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Abstract

Background: Human leukocyte antigen (HLA) class II has shown potential in determining prognosis, understanding medication reactions, and predicting onset of Graves' disease. The aim of this study is to further investigate the association between Graves' disease and HLA class II, specifically HLA-DQ and HLA-DR, via meta-analysis to find HLAs that can be further examined for prognostic reasons.

Methods: Statistical analysis was performed to determine if variants of HLA-DQA1, HLA-DQB1, or HLA-DRB1 were associated with significantly altered odds of Graves' disease. A minimum of three studies pertaining to a particular HLA was required for inclusion. Studies were excluded if they lacked inclusion criteria.

Results: 27 studies were included. Odds of associated HLAs in Graves' disease patients versus controls were increased for HLA-DQA1*03:01 (OR = 1.30 [1.03, 1.63], I^2 =0%, p

Discussion: These findings offer new connections between HLAs and Graves' disease that may be applied to prognosis, treatment, and autoimmune mechanistic understanding for MHC class II in Graves' disease.

Keywords

human leukocyte antigen, HLA, Graves, hyperthyroidism, autoimmune thyroid disease, HLA-DQA1, HLA-DQB1, HLA-DRB1

Conflict of Interest Statement

Authors of this work declare no conflict of interest.

Cover Page Footnote

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META-ANALYSIS/SYSTEMATIC REVIEW

Graves' Disease and Major Histocompatibility Complex Class II: A Meta-Analysis of HLA-DQ and HLA-DRB1

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Background: **Human leukocyte antigen (HLA) class II has shown potential in determining prognosis, understanding medication reactions, and predicting onset of Graves' disease. The aim of this study is to further investigate the association between Graves' disease and HLA class II, specifically HLA-DQ and HLA-DR, via meta-analysis to find HLAs that can be further examined for prognostic reasons.**

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Results: **27 studies were included. Odds of associated HLAs in Graves' disease patients versus controls were increased for HLA-DQA1*03:01 (OR = 1.30 [1.03, 1.63], I^2 =0%, $p < 0.05$) and decreased for HLA-DRB1*07:01 when a study found to be poor on bias assessment was excluded (removed OR = 0.48 [0.39, 0.59], I^2 =16%), $p < 0.05$). No HLA-DQB1 was found to have increased or decreased odds.**

Discussion: **These findings offer new connections between HLAs and Graves' disease that may be applied to prognosis, treatment, and autoimmune mechanistic understanding for MHC class II in Graves' disease.**

Keywords: Human leukocyte antigen, HLA, Graves, Hyperthyroidism, Autoimmune thyroid disease, HLA-DQA1, HLA-DQB1, HLA-DRB1

1. Introduction

Autoimmune thyroid diseases (AITDs), such as Hashimoto's thyroiditis and Graves' disease (GD), are among the most common autoimmune disorders, affecting 2−5% of the world population.[1] The etiology of AITDs is known to be multifactorial in that susceptibility genes (e.g., cytotoxic T lymphocyte antigen-4 (CTLA-4), thyroglobulin, (human leukocyte antigen (HLA)) often interact with environmental triggers (e.g., dietary iodine, stress, smoking) to cause disease.[22] In Hashimoto's and GD, the development of autoantibodies leads to hypothyroidism and hyperthyroidism, respectively, as well as clinical manifestations such as goiter, menstrual abnormalities in women, and cardiovascular changes,[1] among many others.

The Major Histocompatibility Complex (MHC), or the HLA region in humans, encodes molecules involved in antigen presentation, inflammation, and the complement cascade.[3] This locus is on the short arm of chromosome 6 (6p21.3) and is the largest in the human genome. The MHC system is divided into three regions: class I (HLA-A, -B, −C), class II (HLA-DP, -DQ, -DR), and class III. With the exception of class III, which includes components for complement (e.g., C4) and cytokines (e.g., TNF-α),[4] HLA are cell-surface proteins responsible for antigen presentation to immune cells and are thus essential components of adaptive immunity.[5] They

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are considered a principal contributory factor to autoimmune disease as they exhibit a high degree of polymorphism and are pertinent to a vast number of genes involved in the immune response.[6]

Expression of human leukocyte antigens (HLA) and their contribution to the pathogenesis of Graves' hyperthyroidism is especially of interest, as these are the primary elements responsible for autoimmunity. Similar to other autoimmune diseases such as celiac disease,[7] rheumatoid arthritis, and type 1 diabetes,[8] Graves' disease is considered class II-mediated; those with the condition express class II HLA that present exogenous peptides to $CD4^+$ helper T-cells.[5] HLA molecules are ordinarily responsible for maintaining tolerance to self-thyroid antigens,[9] but they are likely to contribute to AITD development when their expression is aberrant. For example, an amino acid substitution at position 74 of the DR beta 1 chain of HLA-DR3 increases GD predisposition.[2]

As the HLA class II region is highly polymorphic, much research has been focused on identifying which specific sequence variants effect disease development. Early research largely involved HLA-DR3, which was found to occur in about 40−55% of patients with GD.[2] Subsequent studies have analyzed a greater variety of variants. For example, Barlow et al.[9] not only observed that HLA-DQA1*0501 was significantly associated with GD, but also that it conferred a greater relative risk than HLA-DR3. Liao et al.[6] found GD to be associated with many class II genotypes (HLA-DPA1*02:02-*02:02, HLA-DPB1*02:01-*05:01, *02:02-*05:01, *04:01-*05:01, HLA-DQA1*03:02, HLA-DRB1*09:01-*15:01, and *09:01-*09:01). Thus, although the association between HLA class II and Graves' disease has been documented for many years now, the primary class II variant leading to the disease is still not known.

Knowing the HLAs of a patient has great importance in prognosis and treatment. For example, there have been studies linking several MHC class I HLAs with recurrence of Graves symptoms.[10−12] HLAs have been linked to the development of Graves symptoms, acting as a tool for prediction of disease course.[13−16] Treatment too can be effected by HLAs, changing potential effects of medications for Graves' disease.[17−19] HLAs additionally have been used to identify patients before symptoms have developed with Graves patients, helping to stop the course of the disease before issues even begin.[20]

Various HLA gene associations with Graves' disease have been largely studied in several independent projects for these reasons, though there are still gaps to be explored. While there have been studies on one specific HLA, and others on specific populations, there has not been an analysis of worldwide populations covering many HLA loci together.[21,22] Additionally, there are studies on MHC class I but not studies to sufficiently cover MHC class II.[10,23] A comprehensive review of HLA-DQA, -DR, and -DQB is still lacking which synthesizes many ethnicities and loci together. The etiology of Graves' disease has yet to be fully elucidated, despite it being the most common cause of hyperthyroidism and one of the most common autoimmune diseases.[24]

Through identification of specific HLAs associated with Graves' disease through meta-analysis, it may be possible to predict incidence of Graves' disease, better understand autoimmunity mechanisms, and elucidate overall HLA effects rather than those that may be specific to specific populations. Through this analysis, this study hopes to evaluate which HLA genes potentially play a role in Graves' disease to aid in defining and identifying populations at risk and to assist with future therapeutic interventions that may target HLAs.

2. Methodology

A protocol was published online at the onset of this research prior to data collection to specify the methods behind searches, data analysis, and interpretation for this study.[25] Studies published before 1990 were not included. If a study was inaccessible or lacked the information to calculate odds ratios, it was excluded. Additionally, meta-analysis was only conducted if a minimum of three published, peer-reviewed articles were found to have sufficient data.

For this study, the databases PubMed and Google Scholar were utilized. These databases were chosen during the protocol stage of development of this study, and therefore no other databases were additionally added. These databases were last searched on July 11, 2022. Institutional access was used for journals that were otherwise restricted. Authors were not contacted for access to articles if access was unavailable via open or institutional access. Searching was conducted using the following terms: "HLA and Graves' disease", "Graves' disease and HLA-DRB1", "Graves' disease and HLA-DQA1", and "Graves' disease and HLA-DQB1". As a limitation, these searches required both the HLA and Grave's disease to appear in the article.

Studies were selected for meta-analysis based on several factors. First, the study was required to pertain to both Graves' disease and the HLA in question. Second, it needed to contain all relevant

data items, or at minimum enough information to calculate the necessary data items. Third, the methodology regarding the data collection process needed to be present somewhere in the publication for proper bias analysis. Fourth, the study needed to be accessible either through open-access databases or through institutional access. To include a particular HLA for meta-analysis, a minimum of three articles pertaining to that HLA was necessary. Studies were excluded if they lacked the necessary data to conduct forest plot meta-analysis, if they did not compare Graves' disease to controls in some fashion regarding an HLA, or if the study was published before 1990. Articles written in a language other than English were excluded; this was chosen to make sure data was not translated incorrectly by the researchers.

Data were gathered to meet the study's objectives. HLA alleles outside of HLA-DRB1, HLA-DQA1, and HLA-DQB1 were not included. HLA belonging to the pertinent groups were divided further into subgroups to analyze the individual HLA in that specific group (such as DQA1*02:01 and DQA1*05:01 being categorized as subgroups under HLA-DQA1). Additional overall analysis of all HLA-DRB1, all HLA-DQA1, and all HLA-DQB1 subgroups was also performed as a secondary analysis to determine if an overall trend across the HLA groups exists. Data items collected included: the number of cases of Graves' disease with the associated HLA, the total number of cases with Graves' disease, the number of healthy controls with the HLA, and the total number of healthy controls. Odds ratios and confidence intervals were calculated from this data as part of the analysis.

Two researchers participated in the data collection process. These researchers involved in data collection put together their findings on a shared online document, placing studies they believed met criteria separately. Both researchers participated in checking the articles to make sure both separately agreed the article was viable. If the researchers disagreed on any article for its inclusion, it would be sent to the PI of the project for a final determination.

Risk of bias was assessed through the NIH Quality Assessment Tool of Case-Control Studies.[26] One researcher was primarily involved in the bias assessment, in which a second researcher would also look over the articles and either agree or disagree with the decisions. If the second researcher disagreed with the assessment made by the first researcher, it would be brought up to the first researcher for a second look. If disagreement continued between the researchers after this re-examination, the article would be sent to the PI of the project for a final determination.

The effect measures used to synthesize our results were the odds ratios and confidence intervals acquired from the data. Revman 5.4.1 software was used for statistical analysis.[27] Visual results were displayed via a forest plot. The inputs for this forest plot were case number with each HLA, case total, control number with each HLA, and control total. As previously stated, studies in the forest plot were included based on their pertinence to both GD and an HLA, if they contained the necessary data items or information to calculate them manually, if the data collection methods were adequately explained, and if the study could be accessed. At least three articles containing a particular HLA were necessary before it could be added to the forest plot. If a study lacked the data needed for forest plot meta-analysis, failed to compare Graves' disease to controls with an HLA, or was published prior to the designated minimum year requirement it was excluded. If bias assessment found an included study to be poor, analysis was repeated including versus excluding the study to determine if it influenced results.

To measure for heterogeneity, data was assessed with I^2, Cochrane's Q, degrees of freedom, and the associated p-value found. In the case of multiple instances of the same HLA type, a subgroup analysis was performed to assess the overall HLA in its totality, as explained previously. LFK index and Doi plotting for bias in meta-analysis used values below -2 and above $+2$ as indicators of major asymmetry.[28,29] Sensitivity analysis was performed using MetaXL.[29] GRADE criteria were additionally used at the end of the analysis to ensure confidence in results.[30]

3. Results

The process of identifying and including studies for meta-analysis is shown in Fig. 1. A total of 4996 records were identified by searching two databases: Google Scholar & PubMed. Before screening by abstract, 866 records were removed due to not being published in English. 2828 records in total were excluded by abstract. Two hundred and eighteen (218) of these records were duplicate studies, while the remaining 2610 were non-specific to Graves' disease or thyroid disorders in general. A total of 1302 reports were sought for retrieval. Nine hundred and eight (908) of these reports were excluded due to lacking either the necessary data to calculate effect size or the information to calculate that necessary data in the first place. Three hundred and

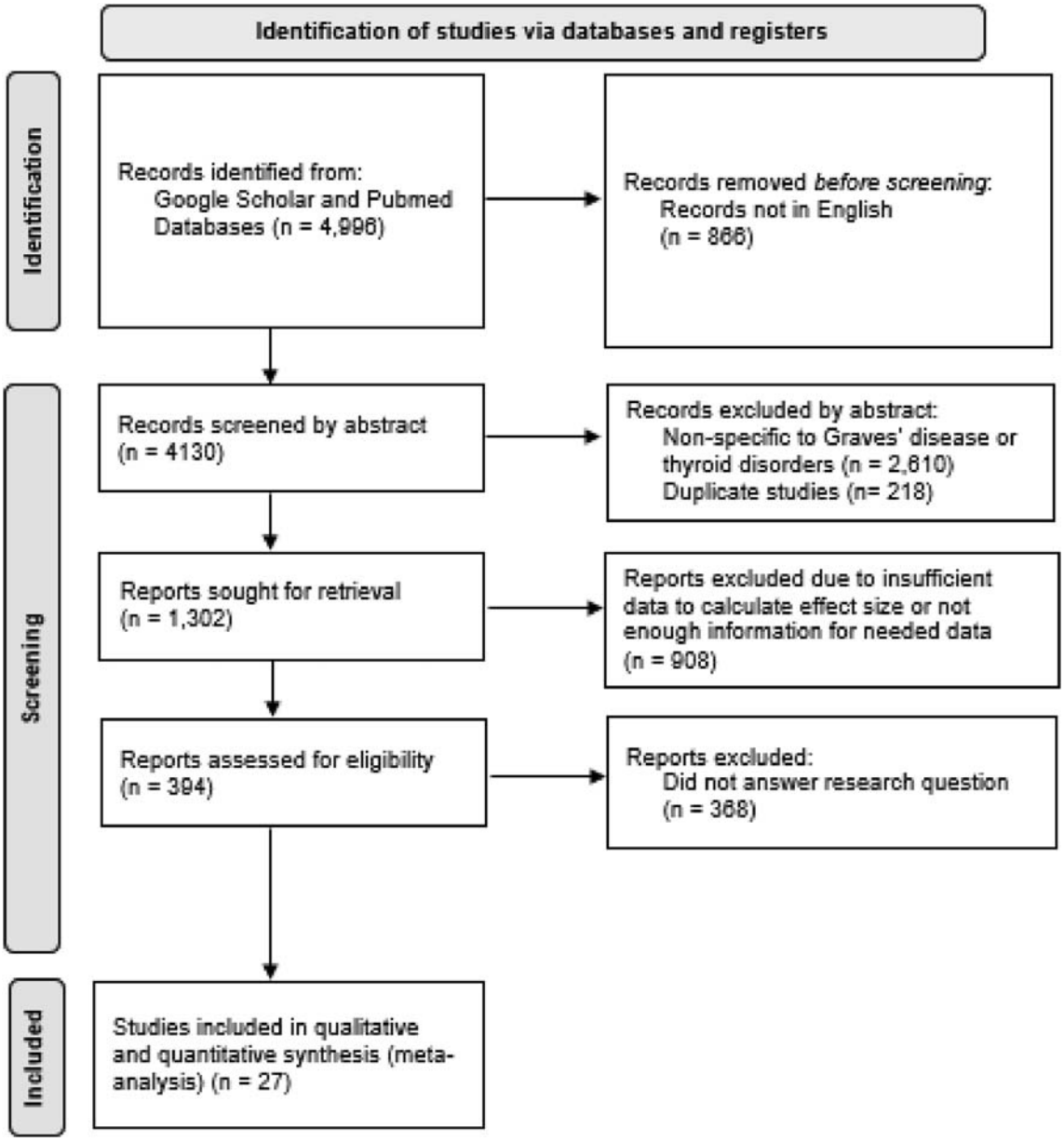

Fig. 1. Meta-analysis flow chart.

ninety-four (394) reports were assessed for eligibility, and 368 of these were excluded because they did not answer the research question posed in this study. Ultimately, a total of 27 studies were included in the meta-analysis.[22,24,31–55]

Some studies seemingly matched set inclusion criteria but were eventually removed as they conflicted with the established protocol requirements set at the inception of the analysis. Simmonds[56] for example lacked information beyond effect size and offered no clear case or control numbers in samples.

Using the NHLBI quality assessment tool, case studies included in the meta-analysis were assessed for internal validity. Out of the 27 studies utilized, 18 were considered "good."[22,24,31,33–36,38–42,46–48,51–53] for these studies, there exists a high probability that risk factor and outcome are truly associated rather than being due to flaws in study design or execution. These studies characteristically have a low risk of bias and contain only minor flaws. For example, the study population may have been thoroughly outlined in terms of age, gender, ethnicity, and location, but lacked a simple description of the time from which the population was chosen. Additionally, many of these studies did not provide a sample size justification to ensure the study was adequately

powered to detect an association. Due to the nature in which these studies are conducted, blinding was not apparent in any.

Eight studies were considered "fair."[32,37,43,44,49,54,55,57] In addition to the flaws mentioned above, many of these studies provided a highly detailed description of cases, but referred to controls as "normal", "healthy", or gave no description other than "control". This is in sharp contrast to many studies which clearly specified controls to be individuals with no history of thyroid disease, no clinical signs of hyperthyroidism, and negative for anti-thyroid antibodies. It is likely that this is due to lack of detailed methodology rather than errors in study design, and therefore is not considered a fatal flaw.

Lastly, one study was considered "poor,"[50] with half of the responses to the quality assessment questionnaire being "no". In addition to flaws mentioned above, this study did not utilize the entire case sample for analysis, failed to report if those analyzed were randomly chosen, and did not use statistical adjustment to adjust for baseline differences in cases and controls. Overall, the case control studies ultimately chosen for meta-analysis were strong studies from which reliable information can be obtained.

Reporting bias is a factor in the analysis of a few of the HLA being studied, as there were articles that could not be accessed due to lack of institutional or open-access options. With requirements to have a minimum of three studies before conducting an analysis, restrictions as to heterogeneity for reporting significant findings, and appropriate confidence intervals for reported odds ratios, relative confidence in results can be derived.

Upon analysis of bias in the meta-analysis with LFK index and Doi plot, asymmetry was major in HLA-DQB1*03:02, HLA-DQB1*03:03, HLA-DQB1*06:02, HLA-DRB1*07:01, HLA-DRB1*09:01, HLA-DRB1*11:01, and HLA-DRB1*13:02. All other analyses reported either minor or low Doi plot asymmetry.

Summary statistics and outcomes of all analyses are summarized in Fig. 2, Fig. 3, and Fig. 4. These outcomes include Graves' disease case numbers with the associated HLA, total number of Graves' disease patients, controls with the associated HLA, total control numbers, odds ratio, confidence interval, and forest plot analysis findings. Table 1 summarizes bias analysis and individual study details. Table 2 summarizes major findings from the meta-analysis.

First, it important to examine results which had low heterogeneity as well as significance. Heterogeneity was indicated as low if $I^2 \leq 25\%$.[58] Odds of associated HLAs in Graves' disease patients versus controls were increased for HLA-DQA1*03:01 (OR = 1.30 [1.03, 1.63], $I^2 = 0\%$). They were decreased for HLA-DRB1*07:01, but the heterogeneity was only low when a study ranked as poor on bias assessment was removed (OR = 0.47 [0.37, 0.59], $I^2 = 28\%$ versus 0.48 [0.39, 0.59], $I^2 = 16\%$). These findings both had low heterogeneity ($I^2 \leq 25\%$) and $p < 0.05$. Findings with moderate heterogeneity ($I^2 = 30\%-50\%$) and significant findings that showed neither higher nor lower HLA odds in Graves' patients versus controls were HLA-DQB1*03:02 (OR = 0.90 [0.66, 1.24]), HLA-DQB1*06:02 (OR = 0.98 [0.67, 1.43]), and HLA-DRB1*10:01 (OR = 0.58 [0.25, 1.34]).

All HLA-DQB1 showed neither increased nor decreased odds of the HLA in Graves' disease. Regarding HLA-DQA1, *02:01 had decreased odds (OR = 0.47 [0.32, 0.69] $I^2 = 57\%$) while *03:01 and *05:01 had increased odds (OR = 1.30 [1.03, 1.63] $I^2 = 0\%$), 2.29 [1.76, 2.97] $I^2 = 66\%$); all three had $p < 0.05$ though only *03:01 had low heterogeneity. HLA-DRB1 showed neither increased nor decreased odds for *09:01, *10:01, and *11:01. There were decreased odds for HLA-DRB1*07:01, *12:02, and *13:02 (OR = 0.46 [0.36, 0.59] $I^2 = 28\%$, 0.43 [0.23, 0.81] $I^2 = 60\%$, 0.42 [0.18, 0.93] $I^2 = 77\%$) with $p < 0.05$; of these, only *07:01 had $I^2 < 25\%$ (this was only <25% when a study ranked as poor in bias assessment was excluded).[50]

When combining all HLA-DQA1, HLA-DQB1, and HLA-DRB1 into one combined analysis for each, no significant finding without high heterogeneity was found. I^2 was above 50% for all other HLA-DQ and HLA-DRB1 analyzed. Out of the three combined analyses, only the HLA-DRB1 examined in this study overall were found to have decreased odds in Graves' disease patients though its high heterogeneity makes this result less useful (OR = 0.65 [0.51, 0.82], $I^2 = 82\%$).

Studies which contributed to the highest heterogeneity were also recorded through sensitivity analysis to determine if there were specific studies influencing heterogeneity results. Of the studies which contributed the most to heterogeneity in individual analyses, four studies were the highest contributor of heterogeneity in multiple of the analyses.[31,41,42,54] One study specifically was indicated as poor in bias analysis and upon its removal, showed low heterogeneity for the analysis for HLA-DRB1*07:01.[50]

4. Discussion

The findings of this study demonstrate that odds of associated HLAs in Graves' disease patients

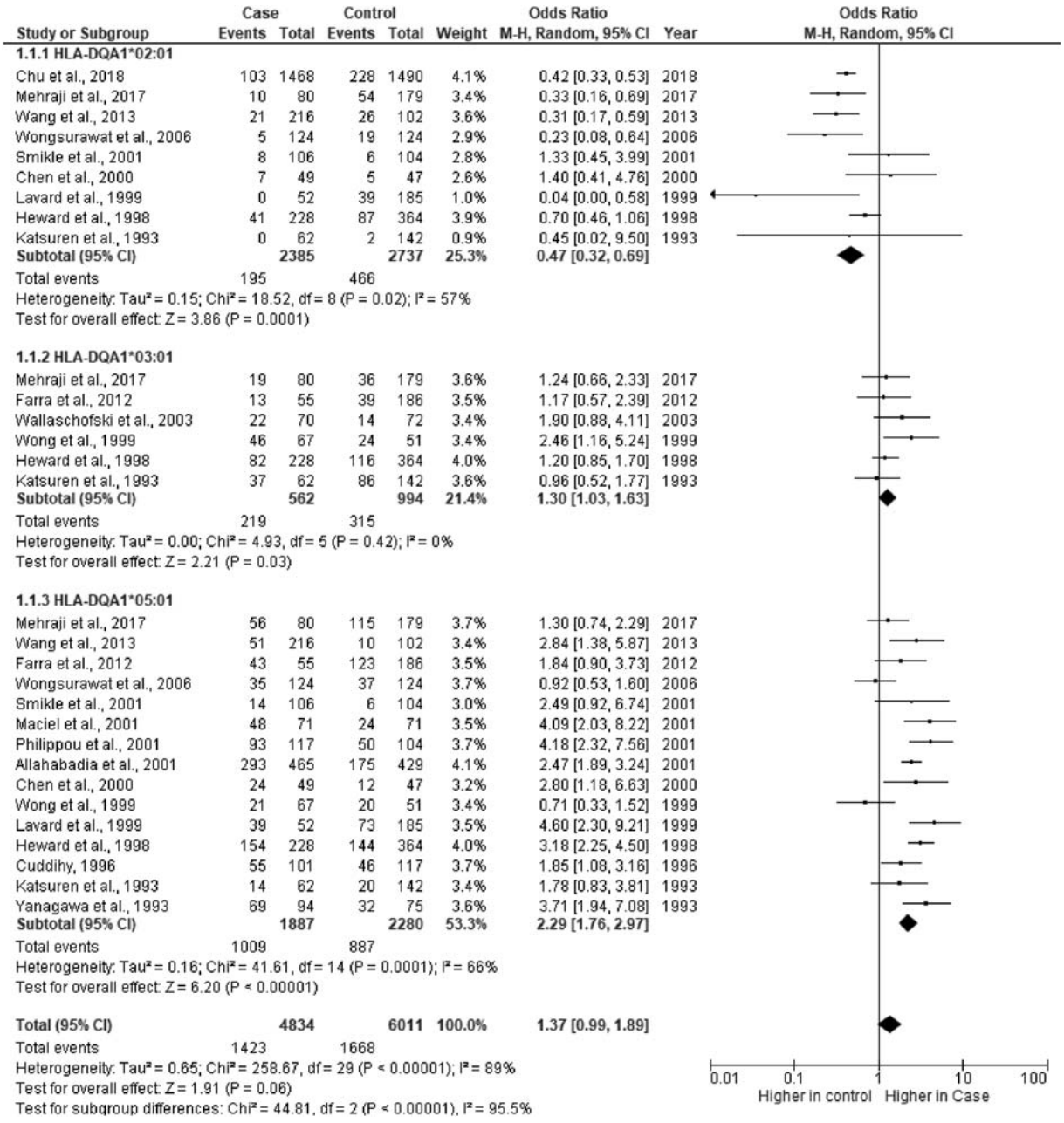

Fig. 2. HLA-DQA1 forest plot.

versus controls were increased for HLA-DQA1*03:01 (OR = 1.30 [1.03, 1.63], I^2 = 0%, $p < 0.05$) and decreased for HLA-DRB1*07:01 when a study found to be poor on bias assessment was excluded (removed OR = 0.48 [0.39, 0.59], I^2 = 16%), $p < 0.05$). These were the only HLAs for which there was a significant result which additionally had low heterogeneity. For these HLAs, there is a consistent result connecting the HLA and GD across different populations based on these findings. Both HLAs were not previously found via meta-analysis to be consistently linked to GD across different populations, making these important considerations in future research.

Several HLAs had moderate heterogeneity, making their results more questionable. These included: HLA-DQA1*05:01 was found in increased frequencies in Graves' disease patients ($p < 0.05$), while HLA-DQA1*02:01, HLA-DRB1*12:02, and HLA-DRB1*13:02 were found in decreased frequencies ($p < 0.05$). No HLA-DQB1 studied through this meta-analysis was found in higher or

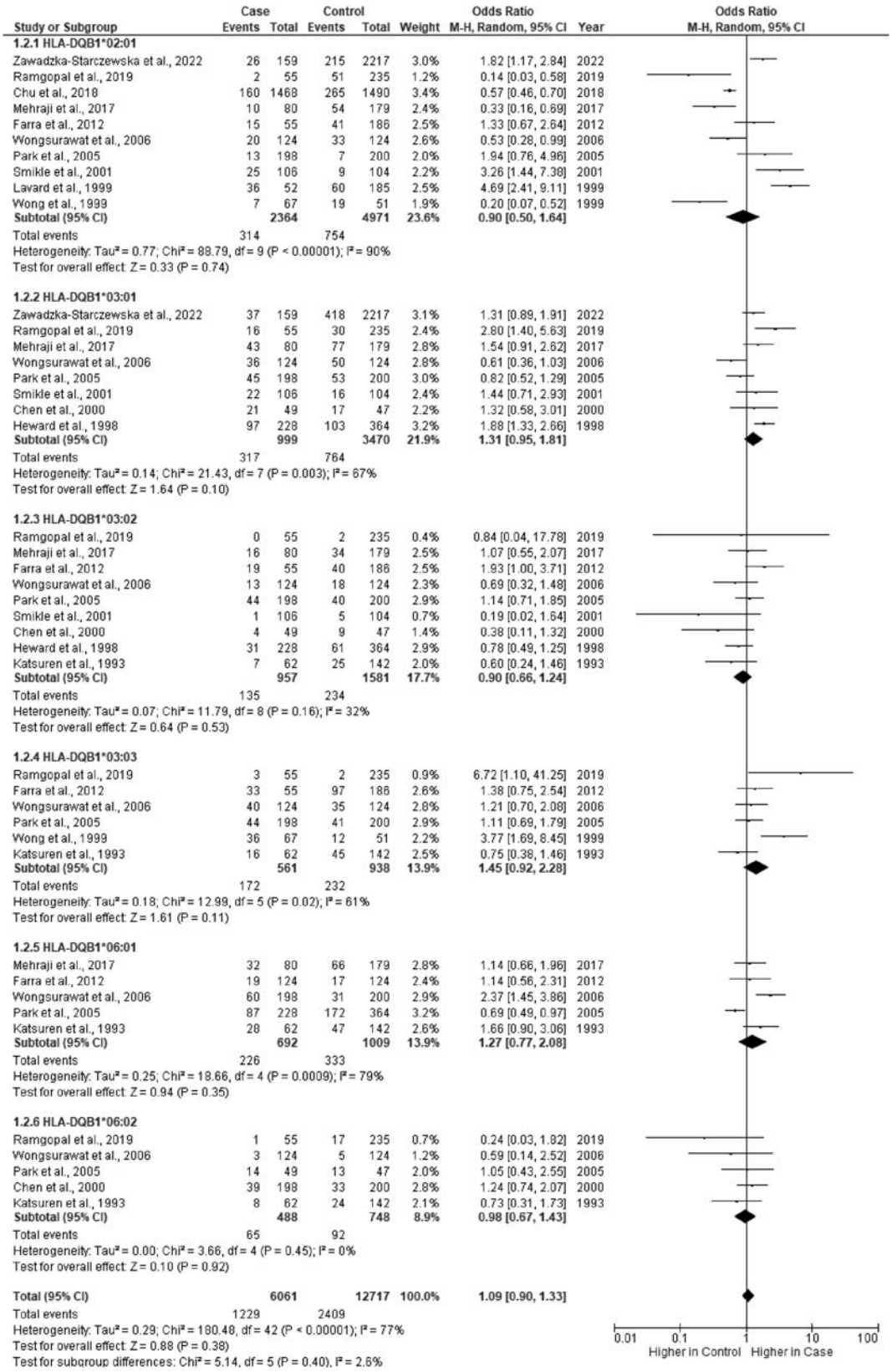

Fig. 3. HLA-DQB1 forest plot.

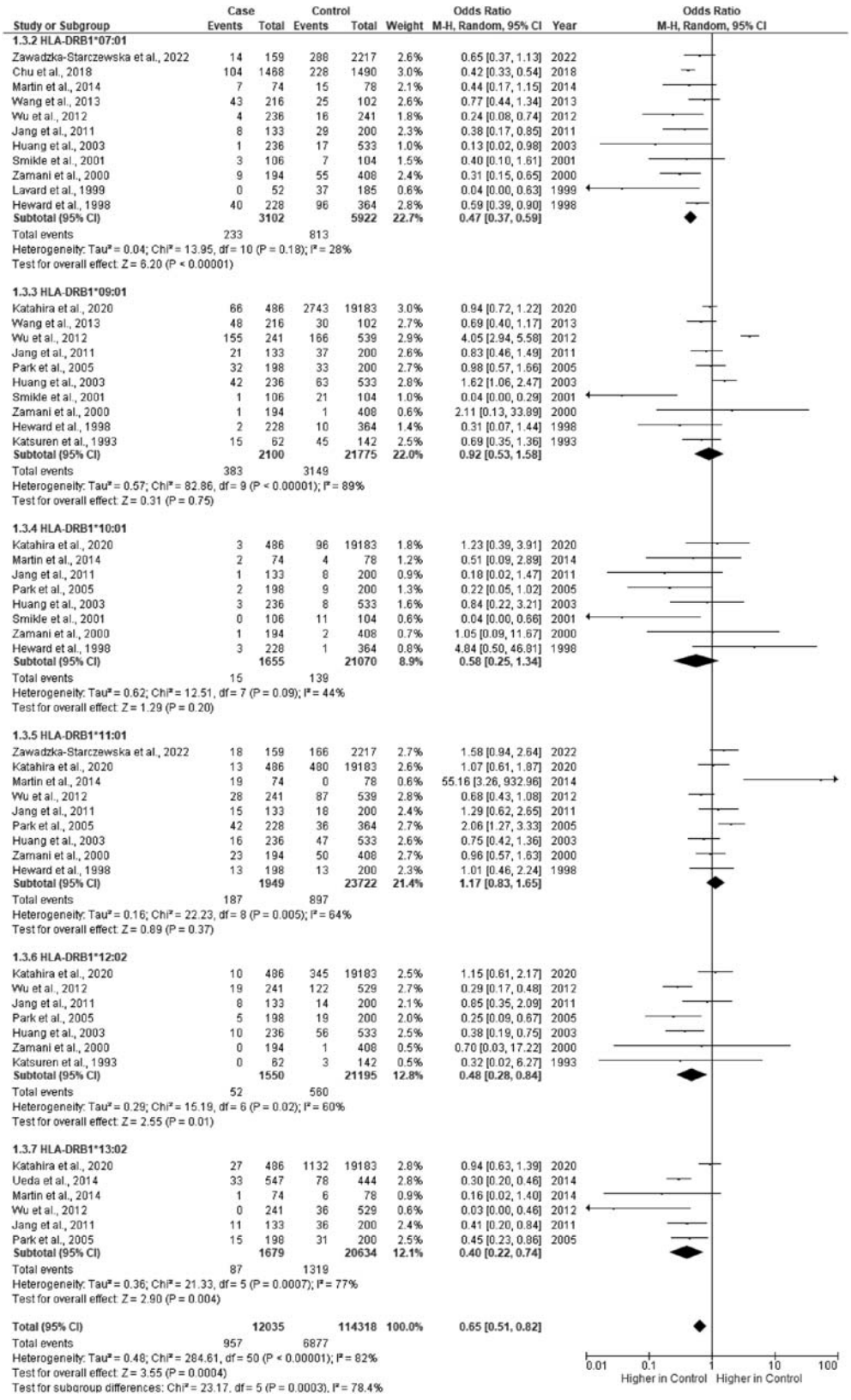

Fig. 4. HLA-DRB1 forest plot.

Table 1. Study data and bias assessment.

Study	Case	Control	Sample	Bias Assessment												
				B	1	2	3	4	5	6	7	8	9	10	11	12
Zawadzka-Starczewska et al., 2022	159	2217	Polish	G	Y	N	N	Y	Y	Y	–	N	Y	Y	0	N
Katahira et al., 2020	286	19183	Japanese	F	Y	Y	N	Y	Y	N	N	N	Y	Y	0	N
Ramgopal et al., 2019	55	235	Indian	G	Y	N	Y	N	Y	Y	–	N	Y	Y	0	N
Chu et al., 2018	1468	1490	Chinese	G	Y	N	N	Y	Y	Y	N	N	Y	Y	0	Y
Mehraji et al., 2017	80	179	Iranian	G	Y	Y	N	Y	Y	Y	–	N	Y	Y	0	N
Martin et al., 2014	74	78	Romanian	G	Y	Y	N	N	Y	Y	–	N	Y	Y	0	N
Ueda et al., 2014	547	444	Japanese	F	Y	N	N	N	Y	N	–	N	Y	Y	0	N
Wang et al., 2013	216	102	Chinese	G	Y	Y	N	Y	Y	Y	–	N	Y	Y	0	Y
Farra et al., 2012	55	186	Lebanese	G	Y	Y	N	N	Y	Y	Y	N	Y	Y	0	N
Wu et al., 2012	241	529	Taiwanese	G	Y	N	Y	Y	Y	Y	–	N	Y	Y	0	N
Jang et al., 2011	133	200	Korean	G	Y	Y	Y	Y	Y	Y	–	N	Y	Y	0	N
Wongsurawat et al., 2006	124	124	Thai	G	Y	N	N	Y	Y	Y	–	N	Y	Y	0	N
Park et al., 2005	198	200	Korean	G	Y	N	N	Y	Y	Y	–	N	Y	Y	0	Y
Huang et al., 2003	236	533	Taiwanese	F	Y	N	N	N	Y	N	–	N	Y	Y	0	N
Wallaschofski et al., 2003	70	72	German	F	Y	N	N	N	Y	N	–	N	Y	Y	0	N
Smikle et al., 2002	106	104	Jamaican	F	Y	N	N	Y	Y	N	–	N	Y	Y	0	N
Allahabadia et al., 2001	465	429	British & Irish	G	Y	N	Y	Y	Y	N	N	N	Y	Y	0	Y
Maciel et al., 2001	71	71	Brazilian	G	Y	N	N	Y	Y	Y	Y	N	Y	Y	0	N
Philippou et al., 2001	117	104	Greek	G	Y	N	N	Y	Y	Y	–	N	Y	Y	0	N
Zamani et al., 2000	194	408	Belgian	F	Y	N	N	Y	Y	N	N	N	Y	Y	0	Y
Chen et al., 2000	49	47	African American	G	Y	N	N	Y	Y	Y	–	N	Y	Y	0	N
Lavard et al., 1999	52	185	Danish	P	Y	N	N	N	Y	N	N	N	Y	Y	0	N
Wong et al., 1999	67	51	Chinese	G	Y	N	N	Y	Y	Y	–	N	Y	Y	0	Y
Heward et al., 1998	228	364	British & Irish	G	Y	N	N	Y	Y	Y	–	N	Y	Y	0	N
Cuddihy & Bahn, 1996	101	117	Caucasian (North American)	G	Y	N	N	Y	Y	Y	–	N	Y	Y	0	Y
Katsuren et al., 1993	62	142	Japanese	F	Y	N	N	Y	Y	N	–	N	Y	Y	0	N
Yanagawa et al., 1993	94	75	Caucasian	F	Y	N	N	N	Y	Y	–	N	Y	Y	0	N

G = good, F = fair, P = poor, Y = yes, N = no, - = not applicable, 0 = not reported, B= Bias.

Table 2. Analysis results.

HLA	Case		Control		OR [95% CI]	Odds	I^2	LFK
	Event	Total	Event	Total				
DQA1								
02:01†	195	2385	466	2737	0.47 [0.32, 0.69]	↓	57%	−1.98
03:01*‡	219	562	315	994	1.30 [1.03, 1.63]	↑	0%	1.9
05:01†	1009	1887	887	2280	2.29 [1.76, 2.97]	↑	66%	−1.34
Total	1423	4834	1668	6011	1.37 [0.99, 1.89]	↔	89%	
DQB1								
02:01	314	2364	754	4971	0.90 [0.50, 1.64]	↔	90%	0.93
03:01	317	999	754	3470	1.31 [0.95, 1.81]	↔	67%	0.16
03:02*	135	957	234	1581	0.90 [0.66, 1.24]	↔	32%	−2.96
03:03	172	561	232	938	1.45 [0.92, 2.28]	↔	61%	2.86
06:01	226	692	333	1009	1.27 [0.77, 2.08]	↔	79%	1.12
06:02*	65	488	92	748	0.98 [0.67, 1.43]	↔	0%	−3.97
Total	1229	6061	2409	12717	1.09 [0.90, 1.33]	↔	77%	
DRB1								
07:01*†	233	3102	813	5922	0.47 [0.37, 0.59]	↓	28%	−3.03
09:01	383	2100	3149	21775	0.92 [0.53, 1.58]	↔	89%	−2.31
10:01**	15	1655	139	21070	0.58 [0.25, 1.34]	↔	44%	−1.65
11:01	187	1949	897	23722	1.17 [0.83, 1.65]	↔	64%	2.17
12:02‡	52	1550	560	21195	0.48 [0.28, 0.84]	↓	60%	0.94
13:02‡	87	1679	1319	20634	0.40 [0.22, 0.74]	↓	77%	−3.62
Total	957	12035	6877	114318	0.65 [0.51, 0.82]	↓	82%	

*$I^2 < 25$, **$I^2 < 50$.
†$p < 0.001$, ‡$p < 0.05$.

lower frequencies. The fact that so many analyses showed moderate or high heterogeneity is indicative that certain populations in this analysis may differ in HLA expression, autoimmunity, or other processes. Due to their moderate to high heterogeneity, finding these HLAs as linked with GD cannot be determined.

This information solidifies both prior and current evidence regarding the association of HLA variants with altered risk of Graves' disease. Through meta-analysis, past studies were consolidated, and the validity of their results was confirmed. HLA-DRB1*1602 was previously shown to be connected to GD risk through previous meta-analysis, though the meta-analysis conducted in this study did not find other DRB1 to be significant without high heterogeneity.[22] HLA-B46, also not examined in this study, has substantial evidence through meta-analysis to be linked to GD.[21] These prior meta-analyses used only one sample group in their analyses, Asian, while this study used diverse worldwide groups to find if there were HLAs ubiquitously associated with GD. The meta-analysis findings of DRB1*07:01 and DQA1*0301 both having heterogeneity at or below I^2 of 30% as well as an increased or decreased link to GD are new insights to further explore that were not in these prior analyses.

Currently, other independent research appears to focus on identifying new HLAs that have not previously been connected to altered GD risk. For example, Takahashi et al.[59] found a significant association between HLA-DPB1*0202 and decreased GD risk in a Japanese population. In another study by Okada et al.,[60] multiple HLA-DPB1, -A, -B, -DRB1, and -DPB1 variants were connected to increased risk of GD in another Japanese population. Naturally, this meta-analysis focused on HLAs that have been analyzed in multiple studies. Thus, due to lacking at least three studies concerning them, several previously undiscovered HLAs linked to Graves' disease that were included in recent studies were excluded from this meta-analysis. Nonetheless, these current projects are instrumental in contributing more HLA alleles to potentially be included in future reviews. Further research could examine information on which HLA alleles contributes most significantly to Graves' disease, analyze how exactly these HLA variants impact its pathogenesis, and influence its treatment and prevention. Perhaps someday, these HLA and others could be screened to determine patients' genetic susceptibility to Graves' disease and influence their healthcare accordingly.

Limitations of this study largely arose due to lack of access to potentially useable articles and external factors that may influence findings (such as specific genes in a certain population influencing the HLA). Additionally, some of the HLAs reviewed had fewer studies to compare for meta-analysis; this low number of comparable studies may have led to less interpretable findings and higher heterogeneity. Heterogeneity was problematic in some of the HLAs studied, making their results problematic.

5. Conclusion

With the identification of these HLAs having effect across different ethnic groups, the potential to better understand autoimmunity of both Graves' disease and other autoimmune conditions may be possible.[61,62] There have been studies that antithyroid medications have specific HLA related effects, especially with HLA-DR, that are just beginning to be known; with this new finding of HLAs and Graves' disease, perhaps more focus can be placed on specific HLAs in these processes.[63–66] HLAs additionally have been connected with Graves' disease prognosis regarding recurrence of symptoms in research, with this study finding a new area for future studies to explore.[13,16,67,68] These studies have largely been broad and have not yet explored more specific loci. Through the findings of this study supporting HLA-DQA1*03:01 and HLA-DRB1*07:01 being involved in odds of Graves' disease, specific loci are identified which can be further explored.

6. Other information

The protocol that was followed to perform this study was made available online prior to conducting the research and can be accessed online.[25] No amendments were made to the original protocol except for an additional measure for quantitatively evaluating bias using LFK index. Authors report no conflict of interest. No funding source was used in this project.

The first author was responsible for creating the topic idea, assembling the research team, assisting in the design of the protocol, performing all searches for studies used in the meta-analysis, data collection, statistical analysis, LFK index calculation, results writing, interpretation of data, design of figures and tables (except the flow diagram), some discussion writing, and leading the research team. The second author assisted in protocol writing, methodology writing, creation of the flow diagram to explain searches and number of studies found, discussion writing, and manuscript editing. The third author did the relevant background research for the introduction, wrote the introduction,

conducted study bias analysis (except the LFK index), and assisted in editing. The fourth author acted as the liaison between the researchers and the institution in which this study was conducted, supported the research, and assisted in management of the project.

Conflict of interest

Authors declare no conflict of interest.

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