

# Association of human leukocyte antigen (HLA)-DQ and HLA-DQA1/DQB1 alleles with Vogt–Koyanagi–Harada disease

## A systematic review and meta-analysis

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### Abstract

**Objective:** The aim of this study was to evaluate the association of human leukocyte antigen (HLA)-DQ and HLA-DQA1/DQB1 alleles with Vogt–Koyanagi–Harada (VKH), providing further evidences on the genetic background of this disease.

**Methods:** A comprehensive literature search was conducted on the relationship of HLA-DQ and/or HLA-DQA1/DQB1 alleles with VKH through PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, VIP, and databases for grey literature. The last search was in October 2017. Pooled odds ratio (OR) with 95% confidence interval (95% CI) was calculated from extracted data to access the strength of the association between a genotype and VKH.

**Results:** HLA-DQ4 was confirmed to increase the risk of VKH significantly (OR = 4.63, 95% CI: 1.74–12.31,  $P = .002$ ), while HLA-DQ1 seemed to reduce VKH occurrence with OR = 0.32 (95% CI: 0.22–0.47,  $P < .00001$ ). HLA-DQA1\*0301-(OR = 4.52, 95% CI: 1.42–14.35,  $P = .01$ ) and HLA-DQB1\*0401-(OR = 23.12, 95% CI: 11.54–46.31,  $P < .00001$ ) positive patients probably had a rising tendency to suffer from VKH. Alleles including HLA-DQA1\*0103, 0401, 0501 and HLA-DQB1\*0301, 0402, 0601, 0603 were significant protective genetic factors.

**Conclusion:** We concluded that HLA-DQ4 carriers had a higher risk of VKH and HLA-DQ1 seemed to be protective. People with positive HLA-DQA1\*0301 and HLA-DQB1\*0401 demonstrated to be more susceptible to VKH. HLA-DQA1\*0103, 0401, 0501 and HLA-DQB1\*0301, 0402, 0601, 0603 could be potential protectors.

**Abbreviations:** CI = confidence interval, HLA = human leukocyte antigen, LOE = level of evidence, MHC = major histocompatibility complex, NOS = Newcastle–Ottawa Scale, OR = odds ratio, VKH = Vogt–Koyanagi–Harada.

**Keywords:** human leukocyte antigen, meta-analysis, systematic review, Vogt–Koyanagi–Harada

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BL, TD, and LZ contributed equally to this work.

**Authorship:** JZ and BL designed this study; BL, TD, and LZ performed the research study, analyzed the data, and wrote the article. JZ resolved discrepancies and provided advices for this research. All authors reviewed, edited, and approved the manuscript.

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## 1. Introduction

Vogt–Koyanagi–Harada (VKH), seldom named idiopathic uveoencephalitis,<sup>[1]</sup> is a kind of autoimmune disease mainly causing pathological changes on eyes, skins, inner ears, meninges, and other tissues containing melanin.<sup>[2,3]</sup> Bilateral diffuse granulomatous uveitis is the most important character of VKH, leading to severe impairment on visual acuity and even blindness when associated with retinal edema, retinal detachment, or retinal pigment epithelial changes due to its recurrent and chronic course.<sup>[2,4]</sup> Besides, VKH patients often suffer from alopecia, vitiligo, tinnitus, and dysacusia as complications apart from ocular symptoms.<sup>[5,6]</sup> Accurate diagnosis depends on typical lesions on fundus fluorescein angiography, combined with adjunct neurological, auditory, and integumentary examinations.<sup>[4]</sup> Topical and systematic application of cortical steroids is still the mainstream treatment for VKH, assisted by immunosuppressive and some novel biological agents especially for patients who are resisted to traditional drugs.<sup>[7]</sup>

Pathogenesis of VKH has been elucidated by scientists to some extent involving a series of complex cell-mediated autoimmune reactions, more detailed and precise mechanisms of which still remain unknown and controversial.<sup>[3]</sup> Typical sunset-glow fundus of this disease represents loss of choroidal melanocytes, main targets of activated and infiltrated T-lymphocytes expressing CD25 and CD26.<sup>[8]</sup> Although both environmental and genetic factors contribute to the occurrence of VKH, genetic

variants play a more vital role containing human leukocyte antigen (HLA) and non-HLA factors such as cytotoxic T-lymphocyte antigen 4,<sup>[9]</sup> interleukins,<sup>[10]</sup> and killer cell immunoglobulin-like receptor gene cluster.<sup>[11,12]</sup> Among HLA types, major histocompatibility complex (MHC) class II antigens including HLA-DR, DQ, and DP have a firm association with VKH by triggering T-cells' immunological responses.<sup>[13]</sup> It is worth noting that the above antigens are strongly ethnic-related and most of VKH patients come from oriental countries such as Japan, China, and India,<sup>[4]</sup> with marked yellow or darker skin. Caucasians were considered to be not susceptible to VKH; however, the number of patients is rising in America with increased descendants of American Indians. HLA-DR4 has been suggested to be related to VKH most closely based on a variety of original studies and a completely performed meta-analysis.<sup>[2]</sup> In former studies, HLA-DRB1\*04 was detected frequently with consistent results among Japanese, Chinese, and American Indians.<sup>[2,6,12]</sup> Some loci were found to be highly expressed in the form of genetic linkage such as HLA-DR4-DR53-DQ4.<sup>[14]</sup> Similar to HLA-DR, HLA-DQ is also a  $\alpha\beta$  heterodimer. DQ- $\alpha$  subunit is encoded by the *HLA-DQA1* gene and DQ- $\beta$  subunit is encoded by the *HLA-DQB1* gene. Each HLA-DQA1 or HLA-DQB1 has multiple alleles, which could be detected by serological test and specific PCR techniques to point out some diseases.<sup>[15]</sup> For example, HLA-DQ2 is confirmed to be related to coeliac disease and Type 1 diabetes, especially with the  $\alpha$  chain encoded by DQA1\*05:01 or DQA1\*05:05.<sup>[16,17]</sup>

HLA-DQ and HLA-DQA1/DQB1 alleles were also widely researched on VKH patients, and among them, HLA-DQ4 was discovered to be probably associated with this disease. As genetic linkage disequilibrium exists apparently between HLA-DQ and DR loci in different ethnicities, varied results were reached in present original studies and frequencies of HLA-DQA1/DQB1 alleles might be impacted by HLA-DRB1\*04 to some extent.<sup>[3]</sup> No conclusive articles or reviews have been published yet to illustrate the relationship of HLA-DQ or HLA-DQA1/DQB1 alleles with VKH. In this article, we decided to conduct a systematic review and meta-analysis on HLA-DQ and HLA-DQA1/DQB1 alleles to search for their associations with VKH, further providing some references for the genetic background of this disease.

## 2. Methods and materials

### 2.1. Search strategy and study selection

A comprehensive research of the literature was performed in online databases, including PubMed, Embase, Medline, Cochrane Library, China National Knowledge Infrastructure, and VIP with related references screened intensively. OpenGrey and Web of Science were also searched to identify the unpublished data. Last search was in October 2017 and no language restrictions existed. Search forms were applied as follows for the search strategy: "uveoencephalitis" OR "Vogt Koyanagi Harada" OR "VKH" AND "MHC" OR "major histocompatibility complex" OR "HLA" OR "human leukocyte antigen." Ethical approval or patients' consent was not applicable in our article, as it was a review based on original studies, having been approved by relevant ethics committee, respectively.

Inclusion criteria were listed as follows: Studies concerning the association of HLA-DQ and/or HLA-DQA1/DQB1 alleles with the occurrence of VKH; and detailed number of participants with positive HLA-DQ and/or HLA-DQA1/DQB1 alleles from both case and control groups could be extracted directly from studies or

through contacting the authors. Researches in the form of animal studies, case reports, abstracts, conference proceedings, repeated publications, reviews, or editorials were excluded. Possible overlapped studies with similar authors and institutions were examined carefully and only latest ones were considered to be included.

### 2.2. Study quality assessment and data extraction

The level of evidence (LOE) of each study was evaluated through the GRADE system<sup>[18]</sup> and all included nonrandomized controlled trials were also assessed by Newcastle–Ottawa Scale (NOS).<sup>[19]</sup> Literature with an assessment score reaching 7 or more stars was considered to be in high quality.

Two investigators screened all related studies independently meeting the inclusion criteria strictly, with the inconsistency solved by a third reviewer and open discussion. Information were collected as follows: first author, year of publication, country of study, ethnicity, study design, patients' baseline data, and number or frequency of HLA-DQ and/or HLA-DQA1/DQB1-positive alleles from case and control groups.

### 2.3. Statistics analysis

All data analyses were conducted by RevMan (version 5.3; Cochrane Collaboration, Oxford, UK) and statistics should be considered significantly with a 2-sided *P* value less than .05. Unadjusted odds ratio (OR)s were calculated to be synthesized for further confirmation of the association between HLA-DQ or HLA-DQA1/DQB1 alleles and VKH. Statistical model was chosen depending on the sampling frame. If the sample was all from 1 population, we used the fixed-effect model. On the contrary, the random-effect model should be applied. In a meta-analysis, samples in different studies were from a universe of populations, so random-effect model was selected for all pooled results in our article.<sup>[20]</sup> The publication bias of all included studies was examined by inverted funnel plot visual inspection.

## 3. Results

### 3.1. Studies characteristics

A total of 3076 patients from 14 studies were included in this systematic review and relevant basic information is listed in Table 1. Flow chart of the screening process is in Fig. 1. Published time of these 14 case-control studies distributed from 1990 to 2011. Researches were conducted in countries as follows: 3 in USA,<sup>[21–23]</sup> 3 in China,<sup>[24–26]</sup> 3 in Mexico,<sup>[27–29]</sup> 2 in Japan,<sup>[30,31]</sup> 1 in Italy,<sup>[32]</sup> 1 in Brazil,<sup>[33]</sup> and 1 in Korea.<sup>[34]</sup> Ethnicities of related studies involved Asian (6 studies), Mexico Mestizo (4 studies), Caucasian (1 study), Hispanic (1 study), and mixed (2 studies). Two articles were in Chinese<sup>[25,26]</sup> and other 12 were all in English.

### 3.2. Quality assessment of eligible studies

Table 1 listed the quality of included studies. According to the LOE assessment, all studies were rated Level 3. Nine studies were scored  $\geq 7$  stars and considered to be in high quality<sup>[22,26–31,33]</sup> on the basis of NOS, while 4 were 6 stars<sup>[21,23–25]</sup> and the rest 1 achieved 5 stars.<sup>[32]</sup>

### 3.3. HLA-DQ

Four studies examined HLA-DQ types with the occurrence of VKH. HLA-DQ4 was analyzed in all 4 studies, regarded as a

**Table 1****Baseline characteristics of included studies.**

Included study	Country	Institution	Main ethnicity	Study design	LOE	Group matched characteristics	Sample (n)		Technique of HLA typing	NOS scores
							Case	Control		
Davis et al <sup>[21]</sup>	USA	National Eye Institute	Mixed*	CCS	3	Race	23	368	Serological	*****
Zhang et al <sup>[24]</sup>	China	Peking Union Medical College Hospital	Asian	CCS	3	Race	32	52	Serological	*****
Islam et al <sup>[30]</sup>	Japan	Multicenter	Asian	CCS	3	Race	57	461	Serological and genotyping	*****
Shindo et al <sup>[31]</sup>	Japan	Yokohama City University Hospital.	Asian	CCS	3	Race, age, and gender	62	140	Serological and genotyping	*****
Weisz et al <sup>[22]</sup>	USA	Multicenter	Hispanic	CCS	3	Race	25	217	Serological	*****
Pivetti-Pezzi et al <sup>[32]</sup>	Italy	NA	Caucasian	CCS	3	Race	16	116	Serological	*****
Arellanes-García et al <sup>[27]</sup>	Mexico	Dr. Luis Sanchez Bulnes' Hospital	Mexican Mestizo <sup>†</sup>	CCS	3	Race	48	100	Serological	*****
Goldberg et al <sup>[33]</sup>	Brazil	Multicenter	Mixed <sup>‡</sup>	CCS	3	Race	37	230	Serological and genotyping	*****
Alaéz et al <sup>[28]</sup>	Mexico	Dr. Luis Sanchez Bulnes' Hospital	Mexican Mestizo	CCS	3	Race	46	170	Genotyping	*****
Liu et al <sup>[25]</sup>	China	Peking Union Medical College Hospital	Asian	CCS	3	Race	70	50	Genotyping	*****
Kim et al <sup>[34]</sup>	Korea	Kangnam St Mary's Hospital	Asian	CCS	3	Race	18	128	Genotyping	*****
Levinson et al <sup>[23]</sup>	USA	Multicenter	Mexican Mestizo	CCS	3	Race	29	73	Genotyping	*****
Min et al <sup>[26]</sup>	China	Peking Union Medical College Hospital	Asian	CCS	3	Race	88	88	Genotyping	*****
Aláez et al <sup>[29]</sup>	Mexico	Dr. Luis Sanchez Bulnes' Hospital	Mexican Mestizo	CCS	3	Race	76	256	Genotyping	*****

CCS=case-control study, HLA=human leukocyte antigen, LOE=level of evidence, NOS=Newcastle-Ottawa Scale.

\* Composed of American Blacks, Whites, and Hispanics.

<sup>†</sup> Mestizos are an admixed group composed mainly by Caucasian and Indian genes with some Black component introduced to the country by the African slaves brought by the Spanish conquerors.

<sup>‡</sup> Composed of Whites, Blacks, Asiatics, and mixed Black and Whites.

significant risk factor of VKH (OR=4.63, 95% CI: 1.74–12.31,  $P=.002$ ). HLA-DQ1 was detected in 3 studies with OR=0.32 (95% CI: 0.22–0.47,  $P<.00001$ ), indicating a significant protective role, while HLA-DQ3 in 3 studies pointed out no significant association with VKH (OR=0.51, 95% CI: 0.25–1.03,  $P=.06$ ). Figure 2 provided forest plots of associations of the above 3 HLA-DQ factors with VKH. Heterogeneity existed in HLA-DQ4 and DQ3 statistics ( $I^2=83%$ ,  $P<.001$  and  $I^2=67%$ ,  $P=.05$ , respectively). HLA-DQw3, HLA-DQw7, and HLA-DQ8 was tested in less than 3 studies individually (Table 2), and heterogeneity could not be evaluated on them.

### 3.4. HLA-DQA1 alleles

Ten HLA-DQA1 alleles were analyzed in 5 studies and 8 of them could be extracted for meta-analysis. Four alleles were found to be significantly associated with VKH. HLA-DQA1\*0301 tested in 5 studies seemed to be a risk allele (OR=4.52, 95% CI: 1.42–14.35,  $P=.01$ ), while other 3 might be protective: HLA-DQA1\*0103 in 4 studies (OR=0.22, 95% CI: 0.12–0.40,  $P<.00001$ ), HLA-DQA1\*0401 in 4 studies (OR=0.44, 95% CI: 0.21–0.96,  $P=.04$ ), and HLA-DQA1\*0501 (OR=0.31, 95% CI: 0.19–0.50,  $P<.00001$ ) (Fig. 3). HLA-DQA1\*0101, 0102, 0201, and 0601 were tested not significantly associated with VKH (Supplementary Figure 1, <http://links.lww.com/MD/C125>). Apparent heterogeneity was reached in the cumulative analysis of HLA-DQA1\*0101, 0102, and 0301, while other 5 alleles demonstrated no heterogeneity in their results. Only 1 study detected HLA-DQA1\*0104 and 0302, respectively, and none of

them implicated a significant relationship (Table 3). Heterogeneity analysis was not applied on them.

### 3.5. HLA-DQB1 alleles

A total of 17 HLA-DQB1 alleles were tested in 7 studies and 13 of them could be combined for pooled OR. We discovered 6 alleles to be significantly related to the occurrence of VKH. HLA-DQB1\*0401 was a significant risk allele after combining 5 studies (OR=23.12, 95% CI: 11.54–46.31,  $P<.00001$ ), and others could act as protectors: HLA-DQB1\*0301 (OR=0.50, 95% CI: 0.33–0.48,  $P=.002$ ), HLA-DQB1\*0402 (OR=0.55, 95% CI: 0.34–0.89,  $P=.01$ ), HLA-DQB1\*0601 (OR=0.21, 95% CI: 0.13–0.34,  $P<.00001$ ), and HLA-DQB1\*0603 (OR=0.29, 95% CI: 0.09–0.89,  $P=.03$ ) (Fig. 4). HLA-DQB1\*0201, 0302, 0303, 0501, 0502, 0503, 0602, and 0604 had no significant association with VKH (Supplementary Figures 2 and 3, <http://links.lww.com/MD/C125>). HLA-DQB1\*0304, 0504, 0605, and 0605 was tested in less than 3 studies, respectively, and none of them referred to a significant association (Table 4).

### 3.6. Publication bias

We chose HLA-DQ4, HLA-DQA1\*0301, and HLA-DQB1\*0301 to make the inverted funnel plot, which was tested in most studies in each subgroup (4, 5, and 7 studies, respectively). No publication bias was detected among these studies in this meta-analysis through 3 inverted funnel plots (Figs. 5–7).

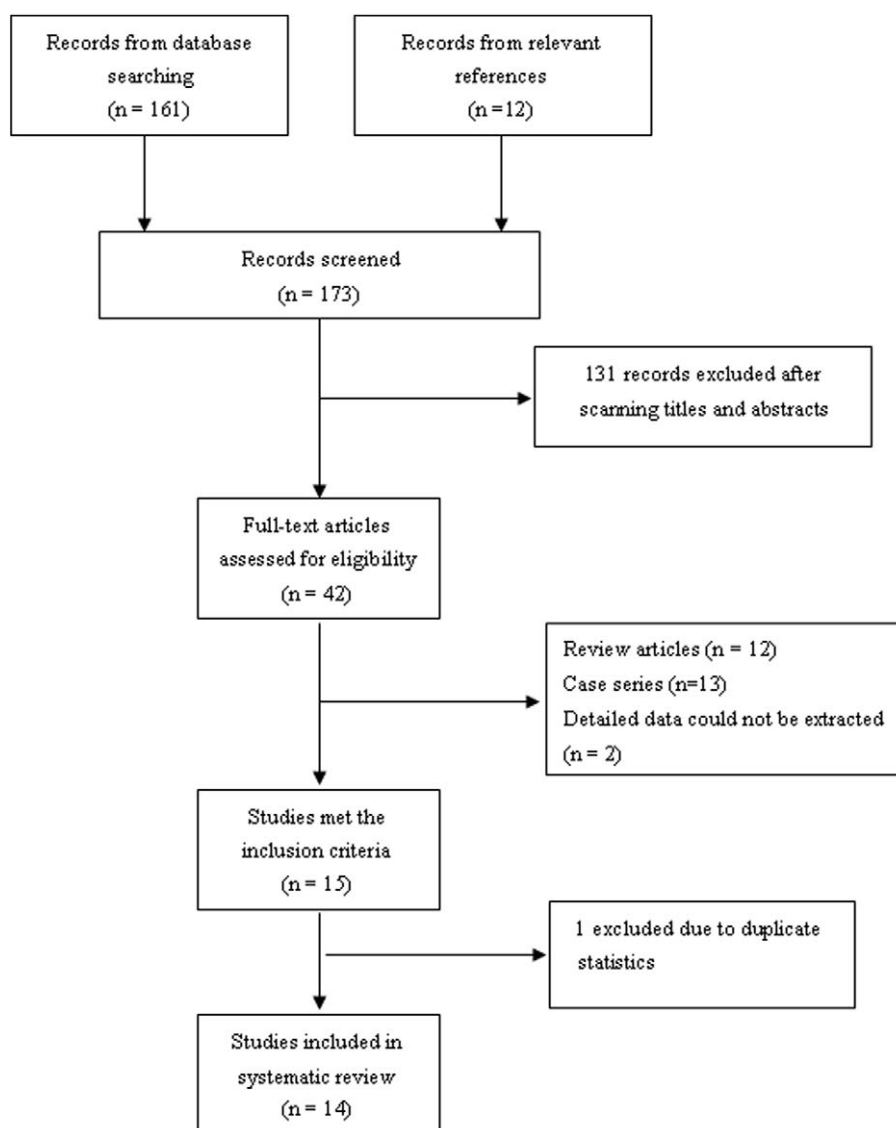


Figure 1. Flow chart of study selection.

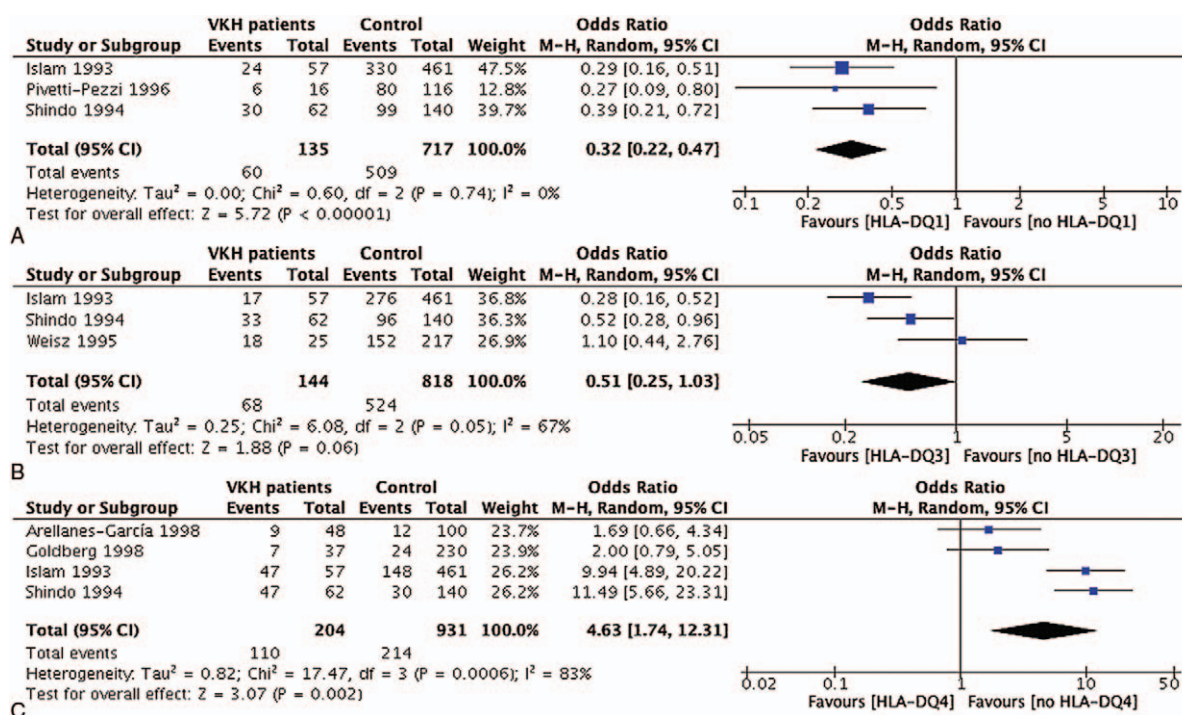
#### 4. Discussion

Comprehensive analyses were performed on all included articles about the association of HLA-DQ and HLA-DQA1/DQB1 alleles with VKH in our study. To the best of our knowledge, it is the first systematic review and meta-analysis concentrating on them. We conclude that patients with positive HLA-DQ4 have a higher risk of VKH, while HLA-DQ1 seems to be a protective factor. Concerning HLA-DQA1/DQB1 alleles, HLA-DQA1\*0301 and HLA-DQB1\*0401 carriers have an increased tendency to suffer from VKH. HLA-DQA1\*0103, 0401, 0501, and HLA-DQB1\*0301, 0402, 0601, 0603 are negatively associated with VKH, indicating these patients have a lower susceptibility of the disease.

VKH is an autoimmune disease in which genetic risk factors contribute more than environments.<sup>[30]</sup> HLA-DQ is type MHC II, consisting of double chains encoded by 2 loci, HLA-DQA1 and HLA-DQB1.<sup>[35]</sup> Expressed mainly on antigen-presenting cells, HLA-DQ not only reacts to recognize foreign antigens but also functions on common self-antigens and presents them to the immune system for tolerance at a very young age.<sup>[36,37]</sup> However,

if the immune tolerance is disturbed, HLA-DQ could become the resource of many autoimmune diseases, such as coeliac disease<sup>[16]</sup> and diabetes mellitus type 1.<sup>[17]</sup>

Obvious varied prevalence rate of VKH existed in former studies based on different ethnicities. Similar to HLA-DR, HLA-DQ loci appears more frequently in oriental populations than in Caucasians. In our meta-analysis, HLA-DQ4 played the most important role for the onset and development of VKH, sharing same results with studies by Islam et al<sup>[30]</sup> and Shindo et al<sup>[31]</sup> on Japanese patients, while Arellanes-García et al<sup>[27]</sup> found no significant association among Mexican Mestizo patients of mixed-Caucasian and Indian descents. HLA-DQ1 carriers had a lower tendency to suffer from VKH in our results, while controversial results existed in several other studies.<sup>[30–32]</sup> Furthermore, significant associations were discovered on HLA-DQw3,<sup>[21]</sup> DQw7,<sup>[24]</sup> and DQ8<sup>[27]</sup> in less than 3 studies, which could not be combined in our meta-analysis. According to the study by Zhang et al,<sup>[24]</sup> HLA-DQw7 coexpressed with HLA-DR4 in Chinese, partially explaining its positive association with VKH, while HLA-DQw1 might inhibit the expression of HLA-DR4.



**Figure 2.** Meta-analysis of the association of HLA-DQ with VKH. (A) Unadjusted OR and 95% CIs of HLA-DQ1 with VKH. (B) Unadjusted OR and 95% CIs of HLA-DQ3 with VKH. (C) Unadjusted OR and 95% CIs of HLA-DQ4 with VKH.

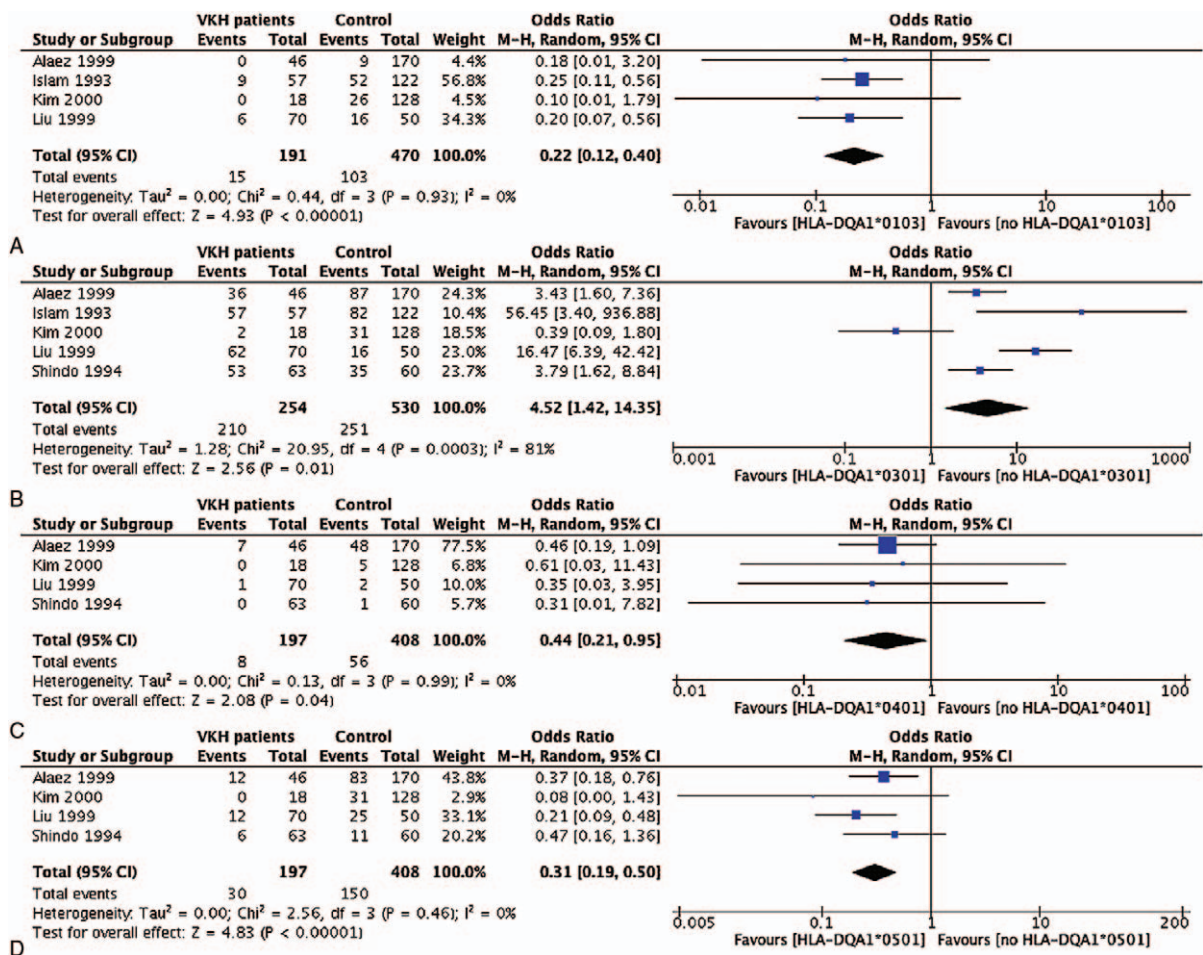
HLA-DQA1/DQB1 alleles from all included studies were extracted and analyzed thoroughly. HLA-DQA1\*0301 and HLA-DQB1\*0401 had a relative strong association with the increased number of VKH patients and Liu et al<sup>[25]</sup> and Kim et al<sup>[34]</sup> drew the same conclusion in their studies, both of whom concentrated on Asians. HLA-DQ had the closest relationship with HLA-DR with prominent genetic linkage. Among these alleles, HLA-DQA1\*0301 was associated with HLA-DR4 tightly, which has been proved to be significantly positive in a number of VKH patients in former studies.<sup>[37]</sup> HLA-DQA1\*0301 was linkage with HLA-DQB1\*0401 in most patients according to the study by Liu et al,<sup>[25]</sup> explaining the increased frequencies of both alleles in this disease. In the study by Islam et al,<sup>[30]</sup> HLA-DQA1\*0301 was considered to precipitate the onset of VKH regardless of age or sex. HLA-DR4 functioned significantly only in both HLA-DQA1\*0301 positive case and control groups, acting as an additive factor based on HLA-

DQA1\*0301.<sup>[30]</sup> Same linkage existed in HLA-DQB1\*0401 and HLA-DRB1\*0405, and the latter has been reported to be significantly more frequent in VKH patients in Japan and Brazil.<sup>[30,31,33]</sup> HLA-DQA1\*0103 seemed to be protective of VKH after our cumulative analysis and similar conclusions were drawn by researches by Islam et al<sup>[30]</sup> and Liu et al.<sup>[25]</sup> HLA-DQB1\*0601, 0603 were linked with HLA-DQA1\*0103 in Asians and their frequencies undoubtedly would reduce together,<sup>[38]</sup> also acting as protective factors. Other alleles that were considered to be significantly associated with VKH varied in different studies, partially owing to techniques applied in genetic typing. PCR-SSCP,<sup>[30]</sup> PCR-RFLP,<sup>[31]</sup> PCR-SSOP,<sup>[34]</sup> and PCR-SSP<sup>[25,26]</sup> were all common methods on testing MHC-II subtypes. Nevertheless, no researches existed yet comparing the effectiveness of detecting HLA-DQA1/HLA-DQB1 alleles with different techniques, requiring more advanced studies with larger sample sizes for confirmation.

**Table 2**  
**Results of meta-analysis of the association of HLA-DQ subtypes with VKH.**

Subtypes	Number of studies	Cases	Controls	Pooled OR (95% CI)	Heterogeneity	
					I <sup>2</sup> (%)	P
DQ4	4	204	931	<b>4.63 (1.74–12.31)</b>	83	<.001
DQ3	3	144	818	0.51 (0.25–1.03)	67	.05
DQ1	3	135	717	<b>0.32 (0.22–0.47)</b>	0	.74
DQw3	1	55	420	2.06 (0.44–9.72)	83	.02
DQw7	1	32	52	<b>2.54 (1.03–6.27)</b>	NA	NA
DQ8	1	48	100	<b>3.24 (1.59–6.63)</b>	NA	NA

The bold numbers mean the P value is <.05.  
CI=confidence interval, NA=not available, OR=odds ratio.



**Figure 3.** Meta-analysis of the association of HLA-DQA1 alleles with VKH (with significant differences). (A) Unadjusted OR and 95% CIs of HLA-DQA1\*0103 with VKH. (B) Unadjusted OR and 95% CIs of HLA-DQA1\*0301 with VKH. (C) Unadjusted OR and 95% CIs of HLA-DQA1\*0401 with VKH. (D) Unadjusted OR and 95% CIs of HLA-DQA1\*0501 with VKH.

Self-melanocytes are the main target of VKH's autoimmune responses; therefore, alleles that are related to melanocyte epitopes could lead to higher morbidity of VKH. In our systematic review, most included studies were carried out in Asian or American countries. Previous investigation of HLA-DQ and HLA-DR distribution among various ethnics demonstrated that some certain alleles chiefly existed in Eastern Asians, Indians,

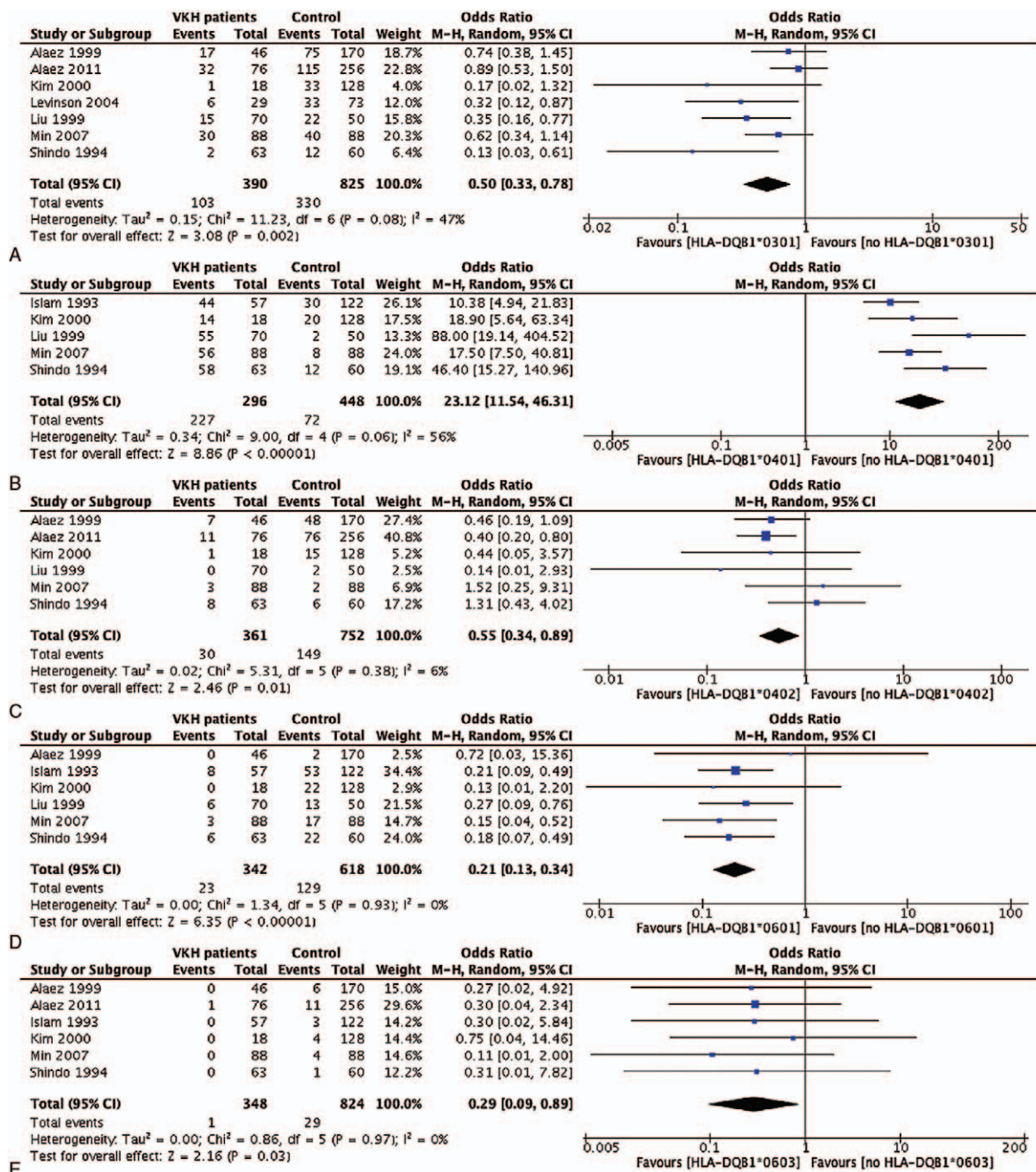
and Native Americans, seldom detected in Caucasians. As above, HLA-DQ4 and HLA-DR4 are frequently involved in the occurrence of VKH in Oriental countries.<sup>[32]</sup> However, disparate results existed in American countries such as America,<sup>[22]</sup> Mexico,<sup>[29]</sup> and Brazil.<sup>[33]</sup> HLA-DQ3, instead of HLA-DQ4, was detected more frequently by Levinson et al<sup>[23]</sup> focusing on Mestizo patients with part of Caucasian background, which

**Table 3**  
Results of meta-analysis of the association of HLA-DQA1 alleles with VKH.

Alleles	Number of studies (n)	Cases (n)	Controls (n)	Pooled OR (95% CI)	Heterogeneity	
					I <sup>2</sup> (%)	P
0101	4	197	408	0.63 (0.21–1.81)	65	.03
0102	4	197	408	0.73 (0.30–1.81)	69	.02
0103	4	191	470	<b>0.22 (0.12–0.40)</b>	0	.93
0104	1	70	50	0.51 (0.11–2.41)	NA	NA
0201	4	197	408	1.16 (0.60–2.24)	8	.35
0301	5	254	530	<b>4.52 (1.42–14.35)</b>	81	<.001
0302	1	18	128	0.19 (0.02–1.50)	NA	NA
0401	4	197	408	<b>0.44 (0.21–0.95)</b>	0	.99
0501	4	197	408	<b>0.31 (0.19–0.50)</b>	0	.46
0601	4	197	408	0.64 (0.25–1.67)	0	.52

The bold numbers mean the P value is < .05.

CI = confidence interval, NA = not available, OR = odds ratio.



**Figure 4.** Meta-analysis of the association of HLA-DQB1 alleles with VKH (with significant differences). (A) Unadjusted OR and 95% CIs of HLA-DQB1\*0301 with VKH. (B) Unadjusted OR and 95% CIs of HLA-DQB1\*0401 with VKH. (C) Unadjusted OR and 95% CIs of HLA-DQB1\*0402. (D) Unadjusted OR and 95% CIs of HLA-DQB1\*0601. (E) Unadjusted OR and 95% CIs of HLA-DQB1\*0603.

could not be confirmed by our combined statistics due to inadequate number of studies. Both America and Brazil are countries with mixed populations and their patients' distribution differed among those studies, leading to heterogeneity of results. It was a pity that we could not perform subgroup analyses based on patients' race due to limited number of included studies on each allele. Further comparative studies concerning HLA-DQ are necessary to achieve more convincing associations with VKH.

Some articles also studied associations of VKH clinical characteristics with varied genotypes. Zhang et al<sup>[24]</sup> found that patients with positive HLA-DR4 had a lower initial visual acuity than negative ones, but the influences on the prognosis were not obvious. Alaez et al<sup>[28]</sup> focused on the severity and response to treatment. DQB1\*0301 patients showed a well response to the immunotherapy, while DRB1\*0101 cases did not. Those with positive DQB1\*0201 seldom had hypertension and headache, demonstrating that some genotypes might control specific

**Table 4**

**Results of meta-analysis of the association of HLA-DQB1 alleles with VKH.**

Alleles	Number of studies (n)	Cases (n)	Controls (n)	Pooled OR (95% CI)	Heterogeneity	
					I <sup>2</sup> (%)	P
0201	4	210	604	0.67 (0.41–1.10)	10	.34
0301	7	390	825	<b>0.50 (0.33–0.78)</b>	47	.08
0302	7	390	825	1.12 (0.41–3.03)	87	<.001
0303	7	390	825	1.76 (0.75–4.13)	57	.03
0304	1	70	50	0.71 (0.04–11.63)	NA	NA
0401	5	296	448	<b>23.12 (11.54–43.61)</b>	56	.06
0402	6	361	752	<b>0.55 (0.34–0.89)</b>	6	.38
0501	7	390	825	0.87 (0.40–1.90)	72	.001
0502	7	390	825	0.54 (0.26–1.14)	0	.83
0503	7	390	825	0.52 (0.24–1.12)	0	.96
0504	1	46	170	11.24 (0.45–280.09)	NA	NA
0601	6	342	618	<b>0.21 (0.13–0.34)</b>	0	.93
0602	6	291	702	0.81 (0.52–1.28)	0	.51
0603	6	348	824	<b>0.29 (0.09–0.89)</b>	0	.97
0604	6	355	814	0.45 (0.17–1.23)	22	.27
0605	1	18	128	0.36 (0.02–6.92)	NA	NA
0609	1	46	170	1.22 (0.05–30.32)	NA	NA

The bold numbers mean the P value is < .05.

CI = confidence interval, NA = not available, OR = odds ratio.

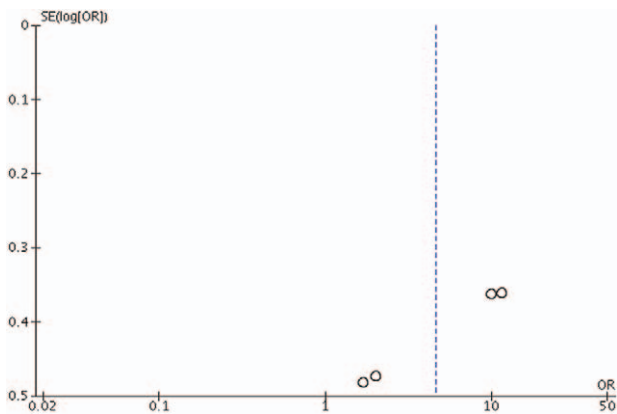


Figure 5. Funnel plot of pooled OR of HLA-DQ4.

symptoms.<sup>[28]</sup> Kim et al<sup>[34]</sup> thoroughly collected the follow-up statistics of DRB1\*0405-DQA1\*0301-DQB1\*0401 haplotypes. Their results turned out that compared with negative cases, these patients had a relative poorer visual acuity, more ocular complications (post synechia, cataract, glaucoma, and choroidal neovascularization), and a higher recurrence rate. However, Liu et al<sup>[25]</sup> concluded that frequencies of HLA-DQ alleles had little influences on the recurrence, complications, and prognosis of visual acuity, partly because most included cases were in the relative late phase of the disease. Above all, the sample size in each study was not large enough and more typical VKH cases are needed to be followed up to a longer period for more rigorous conclusions.

Our systematic review and meta-analysis has some limitations. First, published time of included studies was from 1990 to 2011, during which the diagnostic criteria and technique improved rapidly, causing biases in our combined results. Some data from older studies were insufficient and it was hard to contact with authors. Second, number of studies was not enough to get a valid

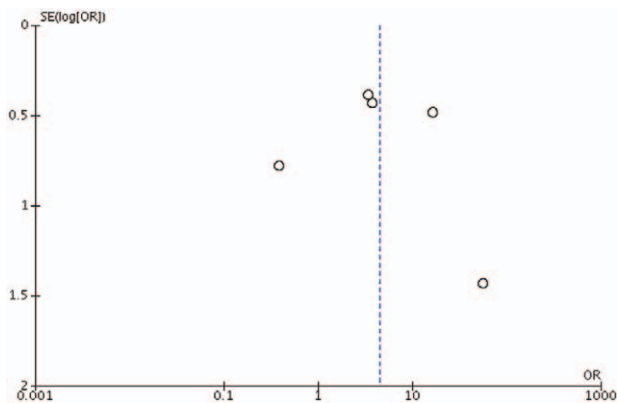


Figure 6. Funnel plot of pooled OR of HLA-DQA1\*0301.

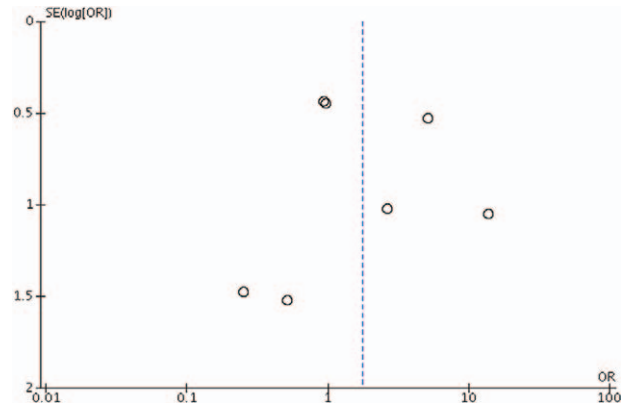


Figure 7. Funnel plot of pooled OR of HLA-DQB1\*0301.



conclusion and some alleles were simply referred in less than 3 studies. Consequently, subgroup analyses based on ethnics and examined techniques could not be conducted, limiting the application of our results on different races. Third, most of included studies were carried out in Asian countries such as Japan, China, Korea, and India. Few analyses were conducted among patients of Caucasian descents, especially the test of HLA-DQA1/DQB1 alleles. Mixed ethnicities in American countries also brought about difficulties in combining statistics. In addition, detailed frequencies of some alleles were given together with other related ones. It was hard for us to extract the data and we had to exclude some information during the process of cumulative analysis.

## 5. Conclusion

In our systematic review and meta-analysis on the association of HLA-DQ and HLA-DQA1/DQB1 alleles, we reach the conclusions that HLA-DQ4 positive patients have a higher risk of VKH, while HLA-DQ1 seems to be protective. In the results of alleles, risk factors are HLA-DQA1\*0301 and HLA-DQB1\*0401, while protective ones may include HLA-DQA1\*0103, 0401, 0501 and HLA-DQB1\*0301, 0402, 0601, 0603. Although some limitations restrict our findings to some extent, we could still supply some evidences on the genetic characteristics of VKH. Further studies with more patients and miscellaneous ethnics are needed to provide more credible information.

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