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

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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 (I² = 71%). Subgroup analysis indicated that ethnicity was the source of heterogeneity (all I² = 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. 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.

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. Therefore, HLA plays an important role in immune system function as well as in the pathogenesis of autoimmune diseases, including VKH. Almost 40 years ago, the association of HLA-BW22] and VKH was reported. However, it could not be replicated in subsequent studies. 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. 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. 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 with HLA-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
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-DRB1 allele/sub-alleles 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 6 domains suggested in the HuGENet handbook: bias in population stratification, confounding bias, multiple tests, 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 | Age(Y) | %Male of VKH | African Male of control | Typing technique | Diagnostic criteria | Ethnicity | Study design |
|------------|--------------|---------|--------|--------------|------------------------|------------------|-------------------|----------|-------------|
| 1990⁶ | Davis et al. | U.S.A. | NA | NA | NA | Serological | NA | Hispanic | Case-control, ethnic-matched |
| 1991³² | Zhao et al. | China | NA | NA | 36.2 | Serological | A.U.S./Sugiuira/ Snyder/Tessler | Eastern | Case-control, ethnic-matched |
| 1991³³ | Numaga et al. | Japan | NA | NA | NA | Serological | NA | Asian | Case-control, ethnic-matched |
| 1992³⁴ | Zhang et al. | China | NA | NA | NA | Serological | Sugiuira | Eastern | Case-control, ethnic-matched |
| 1994¹⁰ | Islam et al. | Japan | NA | NA | 50.9 | Serological/ genotyping | NA | Asian | Case-control, ethnic-matched |
| 1994⁹ | Shindo et al. | Japan | 22-75 | NA | 42.9 | Serological/ genotyping | A.U.S | Eastern | Case-control, ethnic-matched |
| 1995³⁵ | Weisz et al. | U.S.A | NA | NA | 24 | Serological | NA | Hispanic | Case-control, ethnic-matched |
| 1996³⁶ | Pivetti et al. | Italy | 39.5 | NA | 12.4 | Serological | Sugiuira | Italian | Case-control, ethnic-matched |
| 1997³⁷ | Xiao et al. | China | 19-56 | 17-60 | 61.1 | Genotyping | Snyder | Eastern | Case-control, ethnic-matched |
| 1998³⁸ | Arellanes et al. | Mexico | 36.79 | NA | 25 | Serological | A.U.S | Eastern | Case-control, ethnic-matched |
| 1998³⁹ | Goldberg et al. | Brazil | 10-54 | NA | 35.1 | Serological/ genotyping | A.U.S | Asian mixed | Case-control, ethnic-matched |
| 2000⁴⁰ | Kim et al. | Korea | NA | NA | 38.9 | Serological/ genotyping | A.U.S | Eastern | Case-control, ethnic-matched |
| 2000⁴¹ | Zhang et al. | China | 35.5 | 22-65 | 47.1 | Genotyping | A.U.S | Asian | Case-control, ethnic-matched |
| 2004⁴² | Levinson et al. | U.S.A. | NA | NA | NA | Genotyping | Revised A.U.S. | Hispanic | Case-control, ethnic-matched |
| 2006⁴³ | Horie et al. | Japan | NA | NA | NA | Genotyping | Revised A.U.S. | Eastern | Case-control, ethnic-matched |
| 2008⁴⁴ | Hou et al. | China | NA | NA | 128 | Genotyping | Revised A.U.S. | Eastern | Case-control, ethnic-matched |
| 2009⁴⁵ | Igkeni et al. | Saudi Arabia | 33.6 ± 12.4 | NA | 40 | Genotyping | Revised A.U.S. | Arabian | Case-control, ethnic-matched |
| 2010⁴⁶ | Tieryc et al. | India | 40 | 56 | 26.6 | Genotyping | Revised A.U.S. | Indian | Case-control, ethnic-matched |
| 2011³¹ | Alaez et al. | Mexico | NA | NA | NA | Genotyping | Revised A.U.S. | Hispanic | Case-control, ethnic-matched |
| 1998⁴⁸ | Normura et al. | Japan | NA | NA | NA | Serological/ genotyping | Revised A.U.S. | Asian | Case-control, ethnic-matched |
| 2007⁴⁷ | Gupta et al. | India | 32.5 | NA | 29.3 | Genotyping | Revised A.U.S. | Indian | Case-control, ethnic-matched |

Case means VKH patients; Include White, 23 (62.1%), Black, 2 (5.4%), Asian, 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.*

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Figure 1 | Flow diagram showing the result of literature screening for meta-analysis.
### 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                           | NO                               | 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                          | NO                                | 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 | Tieryc 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 | Numgo 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.
The heterogeneity across studies was high with $I^2$ with VKH, the ORs of individual studies ranged from 1.57 to
studies investigating the association of HLA-DR4/DRB1
or animal studies. After reviewing the full text, 11 studies were
databases, 169 were excluded in initial screening, 197 were
was showed in Figure 1. Among 404 records retrieved from
General characteristic of included studies
Results
General characteristic of included studies. Studies selection process
was shown 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, and 4 were excluded
because they investigated other variants but not HLA-DR4/HLA-DRB1*04.
Eventually, 21 studies were retained that contributed data
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
shown in Table 2. Overall the quality of included studies was
good. Two (10%) studies had bias of ascertainment in cases, 2
(10%) studies were unclear in bias in population stratification,
and one (5%) study had bias in ascertainment of controls. No study
had bias in genotyping controls, confounding bias or selective
outcome report.
Association of HLA-DR4/DRB1*04 with 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 $I^2 = 71\%$, $p < 0.0001$. 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).

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 | 899 |
| DRB1*0402  | 3                     | 194         | 411           | 0.90 (0.29, 2.77) | 0.85 | 0 | 513 |
| DRB1*0403  | 11                    | 718         | 1198          | 1.24 (0.62, 2.46) | 0.55 | 45 | 258 |
| DRB1*0404  | 5                     | 285         | 650           | 2.57 (1.54, 4.32) | <0.01 | 0 | 243 |
| DRB1*0405  | 12                    | 771         | 1512          | 10.31 (5.56, 19.11)| <0.01 | 77 | 238 |
| DRB1*0406  | 9                     | 454         | 718           | 0.86 (0.50, 1.51) | 0.61 | 0 | 543 |
| DRB1*0407  | 9                     | 603         | 1016          | 1.30 (0.85, 1.97) | 0.22 | 26 | 410 |
| DRB1*0408  | 6                     | 330         | 503           | 0.84 (0.24, 3.00) | 0.79 | 0 | 822 |
| DRB1*0410  | 8                     | 546         | 862           | 6.52 (3.23, 13.18)| <0.01 | 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 14.0.0.666, 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 assessed 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). Pooled ORs and 95% CIs were computed using fixed-effects models when $I^2 < 25\%$, or 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 were considered as significant level.

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. It is known that the strength of HLA-disease associations can vary among different racial groups. 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), 4.79 (95%CI: 3.24, 7.09) and 2.09 (95%CI: 1.25, 3.48) in Eastern Asian, Italian, Hispanic and Indian respectively.
In this meta-analysis, we not only confirmed the association of 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. 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. The functional correlation of HLA-DRB1*0404, 0410 with melanocyte epitopes has not been reported. Possibly HLA-DRB1*0404 and 0410 may have broader
melanocyte-derived peptide repertoire as 0.405, 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. Our meta-analysis confirmed the positive association of HLA-DRB1*0405 with VKH, although there was some heterogeneity that cannot be explained. Statistically 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, 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 addition, 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.

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