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Correspondence and requests for materials should be addressed to H.Y.C. (drchenhaoyu@gmail.com)

Association of HLA-DR4/*HLA-DRB1*04* with Vogt-Koyanagi-Harada disease: A Systematic Review and Meta-analysis

Tingkun Shi, Wenjuan Lv, Li Zhang, Jianhuan Chen & Haoyu Chen

Joint Shantou International Eye Center, Shantou University & the Chinese University of Hong Kong.

Human leukocyte antigen (HLA)-DR4/*HLA-DRB1*04* has been reported to be a risk factor for Vogt-Koyanagi-Harada disease (VKH) with various strength of association. Its sub-alleles were also found to be associated with VKH. However the results were inconsistent. In this study, we systematically searched the related literature, pooled the odds ratios (ORs) and 95% confidence interval (CI) of association of HLA-DR4/*HLA-DRB1*04* or its sub-alleles with VKH from individual studies, and explored the potential source of heterogeneity. A total of 1853 VKH patients and 4164 controls from 21 articles were included in this meta-analysis. The pooled OR of association of HLA-DR4/*HLA-DRB1*04* and VKH was 8.42 (95% CI: 5.69–12.45). There were significant heterogeneity ($I^2 = 71\%$). Subgroup analysis indicated that ethnicity was the source of heterogeneity (all $I^2 = 0$, ORs ranged from 2.09–13.69 in subgroups). The sub-alleles, *HLA-DRB1*0404* (OR = 2.57), *0405* (OR = 10.31) and *0410* (OR = 6.52) increased the risk of VKH; *0401* (OR = 0.21) protected VKH; while other sub-alleles were not associated with VKH. Our meta-analysis confirmed the association between VKH and HLA-DR4/DRB1*04, found the strength of association is different in different ethnic groups, and identified *HLA-DRB1*0404, 0405 and 0410* as risk sub-alleles while *0401* as protective sub-allele.

Vogt-Koyanagi-Harada disease (VKH) is a systematic autoimmune disorder that affects tissues containing melanin such as the eyes, inner ears, meninges, and skin[1]. The ocular manifestations are characterized by chronic bilateral, diffuse, granulomatous uveitis, which may lead to blindness. Several risk factors have been identified for VKH, including dark skin pigmentation, females, aged between 20 to 50 years, and genetic factors[2–4].

Human leukocyte antigen (HLA) system is the locus of genes that encode for major histocompatibility complex (MHC), which is a set of cell surface molecules mediating interaction of leukocyte[5]. Therefore, HLA plays an important role in immune system function as well as in the pathogenesis of autoimmune diseases, including VKH[6]. Almost 40 years ago, the association of HLA-BW22J and VKH was reported[7]. However, it could not be replicated in subsequent studies[8]. Later on, more articles have been published on the association of different types of HLA and VKH. Among them, the HLA-DR4 serotype, its corresponding allele *HLA-DRB1*04* were mostly investigated[9,10]. Their results, however, are inconsistent, especially on the strengths of association with reported risk increases variably. The sample size of most studies is small. Recently, there is a review summarizing the genetic studies of VKH[11]. However, it is a narrative review and did not quantitatively synthesize the results from individual studies.

In this study, we performed a systematic review and meta-analysis to investigate the association between VKH withHLA-DR4/*HLA-DRB1*04* and its sub-alleles, combine the small sample size studies and explore the sources of the inconsistency.

Methods

Search strategy. Literature search was performed on MEDLINE, Science citation index, SCOPUS databases using PubMed, Web of Science and SCOPUS search engines up to June 1, 2014. The following medical subject headings and keywords were used for search strategy: "human leukocyte antigen" OR "HLA" OR "major histocompatibility complex" OR "MHC" AND ("VKH" OR "Vogt Koyanagi Harada"). No language or year of publication restrictions was imposed.

Study selection. The retrieved records from literature search were reviewed by two reviewers independently (T.K.S, W.J.L). Any disagreement was solved by discussion and consensus together with a third author (H.Y.C). Included studies met the following pre-specified criteria: 1) Association study of HLA-DR4/*HLA-DRB1*04* or its sub-alleles with VKH; 2) The number or percentage of HLA-DR4 serotype

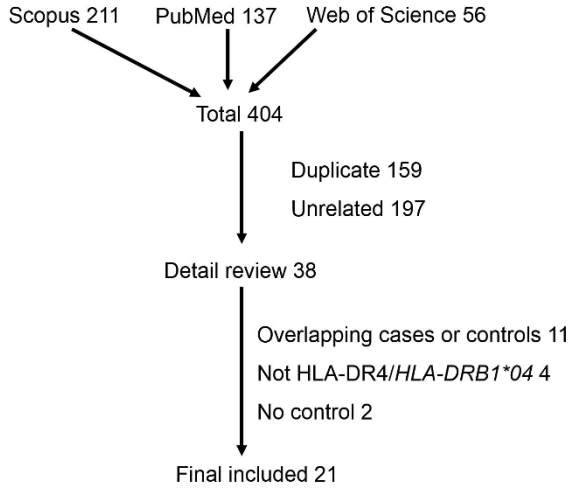

Figure 1 | Flow diagram showing the result of literature screening for meta-analysis.

and/or *HLA-DRB1*04* allele/sub-alleles must be provided in VKH cases and controls; 3) The type of article is an original research study, not a review, case report, or editorial comment. The studies that did not provide sufficient information even after contacting the corresponding author were excluded. Considering some studies may contain overlapping cases and/or controls, we paid close attention to the authors, study subject's geographic location, and numbers of subjects. For duplicated studies, we selected the publication that contained the most number of VKH cases.

Data extraction. Data extraction was carried out by two reviewers independently (T.K.S, W.J.L). Any disagreement was solved by discussion and consensus together with a third author (H.Y.C). The following data from each included study were collected: author, year of publication, study design, ethnicity, the mean age and gender of cases and controls, diagnostic criteria used for VKH, counts or frequencies of HLA-DR4/*HLA-DRB1*04* and its sub-alleles in cases and controls.

Risk of bias assessment. The quality evaluation was also carried out by two reviewers (T.K.S, W.J.L) independently. Further independent review and resolution by a third reviewer (C.H.Y.) was sought if the two reviewers disagreed. The risk of bias assessment considered 6domainsas suggested in the HuGENet handbook[12]: bias in ascertainment of cases, bias in ascertainment of controls, bias in genotyping controls, bias in population stratification, confounding bias, multiple test and selective outcome reports. Each item was classified by "yes/no" to risk of bias or as "unclear" if there was no sufficient information to assess.

Table 1 | The general characteristic information of included studies

Year(Ref.)	First author	Country	Mean age(Y) of VKH	Mean age(Y) of control	%Male of VKH	%Male of control	Typing technique	Diagnostic criteria	Ethnicity	Study design
1990[6]	Davis et al.	U.S.A.	NA	NA	NA	NA	Serological	NA	Hispanic	Case-control, ethnic-matched
1991[32]	Zhao et al.	China	NA	NA	36.2	NA	Serological	A.U.S./Sugiura/ Snyder/Tessler	Eastern Asian	Case-control, ethnic-matched
1991[33]	Numaga et al.	Japan	NA	NA	NA	NA	Serological	NA	Eastern Asian	Case-control, ethnic-matched
1992[34]	Zhang et al.	China	NA	NA	NA	NA	Serological	Sugiura	Eastern Asian	Case-control, ethnic-matched
1994[10]	Islam et al.	Japan	NA	NA	50.9	NA	Serological/ genotyping	NA	Eastern Asian	Case-control, ethnic-matched
1994[9]	Shindo et al.	Japan	22-75	NA	42.9	NA	Serological/ genotyping	A.U.S	Eastern Asian	Case-control, ethnic-, age-, sex-, matched
1995[35]	Weisz et al.	U.S.A	NA	NA	24	NA	Serological	NA	Hispanic	Case-control, ethnic-, age-, sex-, matched
1996[36]	Pivetti et al.	Italy	39.5	NA	12.4	NA	Serological	Sugiura	Italian	Case-control, ethnic-matched
1997[37]	Xiao et al.	China	19-56	17-60	61.1	61.3	Genotyping	Snyder	Eastern Asian	Case-control, ethnic-, age-, sex-, matched
1998[38]	Arellanes et al.	Mexico	36.79	NA	25	NA	Serological	A.U.S	Eastern Asian	Case-control, ethnic-matched
1998[39]	Goldberg et al.	Brazil	10-54	NA	35.1	NA	Serological/ genotyping	A.U.S	mixed※	Case-control, ethnic-matched
2000[40]	Kim et al.	Korea	NA	NA	38.9	NA	Genotyping	A.U.S	Eastern Asian	Case-control, ethnic-matched
2000[41]	Zhang et al.	China	35.5	22-65	47.1	48.4	Genotyping	A.U.S	Eastern Asian	Case-control, ethnic-, age-, sex-, matched
2004[42]	Levinson et al.	U.S.A.	NA	NA	NA	NA	Genotyping	Revised A.U.S.	Hispanic	Case-control, ethnic-matched
2006[43]	Horie et al.	Japan	NA	NA	NA	NA	Genotyping	Revised A.U.S.	Eastern Asian	Case-control, ethnic-,matched
2008[44]	Hou et al.	China	NA	NA	128	NA	Genotyping	Revised A.U.S.	Eastern Asian	Case-control, ethnic-, age-, sex-, matched
2009[45]	Iqniebi et al.	Saudi Arabia	33.6 ± 12.4	NA	40	NA	Genotyping	Revised A.U.S.	Saudi Arabia	Case-control, ethnic-matched
2010[46]	Tiercy et al.	India	40	56	26.6	62.5	Genotyping	Revised A.U.S.	Indian	Case-control, ethnic-,age-,sex-, matched
2011[31]	Alaez et al.	Mexico	NA	NA	NA	NA	Genotyping	Revised A.U.S.	Hispanic	Case-control, ethnic-matched
1998[48]	Normura et al.	Japan	NA	NA	NA	NA	Serological/ genotyping	NA	Eastern Asian	Case-control, ethnic-matched
2007[47]	Gupta et al.	India	32.5	NA	29.3	NA	Genotyping	Revised A.U.S.	Indian	Case-control, ethnic-,age-,sex-, matched

Case means VKH patients, ※ Include White, 23 (62.1%), Black, 2 (5.4%), Asiatic, 2(5.4%), Mixed Black and White, 10 (27.0%).
*A.U.S: America Uveitis Society; Revised A.U.S.: revised guidelines of the American Uveitis Society; NA: Not Available.

Table 2 | Assessment of potential bias in included studies

Year	Author	Bias in ascertainment of cases	Bias in ascertainment of controls	Bias in genotyping controls	Bias in population stratification	Confounding bias	Multiple test and Selective outcome reports
1990	Davis et al.	NO	NO	NO	NO	NO	NO
1994	Shindo et al.	NO	NO	NO	NO	NO	NO
1994	Islam et al.	YES	YES	NO	NO	NO	NO
1995	Weisz et al.	NO	NO	NO	NO	NO	NO
1996	Pivetti et al.	NO	NO	NO	NO	NO	NO
1997	Xiao et al.	NO	NO	NO	NO	NO	NO
1998	Arellanes et al.	NO	NO	NO	NO	NO	NO
1998	Goldberg et al.	NO	NO	NO	NO	NO	NO
2000	Kim et al.	NO	NO	NO	NO	NO	NO
2000	Zhang et al.	NO	NO	NO	NO	NO	NO
2004	Levinson et al.	NO	NO	NO	unclear	NO	NO
2006	Horie et al.	NO	NO	NO	NO	NO	NO
2008	Hou et al.	YES	NO	NO	NO	NO	NO
2009	Iqniebi et al.	NO	NO	NO	unclear	NO	NO
2010	Tiercy et al.	NO	NO	NO	NO	NO	NO
2011	Alaez et al.	NO	NO	NO	NO	NO	NO
1992	Zhang et al.	NO	NO	NO	NO	NO	NO
1991	Numaga et al.	NO	NO	NO	NO	NO	NO
1991	Zhao et al.	NO	NO	NO	NO	NO	NO
2007	Gupta et al.	NO	NO	NO	NO	NO	NO
1998	Normura et al.	NO	NO	NO	NO	NO	NO

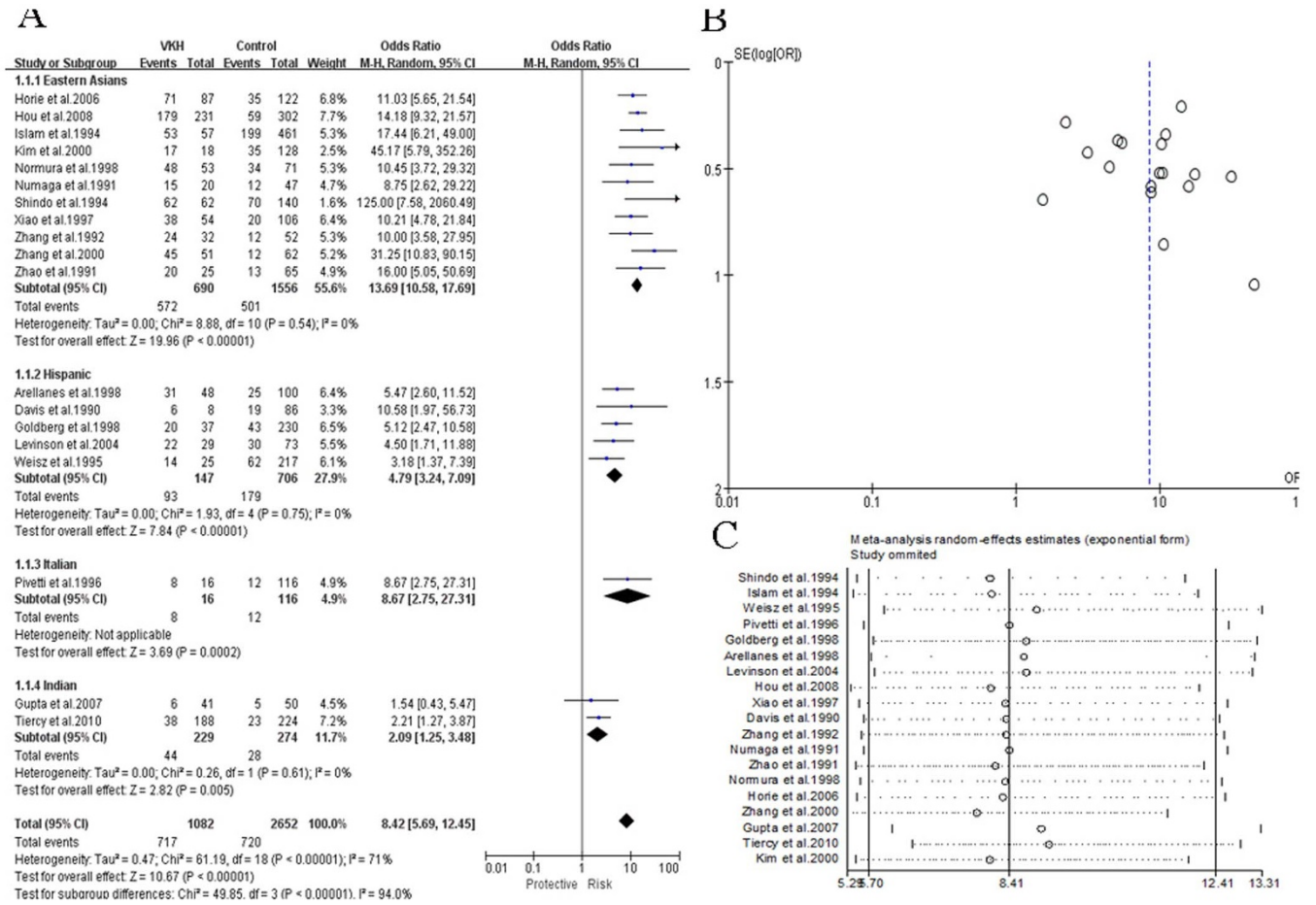

Figure 2 | **Meta-analysis of the association of HLA-DR4/*HLA-DRB1*04* with Vogt-Koyanagi-Harada (VKH) disease.** (A): Forest plot showing the odds ratios (ORs) of VKH carrying HLA-DR4/*HLA-DRB1*04* in individual studies, sub-groups based on ethnicity and the pooled results. (B): Funnel plots for positive rate of HLA-DR4/*HLA-DRB1*04* between VKH cases and controls. (C). Exclusion sensitivity plot showing the results of pooled ORs after omitting each study.

Table 3 | Meta-analysis of the association of *HLA-DRB1*04* sub-alleles with VKH

Sub-alleles	Number of publication	Total cases	Total controls	Pooled OR(95% CI)	P	I^2 (%)	Egger's test
*DRB1*0401*	6	310	463	0.21 (0.07,0.65)	0.007	0	0.899
*DRB1*0402*	3	194	411	0.90(0.29,2.77)	0.85	0	0.513
*DRB1*0403*	11	718	1198	1.24(0.62,2.46)	0.55	45	0.258
*DRB1*0404*	5	285	650	2.57(1.54,4.32)	<0.01	0	0.243
*DRB1*0405*	12	771	1512	10.31 (5.56,19.11)	<0.01	77	0.238
*DRB1*0406*	9	454	718	0.86(0.50,1.51)	0.61	0	0.543
*DRB1*0407*	9	603	1016	1.30(0.85,1.97)	0.22	26	0.410
*DRB1*0408*	6	330	503	0.84(0.24,3.00)	0.79	0	0.822
*DRB1*0410*	8	546	862	6.52(3.23,13.18)	<0.01	0	0.266
*DRB1*0411*	2	156	391	0.85(0.08,8.49)	0.89	61	NA
*DRB1*0417*	1	58	60	0.51(0.04, 5.77)	0.59	NA	NA
*DRB1*0437*	1	58	60	1.04(0.06, 16.95)	0.98	NA	NA

Statistical analysis. Statistical analysis was performed using Review Manager (version 5.2.6.0; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and STATA (version 419.12.0.866, STATA Corp LP, College Station, Texas).For individual study, we calculated the odds ratio (OR) and 95% confidence interval (CI), pooled these data to compare HLA-DR4/*HLA-DRB1*04* frequencies between VKH patients and controls. Between-study heterogeneity was assed using the Q statistics and quantified using the I^2 statistic (I^2 = 0–25%, low heterogeneity; I^2 = 25%–50%, moderate heterogeneity; I^2 = 50%–75% large heterogeneity; I^2 = 75%–100%, extreme heterogeneity)[13]. Pooled ORs and 95% CIs were computed using fix-effects models when $I^2 < 25\%$, or random-effect models when $I^2 >= 25\%$. We performed ethnicity-based sub-group analysis to investigate the strength of association in different ethnicity. If ethnicity cannot explain heterogeneity, univariate random-effects meta-regression was used to investigate the potential sources of heterogeneity, such as, typing technique, publication language, and publication year. Funnel plot and Egger's test were used to assess publication bias, sensitivity analyses were conducted by Exclusion sensitivity plot analysis. P value less than 0.05 were considered significantly except for Q test and Egger's test, where 0.1 was considered as significant level.

Results

General characteristic of included studies. Studies selection process was showed in Figure 1. Among 404 records retrieved from databases, 169 were excluded in initial screening, 197 were excluded because they were unrelated studies, reviews, case reports or animal studies. After reviewing the full text, 11 studies were excluded because they had overlapping information in cases and/or controls with another publications[14–24], and 4 were excluded because they investigated other variants but not HLA-DR4/*HLA-DRB1*04*[25–28], two were excluded because there was no control[29,30]. Eventually, 21 studies[6,9,10,31–48] were retained that contributed data to association of VKH and HLA-DR4/*HLA-DRB1*04*. There were 19 articles in English, 2 in Chinese. The characteristics of included studies are presented in Table 1.

Study bias assessment. Possible bias of the included studies is showed in Table 2. Overall the quality of included studies was good. Two (10%) studies[10,49] had bias of ascertainment in cases, 2 (10%) studies[42,45] were unclear in bias in population stratification, and one (5%) study[10] had bias in ascertainment of controls. No study had bias in genotyping controls, confounding bias or selective outcome report.

Association of HLA-DR4/DRB1*04with VKH. In 19 case-control studies investigating the association of HLA-DR4/*HLA-DRB1*04* with VKH, the ORs of individual studies ranged from 1.57 to 125.00. The heterogeneity across studies was high with $I^2 = 71\%$, $p < 0.00001$. Sub-group analysis based on ethnicity showed the $I^2 = 0$ in all four subgroups, with OR = 13.69 (95%CI: 10.58, 17.69), 8.67 (95%CI: 2.75, 27.31), 4.79 (95%CI: 3.24, 7.09) and 2.09 (95%CI: 1.25, 3.48) in Eastern Asians, Italians, Hispanics and Indians respectively. There was significant difference among the subgroups ($I^2 = 71\%$, $p < 0.00001$, Figure 2A). The pooled OR of all studies was 8.42 (95% CI: 5.69, 12.45). The funnel plot did not show any obvious evidence of asymmetry (Figure 2B), and the p value of Egger's test was 0.457. Therefore, publication bias was not evident in this meta-analysis. Exclusion sensitivity plot showed that pooled OR was not influenced by omitting any study (Figure 2C).

Association of *HLA- DRB1*04* sub-alleles with VKH. The association of *HLA-DRB1*0401, 0402, 0403, 0404, 0405, 0406, 0407, 0408, 0410, 0411, 0417, 0437* with VKH was investigated (Table 3 and Figure 3). Among them, no statistically significant association was found between VKH with *HLA-DRB1*0402, 0403, 0406, 0407, 0410, 0411, 0417, or 0437*. *HLA-DRB1*0401* investigated in 6 studies. The individual OR was statistically significant in only one study, but the pooled OR was 0.21 (95% CI: 0.07–0.65, $I^2 = 0\%$, Figure 3A). *HLA-DRB1*0404* was investigated in 6 articles and only two of them reported significant association with VKH. The pooled OR was 2.57 (95% CI: 1.54–4.32, $I^2 = 0\%$, Figure 3D). *HLA-DRB1*0410* was investigated in 8 studies. Statistically significant association of *HLA-DRB1*0410* with VKH was reported in two of them and the pooled OR was 6.52 (95% CI: 3.23–13.18, $I^2 = 0\%$, Figure 3I). *HLA-DRB1*0405* was investigated in 12 studies, and the pooled OR was 10.31 (95% CI: 5.56–19.11, $I^2 = 77\%$, Figure 3E). Meta-regression found that publication year, ethnicity or publication language cannot explain the between studies heterogeneity (all $p > 0.05$).

Discussion

The present meta-analysis, including 1853 VKH patients and 4164 controls from 21 articles, investigated the association of HLA-DR4/*HLA-DRB1*04* and its sub-alleles with VKH. Our results indicate that HLA-DR4/*HLA-DRB1*04* carriers have an increased risk of VKH with OR 8.42. The strength of this association is highest in Eastern Asian and lowest in Indians. Some of *HLA-DRB1*04*'s sub-alleles *HLA-DRB1*0404, 0405 and 0410* increased the risk of VKH; *0401* reduced risk of VKH; while *0402, 0403, 0406, 0407, 0410, 0411, 0417, or 0437* was not associated with VKH.

The association of HLA-DR4/*HLA-DRB1*04* with VKH was reported in various ethnic populations. Our meta-analysis confirms these previous reports on the association of HLA-DR4/*HLA-DRB1*04* with VKH. VKH appears to occur commonly among communities with dark pigment such as Native American, Arabian, Eastern Asian and Indian but not in blacks of sub-Saharan Africans or Caucasians[50]. It is known that the strength of HLA-disease associations can vary among different racial groups[51]. Also, different racial groups can have distinct HLA associations with a common, clinically identified disease. With the power of meta-analysis, here we pooled all the published results of the association between VKH with HLA-DR4/*HLA-DRB1*04* and demonstrated that ethnicity was the source of heterogeneity. The OR was 13.69 (95%CI: 10.58, 17.69), 8.67 (95%CI: 2.75, 27.31), 4.79CI (95%CI: 3.24, 7.09) and 2.09 (95%CI: 1.25, 3.48) in Eastern Asian, Italian, Hispanic and Indian respectively.

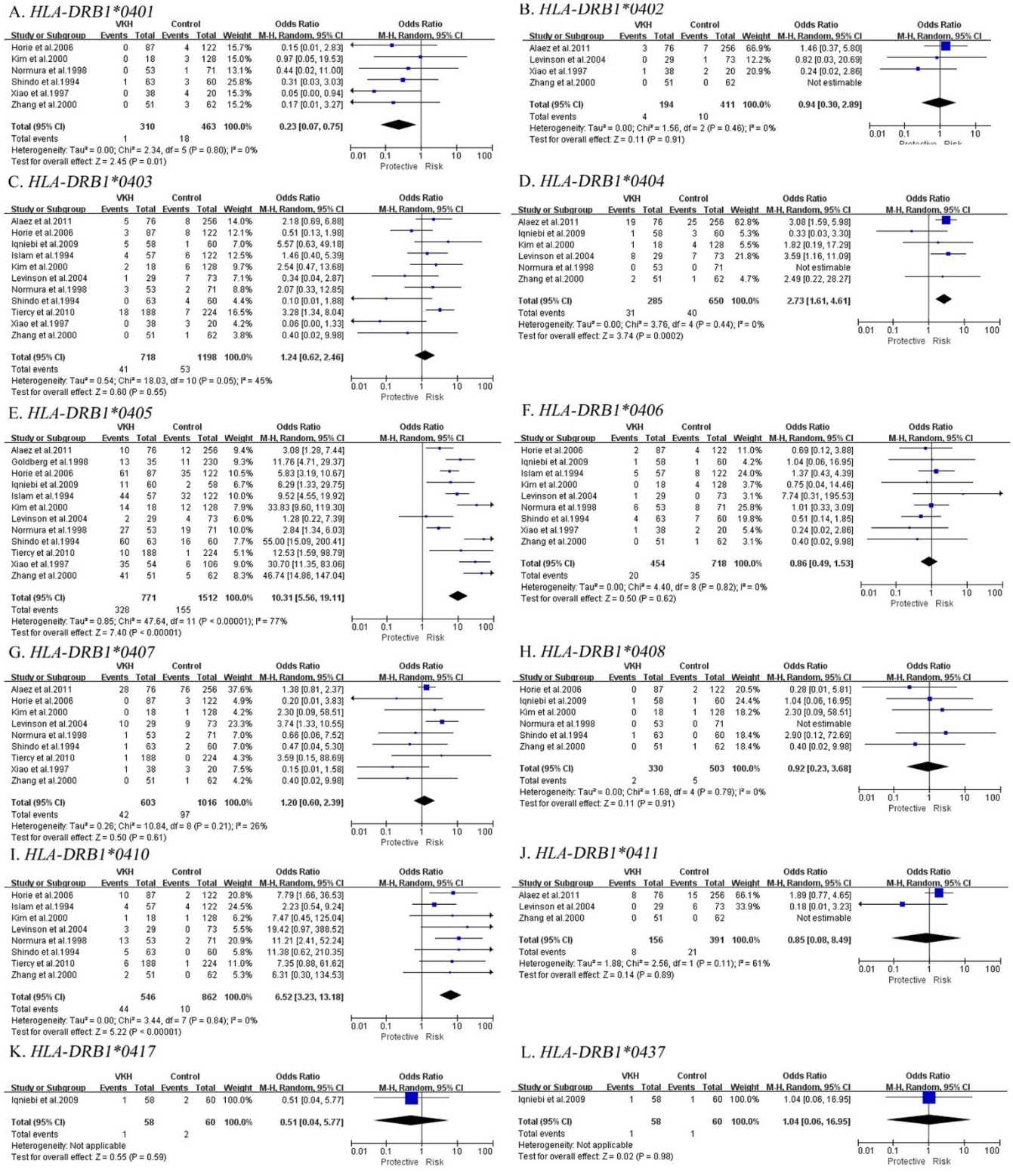

Figure 3 | Forest plots of the association of *HLA-DRB1*04* sub-alleles with Vogt-Koyanagi-Harada (VKH) disease.

In this meta-analysis, we not only confirmed the association of HLA-DR4/*HLA-DRB1*04* with VKH, but also identified the sub-alleles, *HLA-DRB1*0404, 0405, 0410* as the risk alleles of VKH, while *HLA-DRB1*0401* as the protective allele for VKH. HLA genes and proteins are known to be highly polymorphic, i.e. they exist in many different forms among humans, and play an essential role in recognition of immune system[52]. HLA-DR is a MHC class II cell surface receptor, which displays peptides antigens produced from the *HLA-DRB1* gene to the immune system. If the immune system recognizes the peptides as foreign (such as viral or bacterial peptides), it triggers a response to attack the invading viruses or bacteria. It was reported that VKH patients are sensitized to melanocyte epitopes, while patients with *HLA-DRB1*0405* recognize a broader melanocyte-derived peptide repertoire[53]. The functional correlation of *HLA-DRB1*0404, 0410* or *0401* with melanocyte epitopes has not been reported. Possibly *HLA-DRB1*0404* and *0410* may have broader

melanocyte-derived peptide repertoire as 0405, while *HLA-DRB1*0401* may have narrower melanocyte epitopes.

Among the sub-alleles of *HLA-DRB1*04, HLA-DRB1*0405* was the most investigated allele. Statistically significant association of *HLA-DRB1*0405* with VKH was reported in most original studies except in Levinson's article[42]. Our meta-analysis confirmed the positive association of *HLA-DRB1*0405* with VKH, although there was some heterogeneity that cannot be explained. Statistical significant association of VKH with *HLA-DRB1*0404, 0410* or *0401* was reported in only a few studies but not others. The inconsistency of results from different publications may be due to a small sample size in individual studies. With the power of meta-analysis, the sample size was pooled and increased, and we were able to resolve the inconsistency among publications and identify *HLA-DRB1*0404* and *0410* as risk alleles while *0401* as protective allele.

This meta-analysis suggests that in clinical practice, genotyping of *HLA-DRB1*0404, 0410* and *0401* is recommended for VKH patients in addition to *HLA-DRB1*0405*. The genotyping of *HLA-DRB1*0402, 0403, 0406, 0407, 0410, 0411, 0417, or 0437* is not necessary. Further studies are needed to investigate the functional implication of *HLA-DRB1*0404, 0405, 0410* and *0401*, which may provide further insight into the pathogenesis of VKH.

Our study has some limitations. First, we did not identify the source of heterogeneity in the association of *HLA-DRB1*0405* with VKH after exploring ethnicity, publication year and publication language. Some studies did not give detailed data such as onset/study age, gender percentage. Therefore we could not estimate them further in meta-regression. Second, there may be some original studies not retrieved by the current literature search. We did not search the Japanese database. Although some Japanese medical journals are indexed in PubMed, and Embase, we still cannot eliminate if some articles in Japanese or other language were missed. Third, the diagnostic criteria of VKH adopted in individual studies are different, which may contribute to the heterogeneity of association.

In conclusion, this meta-analysis demonstrates a strong association between HLA-DR4/*HLA-DRB1*04* and VKH. The strength of association was variable in different ethnicities. The sub-alleles, *HLA-DRB1*0404, 0405, 0410* were risk factors of VKH, while *HLA-DRB1*0401* was the protective factor.

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Author contributions

H.C. designed the study. T.S., W.L. and L.Z. conducted the study. T.S. and H.C. analyzed the data. T.S. wrote the main manuscript text. J.C. and H.C. revised the manuscript. All authors reviewed and approved the manuscript.

Additional information

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