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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, 6405 and 0410 as risk sub-alleles while 0401 as protective sub-allele.

ogt-Koyanagi-Harada disease (VKH) is a systematic autoimmune disorder that affects tissues containing melanin such as the eyes, inner ears, meninges, and skin¹. 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 factors²⁻⁴.

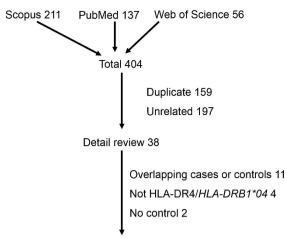
Human leukocyte antigen (HLA) system is the locus of genes that encode for major histocompatibility complex (MHC), which is a set of cell surface molecules mediating interaction of leukocyte⁵. Therefore, HLA plays an important role in immune system function as well as in the pathogenesis of autoimmune diseases, including VKH⁶. Almost 40 years ago, the association of HLA-BW22J and VKH was reported⁷. However, it could not be replicated in subsequent studies⁸. 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 VKH¹¹. 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



Final included 21

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 handbook¹²: 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.

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°	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	NÁ	Eastern Asian	Case-control, ethnic matched
199234	Zhang et al.	China	NA	NA	NA	NA	Serological	Sugiura	Eastern Asian	Case-control, ethnic matched
199410	Islam et al.	Japan	NA	NA	50.9	NA	Serological/ genotyping	NA	Eastern Asian	Case-control, ethnic matched
1994°	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
1 998 38	Arellanes et al.	Mexico	36.79	NA	25	NA	Serological	A.U.S	Eastern Asian	Case-control, ethni matched
1998 ³⁹	Goldberg et al.	Brazil	10-54	NA	35.1	NA	Serological/ genotyping	A.U.S	mixed*	Case-control, ethnic matched
200040	Kim et al.	Korea	NA	NA	38.9	NA	Genotyping	A.U.S	Eastern Asian	Case-control, ethnic matched
200041	Zhang et al.	China	35.5	22-65	47.1	48.4	Genotyping	A.U.S	Eastern Asian	Case-control, ethnia age-, sex-, matched
200442	Levinson et al.	U.S.A.	NA	NA	NA	NA	Genotyping	Revised A.U.S.	Hispanic	Case-control, ethnic matched
200643	Horie et al.	Japan	NA	NA	NA	NA	Genotyping	Revised A.U.S.	Eastern Asian	Case-control, ethni ,matched
200844	Hou et al.	China	NA	NA	128	NA	Genotyping	Revised A.U.S.	Eastern Asian	Case-control, ethni age-, sex-, matched
200945	lqniebi et al.	Saudi Arabia	33.6 ± 12.4	NA	40	NA	Genotyping	Revised A.U.S.	Saudi Arabia	Case-control, ethni matched
201046	Tiercy et al.	India	40	56	26.6	62.5	Genotyping	Revised A.U.S.	Indian	Case-control, ethni ,age-,sex-, matched
201131	Alaez et al.	Mexico	NA	NA	NA	NA	Genotyping	Revised A.U.S.	Hispanic	Case-control, ethni matched
199848	Normura et al.	Japan	NA	NA	NA	NA	Serological/ genotyping	NA	Eastern Asian	Case-control, ethni matched
200747	Gupta et al.	India	32.5	NA	29.3	NA	Genotyping	Revised A.U.S.	Indian	Case-control, ethni ,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.

l able 2	2 Assessment c	ot potential bias in in	cluded 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	lqniebi 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

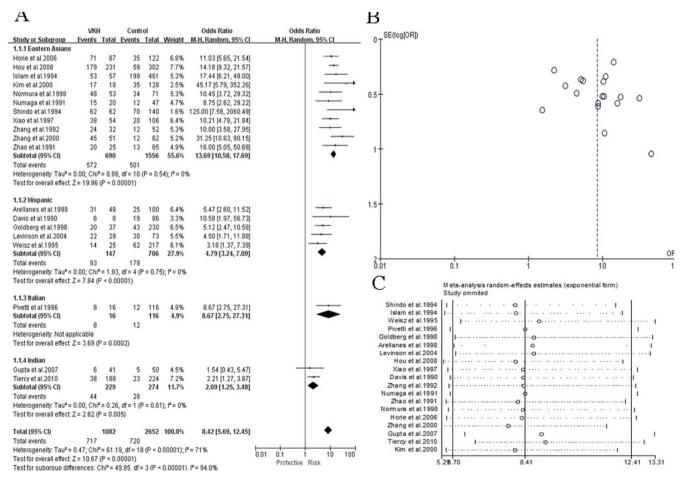


Figure 2 | Meta-analysis of the association of HLA-DR4/HLA-DRB1*04 with Vogt-Koyanagi-Harada (VKH) disease. (A): Forest plot showing the odds ratios (ORs) of VKH carrying HLA-DR4/HLA-DRB1*04 in individual studies, sub-groups based on ethnicity and the pooled results. (B): Funnel plots for positive rate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

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Sub-alleles	Number of publication	Total cases	Total controls	Pooled OR(95% CI)	Р	l² (%)	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 I² statistic (I² = 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 $I^2 \ge 25\%$. 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%) study¹⁰ 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 Caucasians⁵⁰. It is known that the strength of HLA-disease associations can vary among different racial groups⁵¹. 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.

tudy or Subgroup	VKH Events	Total	Contro Events		Weight	Odds Ratio M-H, Random, 95% Cl	N	Odds I-H. Rando	m, 95% CI	
orie et al.2006	Events 0	87	Events 4	122	15.7%	0.15 [0.01, 2.83]	4			
im et al.2000	0	18	3	128	15.0%	0.97 [0.05, 19.53]	_	-		
ormura et al.1998	0	53	1	71	13.1%	0.44 [0.02, 11.00]		-		
hindo et al.1994	1	63	3	60	25.8%	0.31 [0.03, 3.03]		-		
iao et al.1997	0	38 51	4	20	15.3%	0.05 [0.00, 0.94]	-			
hang et al.2000	U		3	62	15.2%	0.17 [0.01, 3.27]	,	-		
otal (95% CI) otal events	1	310	18	463	100.0%	0.23 [0.07, 0.75]				
eterogeneity: Tau ² =			, df = 5 (F	P = 0.8	0); I² = 0%		0.01 0		10	100
est for overall effect	Z = 2.45 (P	e = 0.0	1)						Risk	100
. HLA-DRI	B1*04	03								
	VKH		Contr			Odds Ratio		Odds		
tudy or Subgroup	Events			Total		M-H, Random, 95% Cl	N	I-H, Rando	om, 95% CI	
laez et al.2011 orie et al.2006	5	76 87	8	256 122	14.0%	2.18 [0.69, 6.88]		_		
niebi et al.2009	5	58	1	60	7.0%	0.51 [0.13, 1.98] 5.57 [0.63, 49.18]		_		_
lam et al.1994	4	57	6	122	12.5%	1.46 [0.40, 5.39]		_		
im et al.2000	2	18	6	128	9.7%	2.54 [0.47, 13.68]		-		
evinson et al.2004	1	29	7	73	7.1%	0.34 [0.04, 2.87]		•	_	
ormura et al.1998	3	53	2	71	8.8%	2.07 [0.33, 12.85]		_		
hindo et al.1994	0	63	4	60	4.4%	0.10 [0.01, 1.88]	•			
iercy et al.2010 iao et al.1997	18	188	7	224 20	16.5% 4.2%	3.28 [1.34, 8.04]				
ao et al.1997 hang et al.2000	0	38 51	3	20 62	4.2%	0.06 [0.00, 1.33] 0.40 [0.02, 9.98]				
otal (95% CI)	44	718	53	1198	100.0%	1.24 [0.62, 2.46]		1	•	
otal events eterogeneity: Tau² =	41 = 0.54; Chi ²	= 18.0) (P = 0	1.05); I ² = 4	15%	-	t I		100
est for overall effect				C				1.1 1 Protective	10 Risk	100
. HLA-DRI	B1*04	05					,			
· ILII-DA	VKH	55	Contr	ol		Odds Ratio		Odds	Ratio	
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Ν		om, 95% CI	
laez et al.2011	10	76	12	256	9.4%	3.08 [1.28, 7.44]				
oldberg et al.1998	13	35 87	11	230	9.3%	11.76 [4.71, 29.37]				-
orie et al.2006 niebi et al.2009	11	87 60	35	122 58	10.5% 6.7%	5.83 [3.19, 10.67] 6.29 [1.33, 29.75]				_
lam et al.1994	44	57	32	122	10.0%	9.52 [4.55, 19.92]				
im et al.2000	14	18	12	128	7.9%	33.83 [9.60, 119.30]				• •
evinson et al.2004	2	29	4	73	6.0%	1.28 [0.22, 7.39]			•	
ormura et al.1998	27	53	19	71	10.0%	2.84 [1.34, 6.03]				
hindo et al.1994	60	63	16	60	7.7%	55.00 [15.09, 200.41]				
iercy et al.2010 iao et al.1997	10 35	188 54	1	224 106	5.1% 9.0%	12.53 [1.59, 98.79] 30.70 [11.35, 83.06]			_	-
hang et al.2000	41	51	5						-	
				62	8.3%	46.74 [14.86, 147.04]				
			Ŭ							
otal (95% CI)	220	771			8.3%	46.74 [14.86, 147.04] 10.31 [5.56, 19.11]			•	
otal events	328 = 0.85: Chi ²	771	155	1512	100.0%	10.31 [5.56, 19.11]	L		•	
	= 0.85; Chi ²	771 = 47.6	155 4, df = 11	1512	100.0%	10.31 [5.56, 19.11]		I 0.1 Protective	+ 10 Risk	100
otal events eterogeneity: Tau² = est for overall effect:	= 0.85; Chi ² Z = 7.40 (F	771 = 47.6 ? < 0.01	155 4, df = 11	1512	100.0%	10.31 [5.56, 19.11]		I).1 1 Protective		100
otal events eterogeneity: Tau ² = est for overall effect 6. HLA-DR	= 0.85; Chi [#] Z = 7.40 (F B1*04 VKH	771 = 47.6 < 0.0	155 4, df = 11 0001) Contr	1512 (P < 0	100.0% 1.00001); I	10.31 [5.56, 19.11] *= 77% Odds Ratio	F	Protective Odds	Risk Ratio	100
otal events eterogeneity: Tau ² = est for overall effect G. HLA-DR tudy or Subgroup	= 0.85; Chi ² Z = 7.40 (F B1*04 VKH Events	771 = 47.6 ? < 0.0 ! ?	155 4, df = 11 0001) Contr <u>Events</u>	1512 (P < 0 ol Total	100.0% 1.00001); Weight	10.31 [5.56, 19.11] = 77% Odds Ratio <u>M-H, Random, 95% CI</u>	F	Protective Odds	Risk	100
otal events eterogeneity: Tau ² = est for overall effect 6. HLA-DR tudy or Subgroup aez et al.2011	= 0.85; Chi [*] Z = 7.40 (F B1*04 VKH Events 28	771 = 47.6 2 < 0.0 2 0 7 <u>Total</u> 76	155 4, df = 11 0001) Contr <u>Events</u> 76	1512 (P < 0 ol <u>Total</u> 256	100.0% 0.00001); I <u>Weight</u> 37.6%	10.31 [5.56, 19.11] ² = 77% Odds Ratio <u>M-H, Random, 95% CI</u> 1.38 [0.81, 2.37]	F	Protective Odds	Risk Ratio	100
otal events eterogeneity: Tau ² = est for overall effect c. HLA-DR tudy or Subgroup aez et al.2011 orie et al.2006	= 0.85; Chi [#] Z = 7.40 (F B1*04 VKH Events 28 0	771 = 47.6 ? < 0.0 ? 07 <u>Total</u> 76 87	155 4, df = 11 0001) Contr <u>Events</u> 76 3	1512 (P < 0 ol 256 122	100.0% 0.00001); I Weight 37.6% 4.9%	10.31 [5.56, 19.11] ² = 77% Odds Ratio <u>M-H. Random, 95% CI</u> 1.38 (0.81, 2.37] 0.20 (0.01, 3.83]	F	Protective Odds	Risk Ratio	100
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total events eterogeneity. Tau ² est for overall effect est for overall effect as. <i>HLA-DR</i> . tudy or Subgroup laez et al.2011 orie et al.2000 im et al.2000 orie et al.2000 orial events eterogeneity. Tau ² est est for overall effect: <i>C. HLA-DR</i> .	e 0.85; Chi ² Z = 7.40 (F B1*0.44 VKH Events 22 28 0 0 10 11 1 1 1 1 1 1 1 1 1 1 1 2 2 2 2	771 = 47.66 > <0.00 07 Total 29 53 63 188 38 51 603 = 10.8 51 603 = 10.8 51 603 = 10.8 51 603 188 51 603 = 10.8 51 53 63 53 53 63 51 546 53 53 53 53 53 53 53 53 53 53 53 53 53	155 1 2001) Contr Fevents 76 76 76 76 76 76 76 76 76 76	ol Total 256 122 256 122 128 73 71 60 224 200 62 1016 (P = 0.: 122 128 73 71 100 62 122 128 73 71 100 62 122 24 20 60 122 25 60 224 20 60 224 20 60 224 20 60 20 71 20 60 20 60 20 20 20 80 20 60 20 20 20 80 20 60 20 20 20 20 20 20 20 20 20 2	Weight 100.0% Weight 37.6% 4.9% 23.3% 7.0% 4.9% 23.3% 100.0% 20.8% 20.24.5% 20.24.5% 22.24.5% 5.2% 5.3% 100.0% 11.0% 5.3% 100.0%	10.31 [5.56, 19.11] ² = 77% Odds Ratio <u>MH, Random, 95% CI</u> 1.38 [0.81, 2.37] 0.20 [0.01, 3.83] 2.30 [0.09, 58, 51] 3.74 [1.33, 10.55] 0.66 [0.06, 7.52] 0.47 [0.04, 5.88, 69] 0.15 [0.01, 1.58] 0.40 [0.02, 9.98] 1.20 [0.60, 2.39] 3% Odds Ratio <u>MH, Random, 95% CI</u> 7.79 [1.66, 36, 53] 2.23 [0.54, 9.24] 7.47 [0.45, 125, 04] 19.42 [0.37, 388, 52] 11.21 [2.41, 52, 24] 11.38 [0.52, 210, 35] 6.52 [3.23, 13, 18] Odds Ratio <u>MH, Random, 95% CI</u> 0.51 [0.04, 5.77]		Odds	Risk Ratio T Risk Ratio Ratio Risk Ratio Risk Ratio Risk Ratio Risk Ratio Risk Ratio Risk Ratio	
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tal events terogeneity. Tau ² = st for overall effect . HLA-DR udy or Subgroup aez et al.2011 orie et al.2000 in et al.2000 in et al.2000 in et al.2000 in et al.2000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.0000 tal.00000 tal.00000 tal.00000 tal.00000 tal.000000000000000000000000000000000000	e. 0.85; Chi ² Z = 7.40 (F B1*0.44 VKH Events 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	771 = 47.66 > <0.00 07 Total 29 53 63 188 38 51 603 = 10.8 51 603 = 10.8 51 603 = 10.8 51 603 188 51 603 = 10.8 51 53 63 53 53 63 51 546 53 53 53 53 53 53 53 53 53 53 53 53 53	155 1 2001) Contr Fevents 76 76 76 76 76 76 76 76 76 76	ol Total 256 122 256 122 128 73 71 60 224 200 62 1016 (P = 0.: 122 128 73 71 100 62 122 128 73 71 100 62 122 24 20 60 122 25 60 224 20 60 224 20 60 224 20 60 20 71 20 60 20 60 20 20 20 80 20 60 20 20 20 80 20 60 20 20 20 20 20 20 20 20 20 2	Weight 100.0% Weight 37.6% 4.9% 23.3% 7.0% 4.9% 23.3% 100.0% 20.8% 20.24.5% 20.24.5% 22.24.5% 5.2% 5.3% 100.0% 11.0% 5.3% 100.0%	10.31 [5.56, 19.11] ² = 77% Odds Ratio <u>MH, Random, 95% CI</u> 1.38 [0.81, 2.37] 0.20 [0.01, 3.83] 2.30 [0.09, 58, 51] 3.74 [1.33, 10.55] 0.66 [0.06, 7.52] 0.47 [0.04, 5.88, 69] 0.15 [0.01, 1.58] 0.40 [0.02, 9.98] 1.20 [0.60, 2.39] 3% Odds Ratio <u>MH, Random, 95% CI</u> 7.79 [1.66, 36, 53] 2.23 [0.54, 9.24] 7.47 [0.45, 125, 04] 19.42 [0.37, 388, 52] 11.21 [2.41, 52, 24] 11.38 [0.52, 210, 35] 6.52 [3.23, 13, 18] Odds Ratio <u>MH, Random, 95% CI</u> 0.51 [0.04, 5.77]		Odds	Risk	

... HLA-DRB1*0402

	VKH	1	Contr	lo		Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, R	andom, 9	5% CI	
Alaez et al.2011	3	76	7	256	66.9%	1.46 [0.37, 5.80]			_	-	
Levinson et al.2004	0	29	1	73	12.2%	0.82 [0.03, 20.69]	_		•		
Xiao et al.1997	1	38	2	20	20.9%	0.24 [0.02, 2.86]	_		-		
Zhang et al.2000	0	51	0	62		Not estimable					
Total (95% CI)		194	1 10	411	100.0%	0.94 [0.30, 2.89]			•		
Total events	4										
Heterogeneity: Tau ² =	= 0.00; Chi	² = 1.58	6, df = 2 (P = 0.4	6); I ² = 09	6	-	0.1	<u> </u>	+	
Test for overall effect	Z=0.11 (P = 0.9	1)				0.01		1	10	

LA-DRB1*0404

	VKH	1	Contr	lo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Alaez et al.2011	19	76	25	256	62.8%	3.08 [1.59, 5.98]	
Igniebi et al.2009	1	58	3	60	5.3%	0.33 [0.03, 3.30]	
Kim et al.2000	1	18	4	128	5.5%	1.82 [0.19, 17.29]	
Levinson et al.2004	8	29	7	73	21.8%	3.59 [1.16, 11.09]	
Normura et al.1998	0	53	0	71		Not estimable	
Zhang et al.2000	2	51	1	62	4.7%	2.49 [0.22, 28.27]	
Total (95% CI)		285		650	100.0%	2.73 [1.61, 4.61]	•
Total events	31		40				
Heterogeneity: Tau ² =	0.00; Chi	= 3.7	6, df = 4 (P = 0.4	4); I ² = 09	6	
Test for overall effect	Z= 3.74 ((P = 0.0	002)				0.01 0.1 1 10 100 Protective Risk

ILA-DRB1*0406

	VKI	4	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Horie et al.2006	2	87	4	122	11.0%	0.69 [0.12, 3.88]	
Igniebi et al.2009	1	58	1	60	4.2%	1.04 [0.06, 16.95]	
Islam et al.1994	5	57	8	122	24.0%	1.37 [0.43, 4.39]	
Kim et al.2000	0	18	4	128	3.7%	0.75 [0.04, 14.46]	
Levinson et al.2004	1	29	0	73	3.1%	7.74 [0.31, 195.53]	
Normura et al.1998	6	53	8	71	25.8%	1.01 [0.33, 3.09]	
Shindo et al.1994	4	63	7	60	19.8%	0.51 [0.14, 1.85]	
Xiao et al.1997	1	38	2	20	5.4%	0.24 [0.02, 2.86]	
Zhang et al.2000	0	51	1	62	3.1%	0.40 [0.02, 9.98]	
Total (95% CI)		454		718	100.0%	0.86 [0.49, 1.53]	•
Total events	20		35				
Heterogeneity: Tau ² =	0.00; Ch	² = 4.4	0, df = 8 (P = 0.8	2); I ² = 09	6	
Test for overall effect:	Z = 0.50	(P = 0.6	(2)				0.01 0.1 1 10 100 Protective Risk

ILA-DRB1*0408

	VK	4	Contr	lo		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95%	CI
Horie et al.2006	0	87	2	122	20.5%	0.28 [0.01, 5.81]		
Igniebi et al.2009	1	58	1	60	24.4%	1.04 [0.06, 16.95]		_
Kim et al.2000	0	18	1	128	18.2%	2.30 [0.09, 58.51]		
Normura et al.1998	0	53	0	71		Not estimable		
Shindo et al.1994	1	63	0	60	18.4%	2.90 [0.12, 72.69]		
Zhang et al.2000	0	51	1	62	18.4%	0.40 [0.02, 9.98]		-
Total (95% CI)		330		503	100.0%	0.92 [0.23, 3.68]	-	
Total events	2		5					
Heterogeneity: Tau ² =	0.00; Ch	i ² = 1.6	8, df = 4 (P = 0.7	9); I ² = 09	6		10 100
Test for overall effect	Z=0.11	(P = 0.9	91)				Protective Risk	10 100

LA-DRB1*0411

	VK	1	Contr	ol		Odds Ratio		0	io		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, R	andom,	95% CI	
Alaez et al.2011	8	76	15	256	66.1%	1.89 [0.77, 4.65]			+	-	
Levinson et al.2004	0	29	6	73	33.9%	0.18 [0.01, 3.23]	+		-	-	
Zhang et al.2000	0	51	0	62		Not estimable					
Total (95% CI)		156		391	100.0%	0.85 [0.08, 8.49]				-	
Total events	8		21								
Heterogeneity: Tau ² =	1.88; Chi	2 = 2.5	6, df = 1 (P = 0.1	1); I ² = 61	%	0.01	0.1		10	100
Test for overall effect	Z = 0.14	(P = 0.8	19)				0.01	Protec	tive Ris	10 sk	100

HLA-DRB1*0437

		VKH		Contr	ol		Odds Ratio		Odds Ratio			VKH		Control			Odds Ratio Odd		Odds Ratio				
Stud	v or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	lom, 9	5% CI		Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	N	M-H, Random, 95%	6 CI	
Iqnie	bi et al.2009	1	58	2	60	100.0%	0.51 [0.04, 5.77]				-		Iqniebi et al.2009	1	58	1	60	100.0%	1.04 [0.06, 16.95]	-		_	
	l (95% Cl)		58		60	100.0%	0.51 [0.04, 5.77]		-	-	-		Total (95% CI)		58		60	100.0%	1.04 [0.06, 16.95]	-		-	
Total	l events	1		2									Total events	1		1					20		
	rogeneity: Not ap for overall effect:		P = 0.5	9)				0.01	0.1 Protective	1 Risk	10	100	Heterogeneity: Not a Test for overall effect		(P = 0.)	38)			н 0		0.1 1 Protective Risk	10 1	100

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 suballeles, 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 system⁵². 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 melanocytederived peptide repertoire53. 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 article⁴². 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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