SKIN

IN-DEPTH REVIEW

HLA-DQB1 and its Implication in Scleroderma Pathogenesis: A Systematic Review

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ABSTRACT

This systematic review explores the association between HLA-DQB1 genes and scleroderma, a chronic autoimmune disease characterized by collagen synthesis dysregulation and tissue fibrosis. A thorough investigation was conducted by utilizing Google Scholar and PubMed to search for relevant studies in the English language. Two independent reviewers were involved in the process of screening for appropriate studies. A limitation of the exclusion of non-English studies potentially introduces language bias. Inclusion criteria focused on articles investigating the association between HLA genes and scleroderma, providing data on patient and control groups. Risk of bias was conducted using the NIH Quality Assessment Tool for Case-Control Studies. The analyses focused on odds ratios (OR) as a measure of the strength of the association of HLA genes with disease susceptibility. Subgroup analyses were performed for Caucasian and Asian samples, along with a combined analysis. In Caucasian samples, DQB1*02:02 was associated with lower odds of scleroderma (OR=0.51, 95% CI [0.41, 0.63]), while DQB1*03:01 was associated with higher odds (OR=1.55, 95% CI [1.22, 1.97]). In Asian samples, DQB1*04:02 and DQB1*06:01 were associated with higher odds of scleroderma (OR=1.51, 95% CI [1.01, 2.24] and OR=1.33, 95% CI [1.06, 1.67], respectively), while DQB1*06:04 was associated with lower odds (OR=0.55, 95% CI [0.37, 0.82]). Combined samples showed decreased odds of scleroderma in DQB1*06:03 (OR=0.68, 95% CI [0.48, 0.95]) and DQB1*06:04 (OR=0.56, 95% CI [0.39, 0.81]). Future research should explore the interaction between HLA genes and environmental factors to enhance early detection and intervention strategies for individuals at risk of developing scleroderma.

INTRODUCTION

Scleroderma is a chronic autoimmune disease characterized by dysregulated collagen synthesis, resulting in fibrosis and subsequent dermatological and tissue sclerosis. It primarily manifests as cutaneous involvement, although it can also extend to affect various internal organs. The pathogenesis of this complex disease involves multiple cell types (endothelial cells, epithelial cells, fibroblasts, and lymphocytic cells) interacting through a variety of mechanisms that are dependent on their microenvironment and key mediators.[2] This autoimmune disease can manifest in various forms: limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc). LcSSc primarily affects

specific regions of the skin, resulting in thickening. It is commonly accompanied by symptoms like Raynaud's phenomenon, esophageal dysfunction, and pulmonary arterial hypertension.[3] DcSSc involves extensive thickening of the skin, including the trunk and proximal extremities. It progresses rapidly and can lead to severe complications in internal organs, such as lung fibrosis, heart complications, and kidney issues.[3]

HLA (Human Leukocyte Antigen) DQB1, which is part of the class II major histocompatibility complex gene, serves as a crucial regulator of the immune system, preventing the recognition of self-antigens and the occurrence of autoimmune reactions.[4] HLA-DQB1 is one example which specifically binds to antigenic peptides and presents them to CD4+ T cells, leading to the activation of immune responses against foreign invaders or the regulation of tolerance towards self-antigens.[4] HLA-DQB1 variants have been implicated in the susceptibility to various autoimmune diseases. HLA-DQB1 alleles are associated with an increased risk and susceptibility of developing autoimmune dermatologic conditions such as systemic lupus erythematosus and pemphigus vulgaris.[5-6] The significance of this HLA variant lies in its crucial role in immune recognition, response, and disease susceptibility, making it a key component in various aspects of dermatology, immunology, medicine, and genetic analysis.[7] Additionally, understanding the genetic factors involved with scleroderma can aid in personalized medicine approaches and targeted therapies.[8]

This study aims to investigate whether the presence of HLA-DQB1 variants is linked to a discernible alteration in the likelihood of developing scleroderma. Through combining multiple studies, a better understanding of the overall effect of HLA-DQB1 and scleroderma pathogenesis can be found.[9]

METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analytes (PRISMA) guidelines seen in **Figure 1**.[10] A protocol was established and published online to guide the research prior to starting the search.[11] This protocol had changed researchers from the original group on the project, and the search was instead focused on HLA-DQB1 instead of other HLA alleles.

A comprehensive search strategy was employed to identify relevant articles published in English. Two independent reviewers searched the Google Scholar and PubMed databases using the following search terms: "Scleroderma AND HLA" and "Scleroderma AND HLA AND DQB1." In addition, titles and abstracts of the identified articles were screened for relevance. Full-text articles that potentially met the inclusion criteria were retrieved and assessed for eligibility. Articles were included if they met the following: focused on the association between HLA genes and scleroderma, provided data on the total number of scleroderma patients, scleroderma patients with the HLA gene, controls, and total number of controls with the HLA gene. Data from the included studies were extracted using a standardized data extraction form including study design characteristics, ethnicity, sample size, and HLA genes studied. Articles not meeting these criteria, as well as review articles, case reports, and studies without original data, were excluded from the review. Articles were excluded if the control and scleroderma patients were not from the same ethnicity or population group.

Given the potential heterogeneity among the included studies, a narrative synthesis of the findings will be performed, summarizing the association between HLA genes and scleroderma in different ethnic groups. The heterogeneity was assessed to determine the consistency of the results across the included studies. I^2 was used to quantify the degree of heterogeneity. Odd ratios were calculated for specific HLA genes, such as HLA-DQB1 to measure in determining the strength of the association and impact of HLA genes on disease susceptibility. The NIH Quality Assessment Tool for Case-Control Studies will be used to evaluate the risk of bias and quality of evidence to make informed judgements about validity of case findings.[12] RevMan software program was used for statistical analysis and data management.[13]

RESULTS

Eight studies were chosen for meta-analysis for HLA-DQB1 with fourteen HLA-DQB1 alleles meeting criteria for analysis. Relevant information collected from these studies and calculated meta-analysis results are compiled in **Table 1** and **Table 2**.[14-21] This gathered data includes a sample description, bias assessment finding, total number of cases, and total number of controls found in each study. Each analysis was conducted with subgroup analysis based on Caucasian versus Asian samples as subgroups, with a total analysis also included combining the groups.

Articles that seemingly met criteria include Reveille et al., 2001 and Loubière, 2005.[22-23] The sample used in Reveille et al., 2001 included participants from a group outside of the population the experimenters were using for analysis.[22] Loubière, 2005 did not list the number of controls with the HLA, leading to insufficient data for meta-analysis.[23]

Regarding HLA-DQB1, six HLAs showed linkage to scleroderma and eight were both insignificant and with high heterogeneity, which are calculated in **Table 2** with forest plot results and associated statistics are present in **Figure 2** and **Figure 3**. Of these seven, two were significant when comparing Caucasian samples: DQB1*02:02 and DQB1*03:01. DQB1*02:02 had decreased odds (OR= 0.51, 95% CI [0.41, 0.63], I^2= 0%) and DQB1*03:01 had increased odds (OR= 1.55, 95% CI [1.22, 1.97], I^2= 19%) in scleroderma patients when conducting meta-analyses. When comparing Asian samples, odds of DQB1*04:02 was increased (OR= 1.51, 95% CI [1.01, 2.24], I^2= 0%) in scleroderma patients and odds of DQB1*06:01 was increased (OR= 1.33, 95% CI [1.06, 1.67], I^2= 0%) in scleroderma patients, and odds of DQB1*06:04 were decreased (OR= 0.55, 95% CI [0.37, 0.82], I^2= 0%) in scleroderma patients. Combining both Caucasian and Asian samples together yielded decreased odds of DQB1*06:03 (OR= 0.68, 95% CI [0.48, 0.95], I^2= 0%) and DQB1*06:04 (OR= 0.56, 95% CI [0.39, 0.81], I^2= 0%) in scleroderma patients. HLA-DQB1*02:01, 03:02, 03:03, 05:01, 04:01, 05:01, 05:02, 05:03, and 06:02 all showed findings which did not meet the p-value threshold of 0.05 or had with heterogeneity $I^2 \geq 25\%$.

DISCUSSION

HLA-DQB1 has been shown to have many alleles linked to scleroderma on analysis specific to certain samples in which some are protective, and some are increasing odds of scleroderma development. In Caucasian samples, the odds of having DQB1*02:02 was 0.51 times lower in scleroderma patients (95% CI [0.41, 0.63]) and the odds of having DQB1*03:01 was 1.55 times higher in scleroderma patients (95% CI [1.22, 1.97]).

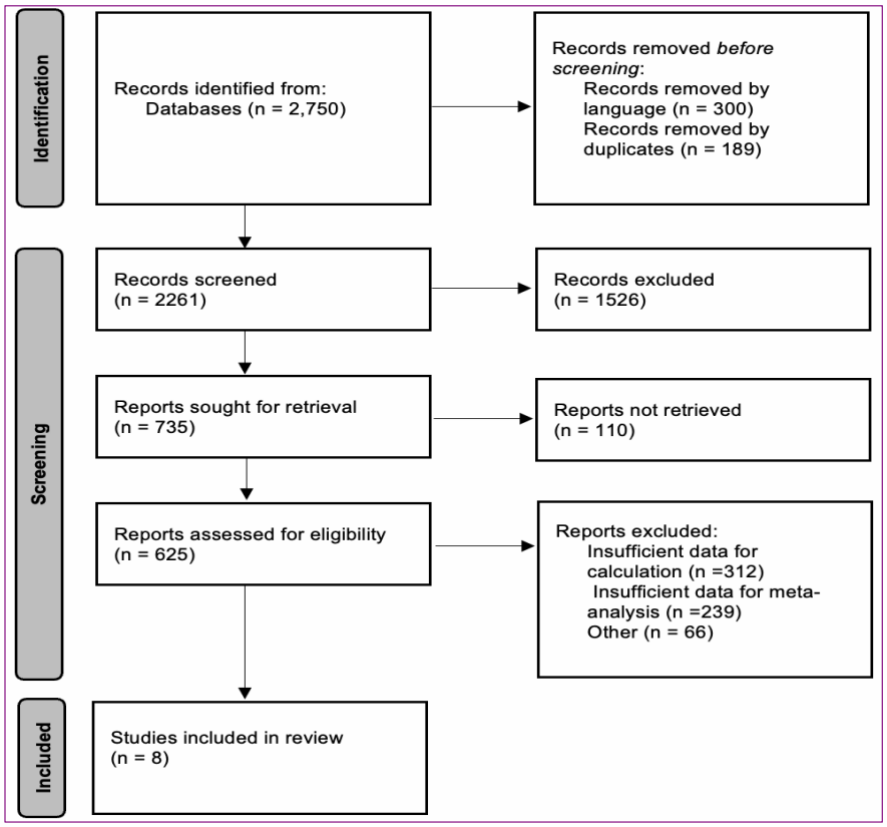
Table 1. Relevant Findings for HLA-DQB1 Meta-Analysis.

Author	Bias	Sample	Case Total	Control Total
Gourh et al., 2020	Fair	Caucasian	723	5437
Stevens et al., 2016	Good	Caucasian	76	581
Arnett et al., 2010	Good	Caucasian	961	539
Vlachoyiannopoulos et al., 2000	Fair	Caucasian	98	130
Morel et al., 1995	Fair	Caucasian	93	175
Furukawa et al., 2016	Good	Asian	463	413
Zhou et al., 2013	Fair	Asian	213	239
Kang et al., 2001	Good	Asian	74	200

Table 2. Meta-Analysis Results.

	Caucasian Samples Only			Asian Samples Only			Combined Samples Only		
HLA	OR [95% CI]	I^2	Trend	OR [95% CI]	I^2	Trend	OR [95% CI]	I^2	Trend
	Significant								
02:02	0.51 [0.41, 0.63]	0	↓	1.12 [0.64, 1.96]	0	↔	0.65 [0.44, 0.96]	60	↓
03:01	1.55 [1.22, 1.97]	19	↑	0.77 [0.51, 1.16]	64	↔	1.16 [0.81, 1.66]	80	↔
04:02	1.21 [0.19, 7.65]	71	↔	1.51 [1.01, 2.24]	0	↑	1.34 [0.85, 2.12]	19	↔
06:01	0.74 [0.16, 3.46]	56	↔	1.33 [1.06, 1.67]	0	↑	1.32 [0.98, 1.77]	21	↔
06:03	0.76 [0.33, 1.73]	NA	↔	0.60 [0.33, 1.09]	10	↔	0.68 [0.48, 0.95]	0	↓
06:04	0.63 [0.24, 1.63]	30	↔	0.55 [0.37, 0.82]	0	↓	0.56 [0.39, 0.81]	0	↓
	Non-Significant								
02:01	0.93 [0.63, 1.38]	0	↔	0.80 [0.42, 1.55]	0	↔	0.89 [0.64, 1.25]	0	↔
03:02	0.92 [0.57, 1.48]	0	↔	1.18 [0.79, 1.77]	43	↔	1.12 [0.85, 1.46]	16	↔
03:03	0.74 [0.28, 1.96]	NA	↔	0.89 [0.68, 1.17]	28	↔	0.88 [0.71, 1.09]	0	↔
04:01	1.69 [0.44, 6.48]	NA	↔	0.75 [0.46, 1.23]	43	↔	0.82 [0.52, 1.28]	43	↔
05:01	1.41 [0.99, 2.00]	44	↔	1.75 [0.81, 3.74]	81	↔	1.53 [1.09, 2.15]	65	↑
05:02	1.56 [0.96, 2.53]	3	↔	1.08 [0.64, 1.80]	0	↔	1.31 [0.93, 1.86]	0	↔
05:03	0.50 [0.14, 1.86]	36	↔	0.80 [0.55, 1.17]	0	↔	0.76 [0.53, 1.09]	0	↔
06:02	0.90 [0.65, 1.25]	0	↔	0.95 [0.50, 1.81]	77	↔	0.94 [0.67, 1.30]	52	↔

Figure 1. PRISMA Flow Chart.

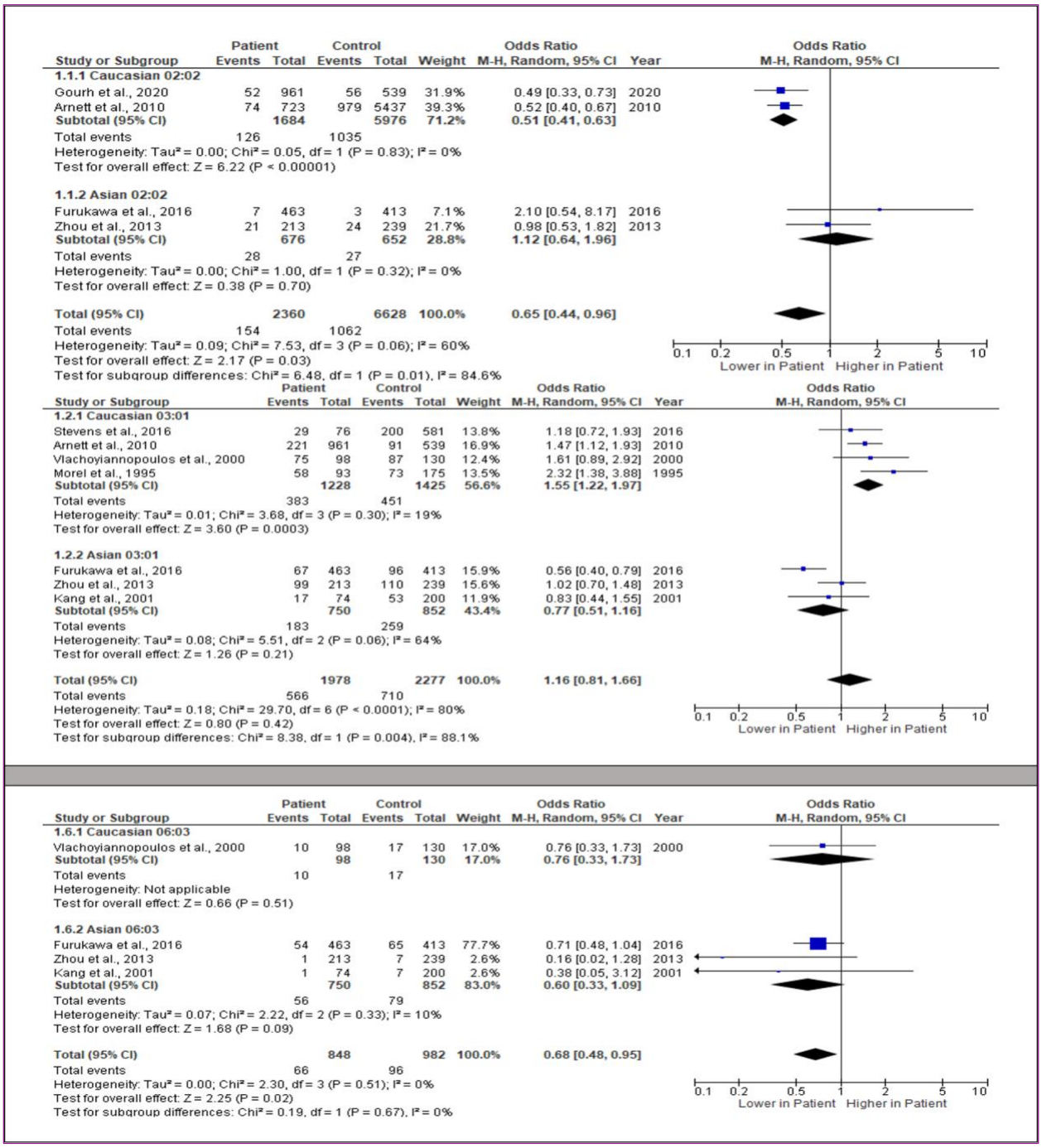


When comparing Asian samples, the odds of having DQB1*04:02 in scleroderma patients was 1.51 higher (95% CI [1.01, 2.24]) and the odds of having DQB1*06:01 are 1.33 times higher (95% CI [1.06, 1.67]). The odds of having DQB1*06:04 was 0.55 times lower in scleroderma patients (95% CI [0.37, 0.82]). Combined samples yielded decreased odds of scleroderma in DQB1*06:03 (OR= 0.68, 95% CI [0.48, 0.95], I^2= 0%) and DQB1*06:04 (OR= 0.56, 95% CI [0.39, 0.81], I^2= 0%).

The systematic review's findings on HLA-DQB1 alleles and their correlations with scleroderma establish a potential genetic link to the diverse manifestations and severity of the disease. The observed odds ratios in Caucasian and Asian populations suggest that genetic susceptibility varies, influencing the specific type of scleroderma that may develop. Notably, the protective role of alleles like DQB1*06:03 and DQB1*06:04 in combined samples underscores their potential across diverse populations. Patients carrying protective alleles (e.g., DQB1*02:02, DQB1*06:04) may experience a reduced risk of severe manifestations in lcSSc as these alleles play a role in modulating inflammation and the immune response.[28] Conversely, those with risk alleles (e.g., DQB103:01, DQB104:02, DQB1*06:01) may be more prone to the rapid progression and severe complications associated with dcSSc because the presence of these alleles may contribute to an overactive immune response causing increased inflammation and tissue damage.[28]

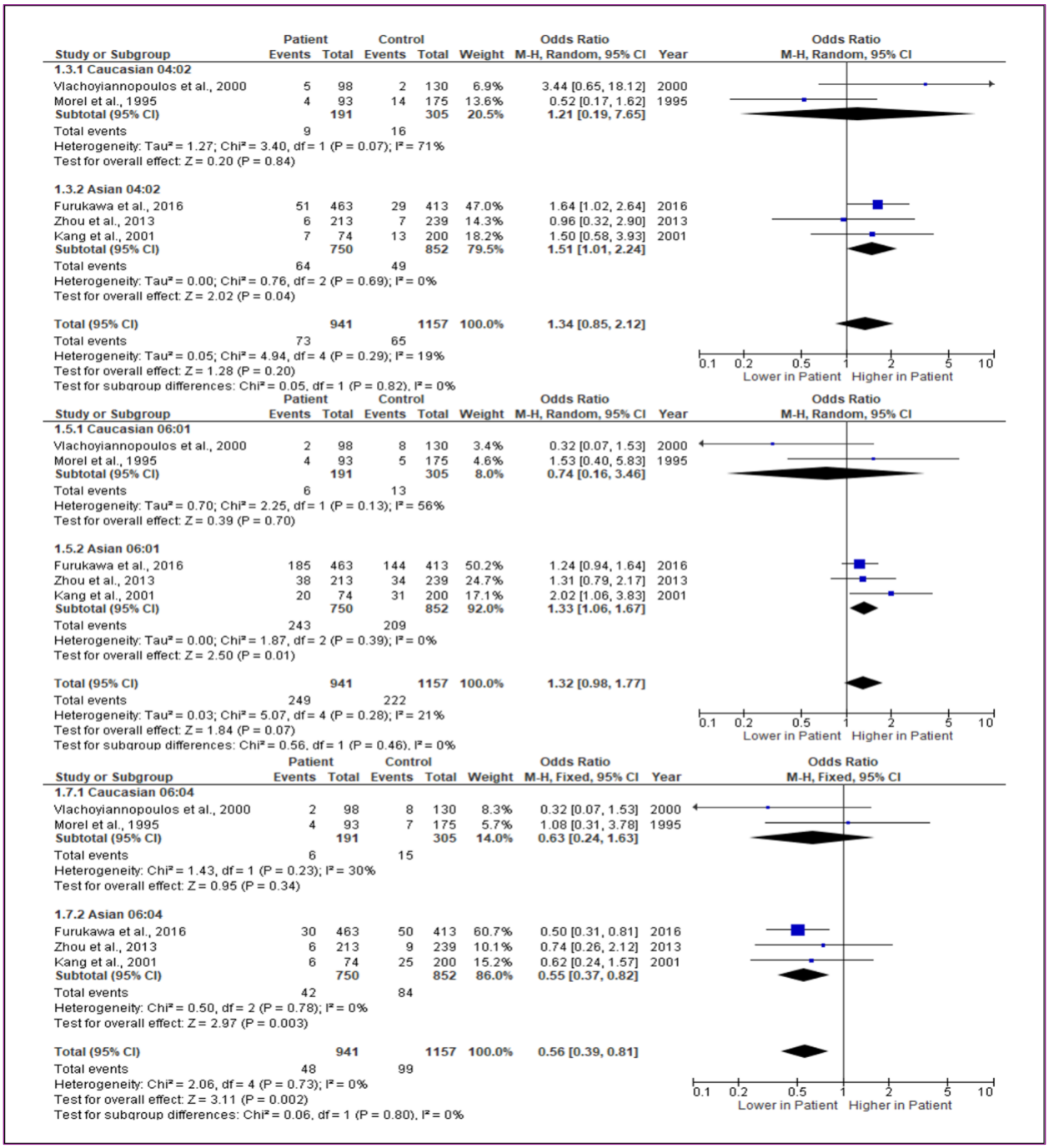
Limitations of this systematic review include the restriction to articles published in English, which may introduce language bias and result in the exclusion of relevant studies conducted in non-English speaking countries. The specific inclusion criteria

Figure 2. Forest Plot with Associated Statistics.



focusing on precise data may have excluded studies with relevant findings but incomplete information. Excluding review articles, case reports, and studies without original data may have missed valuable insights. Future studies could address these limitations by expanding the language search, considering broader study designs, and incorporating information from diverse sources. While this exclusion criterion was implemented to ensure the inclusion of high-quality studies, it may have led to omission of relevant information and potentially valuable insights from review articles and case reports that

Figure 3. Forest Plot with Associated Statistics.



could have contributed to the overall understanding of the association between HLA genes and scleroderma.

Numerous studies and reviews have explored the importance of HLA genes in both autoimmune and non-autoimmune conditions. One comprehensive analysis investigates the potential role of co-occurring class I and class II HLA alleles in cervical cancer development.[24] In contrast, other studies have not identified a direct correlation between HLA DQB1 and autoimmune conditions.[25] Future research should explore

the interaction between HLA genes and environmental factors, such as infections, toxins, and lifestyle factors, to better understand the correlation between genetic susceptibility and environmental triggers in scleroderma.[26] Exploring the potential of prenatal testing for the presence of specific HLA alleles hold promise for detecting diseases earlier in development. Early detection of genetic risk factors could enable timely interventions or lifestyle modifications that may potentially mitigate the development of disease.[27] Understanding the genetic foundations, alongside the immune imbalance in scleroderma's pathogenesis, enhances comprehension of why individuals may exhibit different disease presentations. This ranges from lcSSc with specific skin-related symptoms to the more severe dcSSc involving extensive skin thickening and internal organ complications. This knowledge highlights the necessity for personalized interventions based on an individual's genetic predisposition and the severity of the disease. The potential for personalized and targeted therapeutic strategies emerges as a promising possibility, offering optimism for improved outcomes and enhanced quality of life for those affected by this autoimmune condition. Future research endeavors could delve into distinct genetic profiles associated with scleroderma subtypes, unraveling how specific HLA alleles may influence clinical presentation, disease progression, and treatment response in lcSSc versus dcSSC. This knowledge could pave the way for more targeted and effective interventions to manage and prevent scleroderma in diverse populations.

CONCLUSION

The analysis of HLA-DQB1 alleles in scleroderma patients in different populations have been found to be associated with scleroderma, with some alleles exhibiting protective effects and others increasing the odds of developing the disease. Notable alleles of HLA-DQB1 include HLA-DQB1*02:02, DQB1*03:01, DQB1*04:02, DQB1*06:01, DQB1*06:03, DQB1*06:04. Specific alleles such as HLA-DQB1*02:02 and DQB1*06:04, were found to be potentially protective against scleroderma, while other alleles, such as DQB1*03:01, DQB1*04:02, DQB1*06:01, were associated with increase odds of developing scleroderma. These findings highlight the importance of HLA-DBQ1 in scleroderma susceptibility and provide insights into potential genetic factors influencing the likelihood of disease. Overall, investigating the potential of prenatal testing for specific HLA alleles could aid in early detection and intervention strategies for individuals at risk for developing scleroderma.

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