study. No correlation was found in our study ($OR = 1.42$, $95\%CI = 0.68-2.96$, $p = 0.34$). This difference could be due to the fact that these studies had a larger sample size, resulting in statistical significance in this association.

HLA-DRB1*04 was found to be predisposing against RA in our study, as well as in studies of RA patients from Portuguese [29], Spain [30], and United Kingdom [31]. There are, of course, some multiple theories about this allele. For instance, some study revealed a significant rise in the frequency of HLA-DRB1*04 alleles in RA patients [32], whereas, others found no such associations [25]. Curiously, like many other research, HLA-DRB1*04 was found to be positive association with RA in our pooled effects. But HLA-DRB1*01 and HLA-DRB1*04 alleles appear to be linked to a decreased chance of developing RA [33, 34], which is not consistent with our findings.

Differences in ethnic groupings, geographic region, and HLA genotype might explain the contradictory results. Differences in ethnic groupings, geographic location, HLA genotyping methods, and sample size may be to blame for the mixed results. Because of the high shared epitope (SE) in the area, it would be best to examine at all genotype level in future study.

The lack of a link between HLA-DRB1*04 and RA in Greek patients was confirmed in one study. In general, our findings provide a tremendous insight into HLA-DRB1 and the risk of having RA, which are both consistent with and contradictory to the findings of many research around the world. This could be because our analysis did not include a European group by default, or because the majority of these studies focus on early disease start.

However, this meta-analysis has certain limitations. We do not take European HLA-DRB1 into account by chance, which is something that other researchers may do in the future. Since ethnicity and geographical differences are important variables in gene-association research.

Conclusion

In conclusion, the pooled results of the meta-analysis reveal a robust association between HLA-DRB1 genetic variants and the chance of developing RA in both allele and phenotype groups. In this meta-analysis study, we identified a correlation between HLA-DRB1 alleles and the chances of having RA. This may contribute in disease identification and prevention through early detection and screening of the risk alleles. High allele expression of HLA-DRB1*04 and HLA-DRB1*10 is significantly associated to RA in this finding, suggesting that it could be a risk factor for the disease. Low HLA-DRB1*03, HLA-DRB1*07, HLA-DRB1*11, HLA-DRB1*13, and HLA-DRB1*14 allele expression may be linked to RA and may contribute as a protective factor against disease onset. DRB1*0401 and DRB1*0404 have indeed been found to be predisposing to RA, while DRB1*0403 and DRB1*0407 were found to be protective.

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Tables

Tables 1 *Characteristics of the nine included studies*

First Author, Year [Reference]	Country	Group	Sample size	Gender, F/M	Age (mean $\pm$ SD, years)	HLA-typing
Uçar 2012[35]	Turkey	RA	320	240/ 80	49.93 $\pm$ 16.04	PCR-SSP
		Control	360			
Wang 2015[36]	China	RA	109	Only	50.94 $\pm$ 6.54	PCR-
		Control	111	Female	49.49 $\pm$ 5.38	SBT
Sandoughi 2011[37]	Iran	RA	79	70/9	44.5	PCR-
		Control	93	65/28	45.4	SSP
Oka 2014[20]	Japan	RA	1480	1208/	63.9 $\pm$ 12.2	PCR-
		Control	800	272	36.76 $\pm$ 10.7	SSOP
				562/ 238		
Muazzam 2013[38]	Pakistan	RA	110	NS	40.89 $\pm$ 12.97	PCR
		Control	120	NS	NS	
Govind 2019[19]	South Africa	RA	266	239/ 27	55 $\pm$ 10.8	PCR
		Control	362	NS	NS	
Mourad 2013[39]	Syria	RA	86	69/ 17	41.41 $\pm$ 10.57	PCR-
		Control	200	160/ 40	40.21 $\pm$ 10.11	SSP
Ben 2012[40]	Tunisia	RA	142	119/ 23	39.5	PCR-
		Control	123	73/ 50	42.8	SSP
Uçar 2012[35]	Turkey	RA	320	240/ 80	49.93 $\pm$ 16.04	PCR-
		Control	360			SSP

PCR, polymerase chain reaction; SSOP, sequence-specific oligonucleotide probe; SSO-sequence-specific primers; SBT-sequence-based Typing; NS, not stated

Tables 2 *Association between the HLA-DRB1 alleles and chance of RA*

group	Test of association							Test of heterogeneity	
	Studies (n) [Ref]	Cases (n)	Controls (n)	OR	95%CI	P- value	Model	I ² (%)	P-value
≤01	g ^[19, 35-41]	268	191	1.01	0.69-1.47	0.96	F	40	0.001
≤03	g ^[19, 35-41]	281	404	0.56	0.40-0.77	0.0004	R	53	0.0005
≤04	g ^[19, 20, 35-41]	1598	647	1.75	1.20-2.54	0.004	R	71	<0.00001
≤07	g ^[19, 35-41]	260	322	0.64	0.45-0.92	0.02	F	27	<0.0001
≤08	g ^[19, 20, 35, 36, 38-41]	286	287	0.70	0.45-1.08	0.11	R	59	0.002
≤09	g ^[19, 35-41]	92	67	1.16	0.51-2.64	0.72	R	73	0.0005
≤10	g ^[19, 35-41]	164	97	1.46	1.14-1.88	0.003	F	48	0.06
≤11	g ^[19, 35-41]	308	525	0.52	0.35-0.79	0.002	R	65	<0.00001
≤12	g ^[19, 20, 35, 36, 38-41]	209	180	0.78	0.49-1.24	0.29	R	55	0.006
≤13	g ^[19, 20, 35-41]	393	605	0.57	0.39-0.82	0.003	R	64	<0.00001
≤14	g ^[19, 20, 35-41]	287	261	0.79	0.50-1.24	0.31	F	33	0.0003
≤15	g ^[19, 20, 35-41]	705	599	0.79	0.56-1.12	0.18	R	76	<0.00001
≤16	7 ^[35-41]	96	81	1.02	0.76-1.37	0.89	F	42	0.11

Allele group: studies in which allele counts or frequencies were applied as a statistical approach; OR, odds ratio; CI, confidence interval; P, probability tested for oval effect; R, random; F, fixed-model

Tables 3 Association between the HLA-DRB1 phenotype and chance of RA

type group			Test of association				Test of heterogeneity	
Studies (n) * [Ref]	Cases (n)	Controls (n)	OR	95%CI	P-value	Model	I ² (%)	P-value
4 [*] [19, 36, 37, 41]	213	118	1.55	0.58-4.17	0.38	R	75	0.0002
3 [*] [19, 36, 41]	48	28	0.99	0.37-2.66	0.98	F	24	0.02
6 [*] [19, 35-37, 40, 41]	241	72	1.37	1.05-1.79	0.02	R	57	0.01
5 [*] [19, 35, 36, 40, 41]	42	64	0.41	0.11-1.50	0.18	F	43	<0.0001
5 [*] [35-37, 40, 41]	75	85	0.36	0.19-0.68	0.002	R	52	0.02
6 [*] [19, 35-37, 40, 41]	144	34	1.73	1.19-2.53	0.004	F	5	0.38
6 [*] [19, 35-37, 40, 41]	788	206	1.05	0.54-2.07	0.88	F	0	<0.00001
5 [*] [35-37, 40, 41]	84	81	0.48	0.20-1.13	0.09	R	56	0.02
5 [*] [35-37, 40, 41]	18	26	0.32	0.10-1.04	0.05	R	50	0.04
4 [*] [19, 35, 40, 41]	26	4	2.03	0.81-5.08	0.13	F	0	0.43
4 [*] [19, 36, 37, 41]	76	24	1.26	0.79-1.99	0.33	F	0	0.41
4 [*] [19, 36, 37, 41]	81	33	1.66	0.55-4.97	0.37	R	66	0.006

Phenotype group: studies in which phenotype counts or frequencies were applied as a statistical approach

Competing Interests

The authors declare no competing interests.

Figures

Figure 1

Flow diagram of the study selection process

HLA-DRB1*01

HLA-DRB1*04

HLA-DRB1*10

HLA-DRB1*13

Figure 2

Overall forest plot association of HLA-DRB1 and RA

Figure 3

Frequency of HLA-DRB1 alleles

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