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ORIGINAL PAPER

Comprehensive assessment of the association between genes on JAK-STAT pathway (*IFIH1, TYK2, IL-10*) and systemic lupus erythematosus: a meta-analysis

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Abstract

Previous studies have reported that genes relating to JAK-STAT pathway (*IFIH1, TYK2* and *IL-10*) conferred the susceptibility to SLE. In this study, we performed a meta-analysis (including 43 studies) to evaluate the association between *IFIH1* (9288 patients and 24,040 controls), *TYK2* (4928 patients and 11,536 controls), *IL-10* (3623 patients and 4907 controls) polymorphisms and systemic lupus erythematosus (SLE) in a comprehensive way. We found that *IFIH1* rs1990760_T allele was associated with risk of SLE in overall population under three models (allelic: $P=2.56\times10^{-11}$, OR 1.135, 95% CI 1.094–1.179, dominant: $P=1.8\times10^{-8}$, OR 1.203, 95% CI 1.128–1.284, recessive: $P=2.6\times10^{-7}$, OR 1.163, 95% CI 1.098–1.231). A strong association had been observed between *TYK2* polymorphism rs2304256_C allele and SLE in Europeans ($P=5.82\times10^{-5}$, OR 1.434, 95% CI 1.203–1.710). When coming to overall population, *TYK2* rs2304256_C showed a significant association with SLE under recessive model ($P=8.05\times10^{-3}$, OR 1.314, 95% CI 1.074–1.608). However, the other two SNPs (rs12720270, rs280519) of *TYK2* were not significant. The results also indicated an association between *IL-10* rs1800896_G allele and SLE in Asians under recessive model ($P=4.65\times10^{-3}$, OR 2.623, 95% CI 1.346–5.115), while, *IL-10* rs1800896_G had a trend of association with SLE in European population in dominant model ($P=1.21\times10^{-2}$, OR 1.375, 95% CI 1.072–1.764). In addition, we found *IL-10* rs1800896 GG homozygote might be associated with increased susceptibility to SLE (GG vs AA, $P=4.65\times10^{-3}$, OR 1.539, 95% CI 1.142–2.072). We concluded that *IFIH1* rs1990760_T and *TYK2* rs2304256_C alleles were significantly associated with SLE, and *IL-10* rs1800896 GG homozygote might have an enhancement effect on SLE risk.

Keywords *IFIH1* · *TYK2* · *IL-10* · Meta-analysis · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) was a complex autoimmune disease characterized by pathogenic autoantibody production that could affect multiple organs [1]. The morbidity rate in SLE varied across different races, and it was considered that non-white racial groups were more

Qiong Yin, Liang-Cai Wu and Lu Zheng contributed equally to this work.

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frequently affected, for instance, 31–70/100,000 across China and 200/100,000 in African population, while it was 7–71/100,000 in Europeans [2–4]. Although the pathogenesis was not completely clear, it was generally known that genetic and environmental factors interacting with each other contribute to SLE risk [5]. Previous linkage analyses had identified some regions in genome for SLE, eg:1p13 [6], 1q25.1 [7], 4q24 [8], 19q13.2 [5]; however, linkage analysis could only identify large genomic regions harboring lots of susceptibility genes. The candidate gene association studies had identified some precise susceptibility genes related to SLE, involving *PDCD1* [9], *IRF-5* [1], *FCGR2B* [4], *IL18* [10]. The genome-wide association studies (GWAS), which involved common variations through the entire genome, is a powerful tool to identify SLE-associated genes [7, 8, 11–13].

SLE-associated genes could be classified into three categories: B and T cell function-related genes [14], interferon (IFN) regulatory genes [15], and DNA repair genes [16]. A recent study had revealed that *IFIH1* and *TYK2* might induce the production of interferon [14].

The interferon-induced Helicase C domain 1 (*IFIH1*) gene, localized at chromosome 2p24.3, was a sensitive sensor of dsRNA that triggered IFN-α signaling pathway [14]. Elevated IFN-I was an obvious phenomenon in SLE patients, therefore, interferon regulatory genes were essential in the SLE pathological mechanism [17]. A recent study [18] indicated that *IFIH1* rs1990760 was associated with an increased level of IFN-induced gene expression in SLE patients, in response to a given amount of serum IFN-α. *IFIH1* had been identified to be associated with autoimmune diseases, such as, type I diabetes [19], Graves' disease [20], and psoriasis [21]. Particularly, *IFIH1* was identified as a susceptible gene for type I diabetes in a genome-wide association study [22].

TYK2 was located at chromosome 19p13.2, which was a part of JAK kinase, and phosphorylated and activated by combination of IFNAR and IFN-α [23] and then they signaled through the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway to enhance expression of IFN-stimulated genes [24]. Several genetic studies were performed to analyze the relationship of *TYK2* gene with SLE risk [1, 25–29], but the results were inconclusive. Lee et al. [30] found that *TYK2* rs2304256 had a significant association with SLE in Europeans ($P < 1 \times 10^{-8}$), but not Asians. However, another study showed a significant association between SLE and *TYK2* rs2304256 in Chinese ($P = 1.85 \times 10^{-5}$) [29].

IL-10 was not only a vital immunoregulatory cytokine produced by various immune cells, but also a gene related to B- and T-cells function [31]. *IL-10* is located at the chromosome 1q31–1q32, which was a SLE linkage region [32]. The best-characterized signaling pathway of *IL-10* was the JAK-STAT system, which could induce a series of immune responses using activated B- and T-cell [33]. Several studies have found an association between *IL-10* and SLE in the past few years [31, 34–56], but the results were inconsistent.

A number of studies had tested the relationship between *IFIH1, TYK2, IL-10* and SLE, but as we demonstrated above, the results were inconsistent. Therefore, we performed a comprehensive meta-analysis to evaluate the relationship of *IFIH1* (rs1990760), *TYK2* (rs2304256, rs280519, rs12720270), *IL-10* (rs1800896, rs1800871, rs1800872) and SLE using different association models.

Materials and methods

Identification of eligible studies

To investigate the association between the three genes and SLE risk, we searched relevant articles in PubMed database and Web of Science and China National Knowledge Infrastructure (CNKI) as well as Cochrane and Embase before December 2017, using the following keywords: "*TYK2*", "polymorphism", "*IFIH1*" or "interferon-induced helicase C", "*IL-10*" or "interleukin-10", "SLE" or "systemic lupus erythematosus".

Inclusion and exclusion criteria

The included studies were consistent with following conditions: (a) case/control study design; (b) providing SNP genotype distribution or allele frequency in the paper; (c) providing sample size in the paper; (d) patients were diagnosed through American College of Rheumatology criteria for SLE [57]. Accordingly, the exclusion criteria for the publications were as follows: (a) family study design; (b) repeated or overlapped publications; (c) literature reviews; (d) conference or meeting abstracts.

Data extraction

We collected information including authors, year of publishing, numbers of case and control, ethnicity, and numbers of genotype distribution. If there were no SNP genotype data, we calculated the numbers by the sample size and allele frequency.

Quality assessment

Study quality was evaluated systematically using the Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. The scale assigns a score of zero to nine stars to each article, whereby a greater number of stars indicate a higher quality study. Using this 'star system', each included study was judged on three broad

perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of outcome of interest. Apart from that, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was an guideline for reporting observational studies, we also have applied it to observational studies that we have included in the present study.

Statistical analysis

Pooled ORs and 95% confidence intervals (CIs) were used to evaluate the strength of association between polymorphism and SLE risk for every eligible study. Hardy–Weinberg equilibrium (HWE) was tested in control using Chi square test [58] and it was considered as HWE deviation when P value was less than 0.05 [59]. We performed HWE test for all included studies, and removed studies that were deviated from HWE in controls. Cochran's Q statistics was used to evaluate within- and between-study heterogeneities. And the effect of heterogenicity can be calculated with the following formula: $I^2 = 100\% \times (Q - df)/Q$ [60]. I^2 statistic was used to quantify the extent of heterogenicity, which ranges from 0 to 100%. Mostly, if $I^2 < 25\%$, this indicated that each study was homogeneous, then the fixed model could be applied. When $25\% < I^2 < 75\%$, the heterogenicity between studies could not be ignored. If $I^2 > 75\%$, it evinced that there was high heterogenicity between studies. Apart from I^2 statistic, the P value was also important for test of homogeneity. In our meta-analysis, when $P_{\text{heterogeneity}} > 0.1$, the fixed model would be chosen, otherwise the random model was applied. We carried out sensitivity analysis to evaluate the effect of an individual study on pooled OR. Egger's and Begg's test were used to evaluate the publication bias [61]. The software program STAT12.0 was used in data analysis.

Result

Studies inclusion and characteristics

Figure 1 showed the literature searching process. 548 articles (15 for *IFIH1*, 26 for *TYK2*, 507 for *IL-10*) were found in PubMed database and CNKI, of which 500 studies were excluded by means of reading the title and abstract, therefore, 43 studies were included in our meta-analysis (7 for *IFIH1*, 7 for *TYK2*, 29 for *IL-10*). Characteristics of the included studies were summarized in Table 1. The Newcastle–Ottawa Scale (NOS) used for assessing the quality of studies was also shown in Table 1 and the scores ranged from 4 to 6. No article presented poor quality according to the Newcastle–Ottawa scale. The result of STROBE statement was presented in the TableS1. The STROBE checklist provided guidance on how to report observational research well, but not an instrument to evaluate the quality of observational research [62].

The association between *IFIH1* gene polymorphism and SLE

After testing the HWE deviation, 7 studies including 9288 patients and 24,040 controls were included in the meta-analysis of *IFIH1* rs1990760 polymorphism and SLE. Test of heterogeneity in overall population was not significant ($P_{\text{heterogeneity}} = 0.184$), therefore, the fixed model was applied. In the allelic test, rs1990760 showed a significant association with SLE in overall population (T vs C, OR 1.135, 95% CI 1.094–1.179, $P = 2.56 \times 10^{-11}$, Table 2; Fig. 2a), which reached genome-wide level of significance ($P < 5 \times 10^{-8}$). Stratification analysis by ethnicity demonstrated an association between *IFIH1* rs1990760 and SLE in Europeans (T vs. C, OR 1.148, 95% CI 1.071–1.230, $P = 9.23 \times 10^{-5}$, Table 2; Fig. 2a), but not Asians (T vs. C, OR 1.140, 95% CI 0.972–1.336, $P = 0.107$, Table 2; Fig. 2a). We also tested the recessive and dominant model for the T allele, and the result showed significance in both dominant model and recessive model in overall population (CT + TT vs CC, OR 1.203, 95% CI 1.128–1.284, $P = 1.8 \times 10^{-8}$, Table 2, Fig S1a; TT vs CT + CC, OR 1.163, 95% CI 1.098–1.231, $P = 2.6 \times 10^{-7}$, Table 2, Fig S1b) and in Europeans (CT + TT vs CC, OR 1.233, 95% CI 1.074–1.416, $P = 2.88 \times 10^{-3}$ Table 2, Fig S1a; TT vs CT + CC, OR 1.178, 95% CI 1.070–1.297, $P = 8.38 \times 10^{-4}$, Table 2, Fig S1b). In Brazilians, no association was between the rs1990760 and SLE under allelic model (T vs. C, OR 1.041, 95% CI 0.832–1.302, $P = 0.723$, Table 2; Fig. 2a).

The association between *TYK2* gene polymorphisms and SLE

After testing the HWE deviation, there were 4058 patients and 5985 controls (6 studies). *TYK2* rs2304256_C allele increased SLE risk in Europeans under three models (C vs. A, OR 1.434, 95% CI 1.203–1.710, $P = 5.82 \times 10^{-5}$, Table 3, Fig.S2a), (CC + AC vs. AA, OR 1.599, 95% CI 1.264–2.022, $P = 8.85 \times 10^{-5}$, Table 3; Fig. 2b; CC vs. AC + AA, OR 1.512, 95% CI 1.233–1.855, $P = 7.19 \times 10^{-5}$, Table 3, Fig.S2b). When coming to overall population, *TYK2* rs2304256_C polymorphism showed a significant association with SLE under the recessive model (CC vs AC + AA, OR 1.314, 95% CI 1.074–1.608, $P = 8.05 \times 10^{-3}$, Table 3, Fig.S2b) and a marginal association under the allelic model (C vs A, OR 1.294, 95% CI 1.054–1.589, $P = 0.014$ Table 3, Fig.S2a). However, the C allele of rs2304256 did not confer a significant risk for the development of SLE in Asians under any models in this meta-analysis (Table 3).

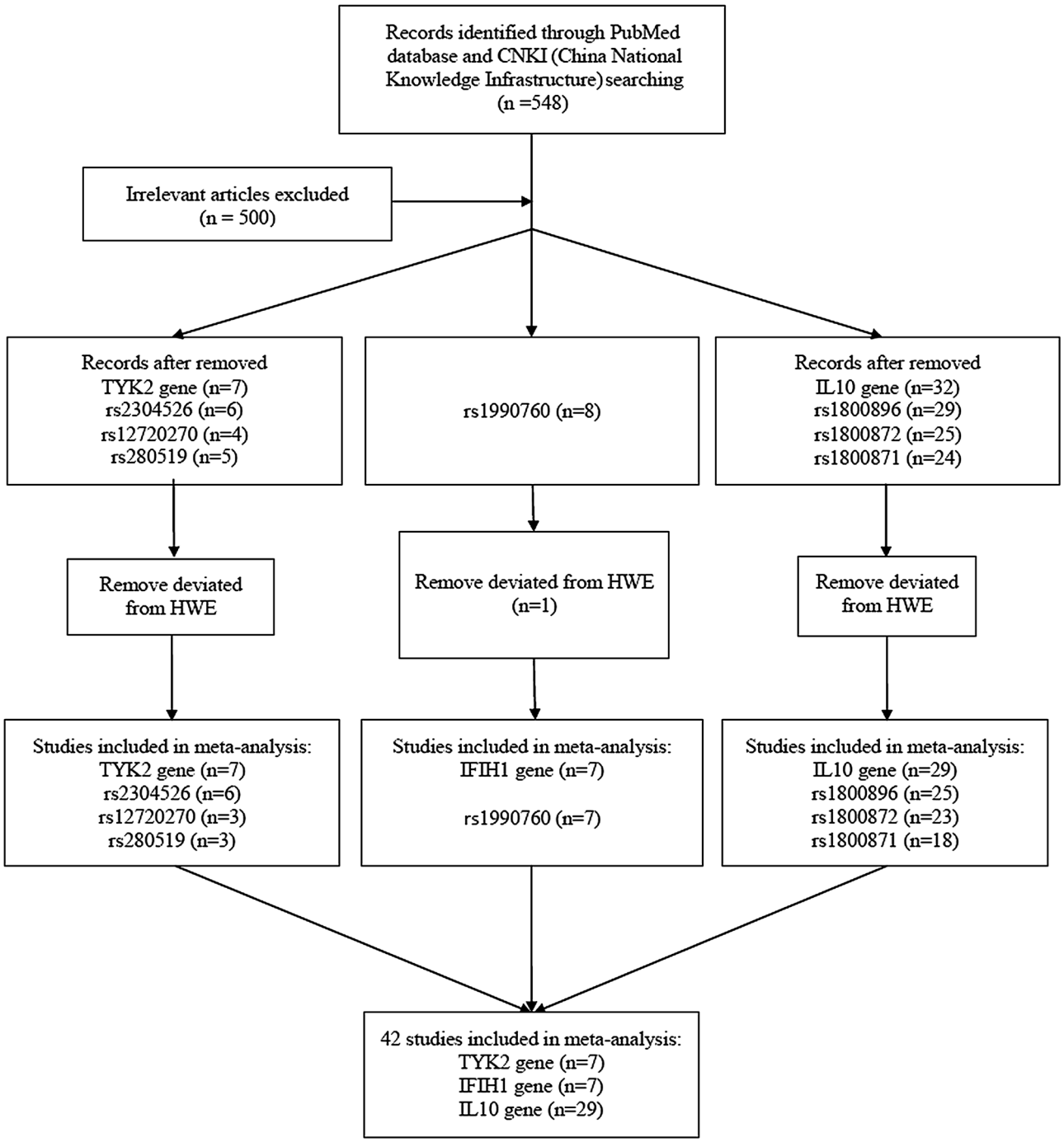


Fig. 1 Flow diagram of literature search

Totally, 1380 patients and 3274 controls (3 studies), and 1608 patients and 8183 controls (3 studies) were recruited for rs12720270 and rs280519 after testing the HWE deviation, respectively. As shown in Table 3, there was no association between rs12720270 and rs280519 polymorphism and SLE under any models in overall population. Stratification analyses by ethnicity were not performed for the two SNPs, because all studies for rs12720270 were from Asian population considering the Hardy–Weinberg equilibrium, and for rs280519, there were only two articles done on Asians and one on Europeans.

Table 1 The characteristics of studies included in our meta-analysis

	Author	Year	Ethnicity	No. of case/ctrl	Genotype (case/ctrl)			HWE	Selection	Comparability	Exposure	Total
IFIH1					CC	CT	TT					
rs1990760	Molineros JE [63]	2013	Africa-Americans	1525/4485	974/3082	489/1272	62/131	Yes	2	2	1	5
			European-Americans	3968/9750	558/1560	1860/4680	1550/3510	Yes	2	2	1	5
	Cunninqhame Graham DS [25]	2011	European	870/5551	114/835	388/2589	343/2025	Yes	2	2	1	5
	Cen H [64]	2013	Asian	877/978	534/637	297/306	46/35	Yes	2	2	1	5
	Wang C [65]	2013	European	1140/2060	148/313	525/981	467/766	Yes	2	1	1	4
	Enevold C [66]	2014	European	142/641	16/107	74/305	52/229	Yes	3	0	1	4
				202/641	22/107	90/305	90/229	Yes	3	0	1	4
	Gono T [67]	2010	Asian	244/268	12/13	90/99	142/156	Yes	2	2	1	5
	Gateval V [6]	2009	American	1129/2991	198/301	550/1683	381/1142	No	2	0	1	3
	Sliva JA [68]	2016	Brazilian	320/307	97/93	163/151	60/63	Yes	2	1	1	4
TYK2					AA	AC	CC					
rs2304256	Li P [69]	2011	Asian	669/2538	230/842	325/1240	114/456	Yes	2	2	1	5
	Tang L [29]	2015	Asian	642/642	367/465	248/160	27/17	Yes	2	2	1	5
	Kyogoku C [27]	2009	Asian	411/467	71/61	180/231	160/175	Yes	2	1	1	4
	Hellquist A [26]	2009	European	277/356	12/34	92/153	173/169	Yes	2	1	1	4
	Suarez-Gestal M [28]	2009	European	1579/1726	86/133	561/694	932/899	Yes	2	1	1	4
	Sigurdsson S [1]	2005	European	480/256	28/26	174/112	278/118	Yes	2	2	1	5
				109/121	5/9	36/15	68/97	No				
					TT	CT	CC					
rs12720270	Li P	2011	Asian	669/2538	207/760	331/1257	131/521	Yes				
	Tang L	2015	Asian	642/642	545/539	95/101	42,768	Yes				
	Kyogoku C	2009	Asian	69/94	13/10	31/50	25/34	Yes				
	Hellquist A	2009	European	277/356	21/28	37/94	200/217	No				
					GG	GA	AA					
rs280519	Li P	2011	Asian	669/2538	283/1049	305/1166	81/323	Yes				
	Tang L	2015	Asian	642/642	183/150	270/256	189/206	No				
	Kyogoku C	2009	Asian	69/94	18/21	33/49	17/24	Yes				
	Cunninqhame Graham DS	2011	European	870/5551	192/1548	434/2666	221/1247	Yes				
IL-10					GG	GA	AA					
rs1800896	Lazarua M [45]	1997	European	76/119	26/31	36/59	14/29	Yes	3	1	1	5
	Chong WP [31]	2004	Asian	554/708	2/0	51/56	501/652	Yes	2	1	1	4
	Guarnizo-Zuccardi P [39]	2007	South American	120/102	14/9	50/42	56/51	Yes	2	1	1	4
	Talaat RM [54]	2015	African	100/119	18/11	42/78	40/30	No	2	1	1	4
	da Silva HD [36]	2014	Mixed	90/100	1/8	81/72	8/20	No	2	1	1	4
	Rianthavorn P [49]	2013	Asian	71/160	1/0	14/21	56/139	Yes	2	1	1	4

Table 1 (continued)

	Author	Year	Ethnicity	No. of case/ctrl	Genotype (case/ctrl)			HWE	Selection	Comparability	Exposure	Total
	Mok CC [47]	1998	Asian	88/83	0/0	7/10	81/73	Yes	2	2	1	5
	Rezaei A [48]	2015	Asian	59/140	2/12	37/75	20/53	No	2	1	1	4
	Khoa PD [44]	2005	Asian	64/57	18/6	31/30	15/21	Yes	2	1	1	4
	Lin YJ [46]	2010	Asian	172/215	0/0	14/21	158/194	Yes	2	1	1	4
	D'Alfonso S [35]	2002	European	205/631	34/100	100/124	21/229	Yes	2	1	1	4
	Crawley E [34]	1999	European	120/274	27/70	65/124	28/80	Yes	2	1	1	4
	Suárez A [53]	2005	European	192/343	37/51	86/158	64/134	Yes	2	2	1	5
	Hrycek A [43]	2005	European	24/36	4/7	14/18	6/11	Yes	2	1	1	4
	Rood MJ [50]	1999	European	92/162	24/50	47/78	21/34	Yes	2	1	1	4
	Rosado S [51]	2008	European	116/151	23/14	55/72	38/65	Yes	3	2	1	6
	Yu HH [56]	2010	Asian	110/138	0/0	9/17	101/121	Yes	2	1	1	4
	Dijstelbloem HM [37]	2002	European	180/163	42/50	94/72	44/41	Yes	2	1	1	4
	Van der Linden MW [55]	2000	Mixed	44/125	9/31	22/64	13/30	Yes	2	1	1	4
	Hirankarn N [42]	2006	Asian	195/159	1/1	24/19	170/139	Yes	2	2	1	5
	Fei GZ [38]	2004	European	52/26	13/8	24/10	15/8	Yes	2	1	1	4
	Sobkowiak A [52]	2009	European	103/300	34/54	45/150	24/96	Yes	2	2	1	5
	Guzowski D [40]	2005	Mixed	51/25	7/4	4/12	25/9	Yes	2	1	1	4
	HEE CS [41]	2008	Asian	44/44	0/1	8/10	36/33	Yes	3	2	1	6
	Shen N [70]	2003	Asian	220/230	11/1	75/21	134/208	Yes	2	1	1	4
	Wang FY [71]	2007	Asian	83/125	7/7	32/46	44/72	Yes	3	2	1	6
	Lan Y [72]	2007	Asian	90/110	0/0	26/18	64/92	Yes	3	2	1	6
	Miteva L [73]	2010	European	157/126	27/17	74/65	56/44	Yes	2	1	1	4
	Zhou H [74]	2007	Asian	137/122	83/99	19/17	35/6	No	3	1	1	5
					CC	CT	TT					
rs1800871	Lazarua M	1997	European	76/119	45/74	27/40	4/5	Yes				
	Chong WP	2004	Asian	554/708	64/47	241/322	249/339	No				
	Guarnizo-Zuccardi P	2007	South American	102/120	56/48	48/50	16/4	No				
	Talaat RM	2015	African	100/119	22/60	70/53	8/6	Yes				
	Rianthavorn P	2013	Asian	71/160	11/10	31/70	29/80	Yes				
	Rezaei A	2015	Asian	58/140	23/71	31/57	4/12	Yes				
	Lin YJ	2010	Asian	172/215	1/10	72/118	99/87	No				
	Crawley E	1999	European	120/274	77/164	33/92	10/18	Yes				
	Suárez A	2005	European	192/343	117/190	59/122	11/31	No				
	Hrycek A	2005	European	24/36	10/19	12/16	2/1	Yes				
	Rood MJ	1999	European	92/162	63/109	16/47	13/6	Yes				
	Rosado S	2008	European	116/151	59/74	50/64	7/13	Yes				

Table 1 (continued)

	Author	Year	Ethnicity	No. of case/ctrl	Genotype (case/ctrl)			HWE	Selection	Comparability	Exposure	Total
	Yu HH	2010	Asian	110/138	12/18	49/64	49/56	Yes				
	Van der Linden MW	2000	Mixed	44/125	27/67	15/49	2/9	Yes				
	Hirankarn N	2006	Asian	195/159	23/13	89/64	83/82	Yes				
	Guzowski D	2005	Mixed	51/25	18/15	24/8	9/1	Yes				
	Lu LY [75]	2005	Asian	136/115	15/11	56/27	65/77	No				
	Sobkowiak A	2009	European	103/300	59/117	35/102	9/21	Yes				
	Mok CC	1998	Asian	88/83	10/9	38/35	40/39	Yes				
	HEE CC	2008	Asian	44/44	7/7	19/21	18/16	Yes				
	Shen N	2003	Asian	220/230	30/22	103/98	87/110	Yes				
	Wang FY	2007	Asian	83/125	13/58	39/54	31/13	Yes				
	Lan Y	2007	Asian	90/110	13/12	44/51	33/47	Yes				
	Zhou H	2007	Asian	137/122	15/9	69/65	53/48	No				
					CC	CA	AA					
rs1800872	Lazarua M	1997	European	76/119	45/74	27/40	4/5	Yes				
	Chong WP	2004	Asian	554/708	64/47	241/322	249/339	No				
	Guarnizo-Zuccardi P	2007	South American	102/120	48/56	50/48	4/16	Yes				
	Rianthavorn P	2013	Asian	71/160	11/10	31/70	29/80	Yes				
	Rezaei A	2015	Asian	58/140	19/71	35/57	4/12	Yes				
	Lin YJ	2010	Asian	172/215	5/32	71/105	96/78	Yes				
	D'Alfonsol S	2002	European	205/631	107/338	82/248	16/45	Yes				
	Crawley E	1999	European	120/274	77/164	33/92	10/18	Yes				
	Suárez A	2005	European	192/343	117/190	59/122	11/31	Yes				
	Hrycek A	2005	European	24/36	10/19	12/16	2/1	Yes				
	Rood MJ	1999	European	92/162	63/109	16/47	13/6	Yes				
	Rosado S	2008	European	116/151	62/74	47/64	7/13	Yes				
	Yu HH	2010	Asian	110/138	12/16	47/61	51/61	Yes				
	Van der Linden MW	2000	Mixed	44/125	27/67	15/49	2/9	Yes				
	Hirankarn N	2006	Asian	195/159	23/13	89/64	83/82	Yes				
	Guzowski D	2005	Mixed	51/25	21/13	21/10	9/2	Yes				
	Mok CC	1998	Asian	88/83	10/9	38/35	40/39	Yes				
	Shen N	2003	Asian	220/230	32/47	103/113	85/70	Yes				
	Wang FY	2007	Asian	83/125	13/58	39/54	31/13	Yes				
	Lan Y	2007	Asian	90/110	13/12	44/51	33/47	Yes				
	Zhou H	2007	Asian	137/122	15/9	69/65	53/48	No				
	Chee Seng HEE	2008	Asian	44/44	7/7	19/21	18/16	Yes				
	Ren XY [76]	2011	Asian	145/80	21/12	56/38	68/30	Yes	3	1	1	5

Table 1 (continued)

Author	Year	Ethnicity	No. of case/ctrl	Genotype (case/ctrl)		HWE	Selection	Comparability	Exposure	Total
Sobkowiak A	2009	European	103/300	59/177	35/102	9/21	Yes			
Lin PW [77]	2007	Asian	119/100	2/15	48/45	66/40	Yes	2	1	1	4

The eleventh to thirteenth columns are scores based on the questions in the NOS scale, whereby a greater number of stars indicate a higher quality study. Selection: evaluation of research population selection (scoring range 0–4); comparability: evaluation of research population comparability (scoring range 0–2); exposure: evaluation of research population exposure (scoring range 0–3)

The association between *IL-10* gene polymorphism and SLE

SNP rs1800896, rs1800871, rs1800872 were regarded as tags of promoter of *IL-10* gene [78, 79]. We recruited 25 studies for *IL-10* rs1800896 polymorphism after testing the HWE deviation, including 3332 patients and 4612 controls. There was a slight association in overall population of three models with rs1800896 (allelic model: Table 4, Fig S3a; recessive model: Table 4; Fig. 2c; dominant model: Table 4, Fig S3b). Under recessive model, the result showed that rs1800896 had a marginal association with Asians (GG vs GA + AA, OR 2.623, 95% CI 1.346–5.115, $P = 4.65 \times 10^{-3}$, Table 4; Fig. 2c), but not Europeans. In the dominant model, we found an association between rs1800896 polymorphism and SLE in Europeans (GG + GA vs AA, OR 1.375, 95% CI 1.072–1.764, $P = 1.21 \times 10^{-2}$, Table 4, Fig S3b), but not in Asians.

We also calculated homozygous OR for genotypes (GG vs. AA) (overall: OR 1.539, 95% CI 1.142–2.072, $P = 4.65 \times 10^{-3}$, Europeans: OR 1.499, 95% CI 1.066–2.106, $P = 1.98 \times 10^{-2}$, Asians: OR 3.032, 95% CI 1.325–6.938, $P = 8.54 \times 10^{-3}$, Fig. 2d), which revealed that GG homozygote may increase the SLE risk. Furthermore, we analyzed the heterozygous OR for genotype GA vs. AA (overall: OR 1.229, 95% CI 0.980–1.541, $P = 0.075$, Europeans: OR 1.343, 95% CI 1.044–1.727, $P = 2.2 \times 10^{-2}$, Asians: OR 1.285, 95% CI 0.857–1.926, $P = 0.226$, Fig S3c).

With respect to *IL-10* rs1800871, 18 articles involving 1685 patients and 2500 controls were included. We included 23 studies for *IL-10* rs1800872, with a total of 2520 patients and 3870 controls. In our meta-analysis, rs1800871 and rs1800872 were not associated with SLE in overall population under any model (Table 4).

Allele frequency of the 3 SNPs in meta-analysis and in the 1000 Genomes Phase3 population

In Table 5, we presented a clear distinction of allele frequencies in different ethnicities in our meta-analysis and 1000 Genomes of the 3 SNPs. In consideration of the sample size and population, the allele frequencies of *IL-10* rs1800896, and *TYK2* rs2304256 in this meta-analysis were consistent with the allele frequencies in 1000 Genome project AMR (Ad Mixed American), EUR (European ancestry), EAS (East Asian ancestry), respectively; however, there was discrepancy between the allele frequencies of *IFIH1* rs1990760 and 1000 Genomes Project (Table 4).

Publication bias and sensitivity analysis

Funnel plot and Bgger's linear regression test has been used to detect the publication bias. We found no publication bias

Table 2 Meta-analysis of the association between *IFIH1* polymorphism and SLE risk

Population	No. of studies	T vs. C allele		TT + CT vs. CC (dominant model)		TT vs. CT + CC (recessive model)		Test of heterogeneity
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	*P*
Overall	7	1.135 (1.094–1.179)	2.56×10^{-11}	1.203 (1.128–1.284)	1.80×10^{-8}	1.163 (1.098–1.231)	2.6×10^{-7}	0.554
Asian	2	1.140 (0.972–1.336)	0.107	1.188 (0.988–1.427)	0.067	1.190 (0.807–1.756)	0.379	0.280
European	3	1.148 (1.071–1.230)	9.23×10^{-5}	1.233 (1.074–1.416)	2.88×10^{-3}	1.178 (1.070–1.297)	8.38×10^{-4}	0.485
European-Americans	1	1.111 (1.053–1.172)	1.23×10^{-4}	1.243 (1.100–1.404)	4.83×10^{-4}	1.409 (1.035–1.916)	2.93×10^{-2}	–
Africa-Americans	1	1.138 (1.096–1.082)	1.91×10^{-4}	1.164 (1.048–1.292)	4.37×10^{-3}	1.140 (1.056–1.230)	7.52×10^{-4}	–
Brazilian	2	1.041 (0.832–1.302)	0.723	–	–	–	–	–

OR odd ratio, *95% CI* confidence interval, *P* value for the test of association, P_h *P* value for heterogeneity analysis

in our meta-analysis under allele genetic model (*IFIH1* rs1990760, $P=0.858$; *TYK2* rs2304256, $P=0.260$; *TYK2* rs12720270, $P=0.296$; *TYK2* rs280519, $P=1$; *IL-10* rs1800896, $P=0.154$; *IL-10* rs1800871, $P=0.112$; *IL-10* rs1800872, $P=0.526$, Fig.S4). We also performed sensitivity analysis to evaluate the influence of an individual study on pooled OR (Fig. S5), and the pooled OR was not substantially altered, when any one study was removed.

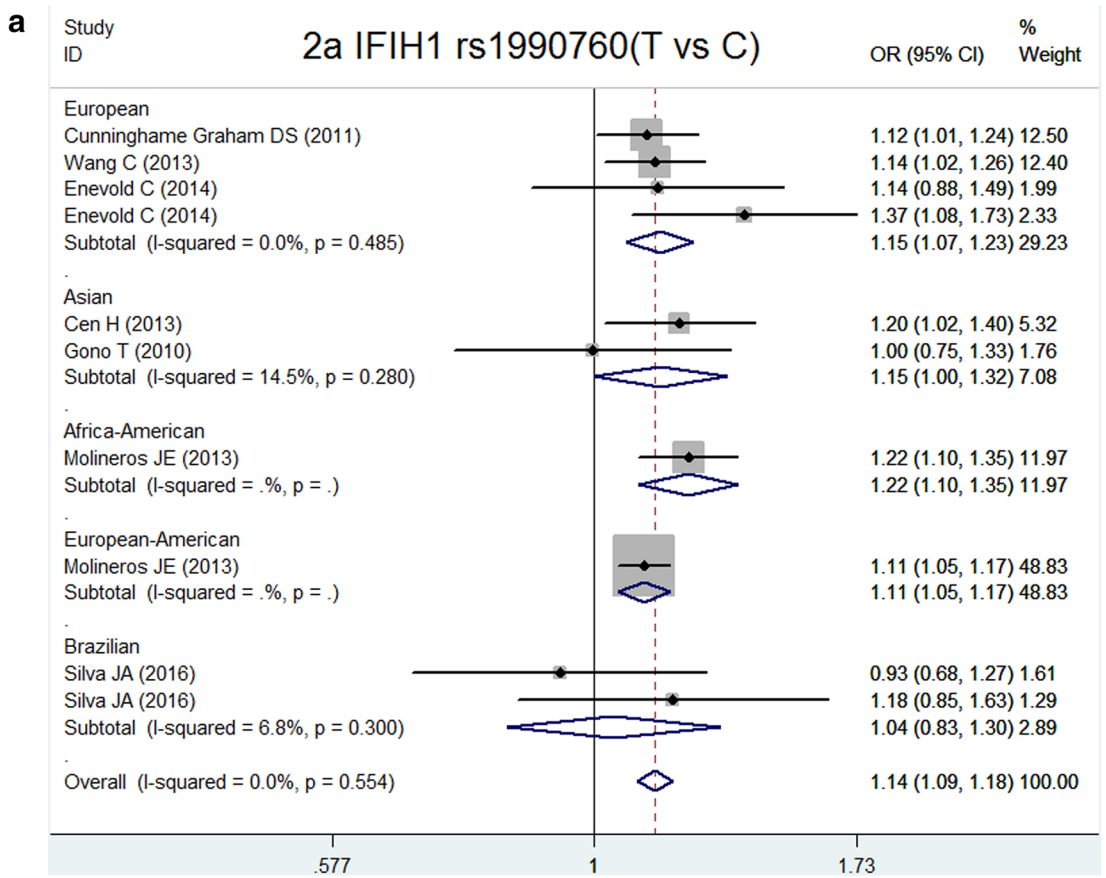
Discussion

JAK-STAT pathway was important for inflammatory conditions and autoimmune diseases including SLE [80], and the genes *IFIH1, TYK2, IL-10* that were related to this pathway [17]. In the present meta-analysis, 43 studies were recruited to evaluate the association between *IFIH1, TYK2, IL-10* and SLE risk. The result provided evidence that *IFIH1* rs1990760, *TYK2* rs2304256 and *IL-10* rs1800896 were associated with SLE. In addition, ethnicity-specific meta-analysis indicated an association between the SNPs and SLE in Europeans but not in Asians; however, ethnicity-stratified results should be interpreted carefully.

As we all know, the progress of combination of IL-10 and its receptor could be divided into two steps. First, IL-10 binds to the IL-10R1. Then, the complex of IL-10/IL-10R1 changed the cytokine conformation through the molecular interaction. Under this condition, the complex could create a binding site which was used for combination of IL-10R2 [81–83]. Subsequently, two members of the Janus kinase family, Janus kinase 1 (on IL-10R1) and tyrosine kinase 2 (TYK2) (on IL-10R2) would bind with the IL-10/IL-10R complex, then creating docking sites for the transcription factor STAT3. Type-I IFN receptors which were found on all nucleated cells can be phosphorylated by *TYK2*, meanwhile, a report demonstrated that *IFIH1* can increase IFN-α production [84].

IFIH1 rs1990760 was associated with increasing IFN-α level in SLE patients [14, 17]. And IFN-α binding to IFNAR would activate JAK-STAT pathway to induce corresponding gene transcription. There was one GWAS study [85] investigating SNP rs1990760 and SLE susceptibility in European, reaching the genome-wide significance ($P=4\times10^{-8}$). Our study also illustrated that T allele of *IFIH1* rs1990760 apparently increased the risk of SLE, but its effect was diverse in different ethnicities. We validated the association between rs1990760 and SLE in overall population and Europeans. These results were also consistent with the previous meta-analysis conducted by the Cen et al., which indicated that rs1990760 had a significant association with SLE risk in Europeans (overall: $P=3.18\times10^{-5}$, European: $P=1.96\times10^{-5}$) [86]. Simultaneously, it was worth mentioning that the study by Gateva et al. [34] was removed from our study due to inconsistency with Hardy–Weinberg equilibrium ($P<0.001$), while it was included in the meta-analysis conducted by the Cen et al. [86]. In terms of the other meta-analysis produced by Silva [68], it also showed *IFIH1* rs1990760 was associated with SLE (overall: $P=0.0266$).

No association was found in our study performed on Asians; however, only two articles were included in the meta-analysis (1120 patients and 1246 controls), and further assessment is needed to clarify the relationship between rs1990760 polymorphism and SLE risk in Asians. Furthermore, the frequency of T allele is very different between Europeans and Asians in 1000 Genomes Phase3 (0.61 in European vs. 0.19 in Asians) (Table 5). Although the frequency of T allele was common in Asians, it was much lower than in Europeans. The discrepancy of T allele



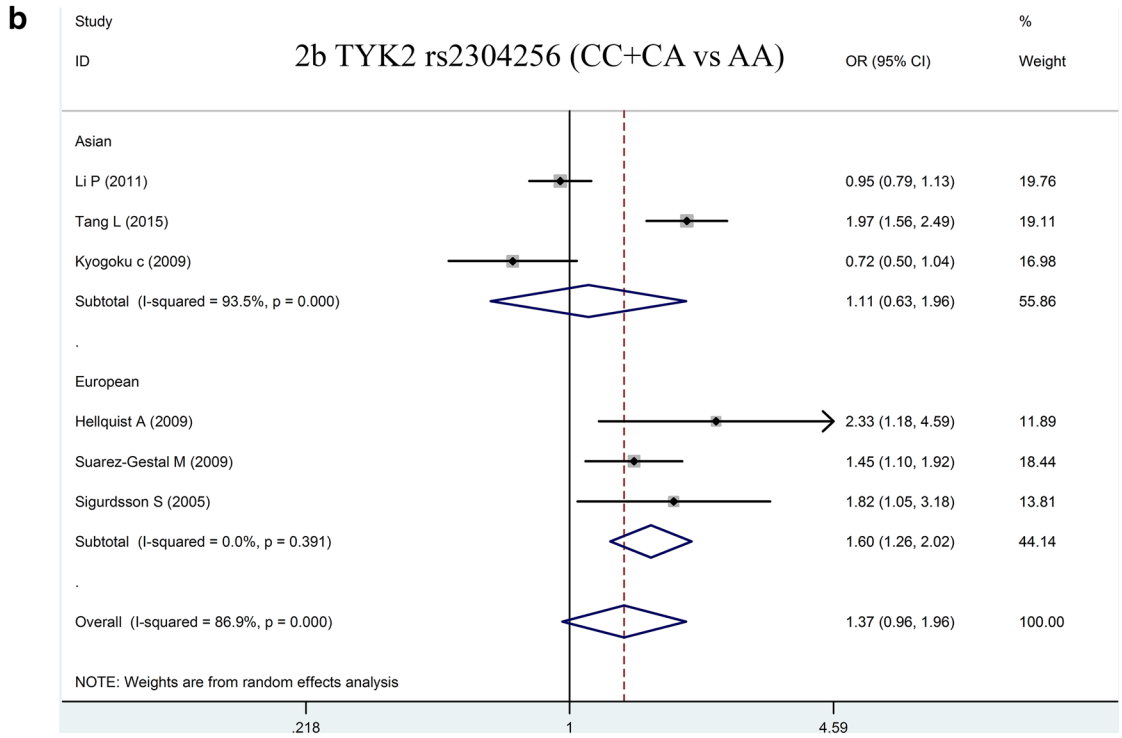


Fig. 2 **a** Forest plot for meta-analysis of *IFIH1* rs1990760 and SLE risk (T vs. C). **b** Forest plot for meta-analysis of *TYK2* rs2304256 and SLE risk (AC/CC vs. AA). **c** Forest plot for meta-analysis of *IL-10* rs1800896 and SLE risk (GG vs. GA/AA). **d** Forest plot for meta-analysis of *IL-10* rs1800896 and SLE risk (GG vs. AA)

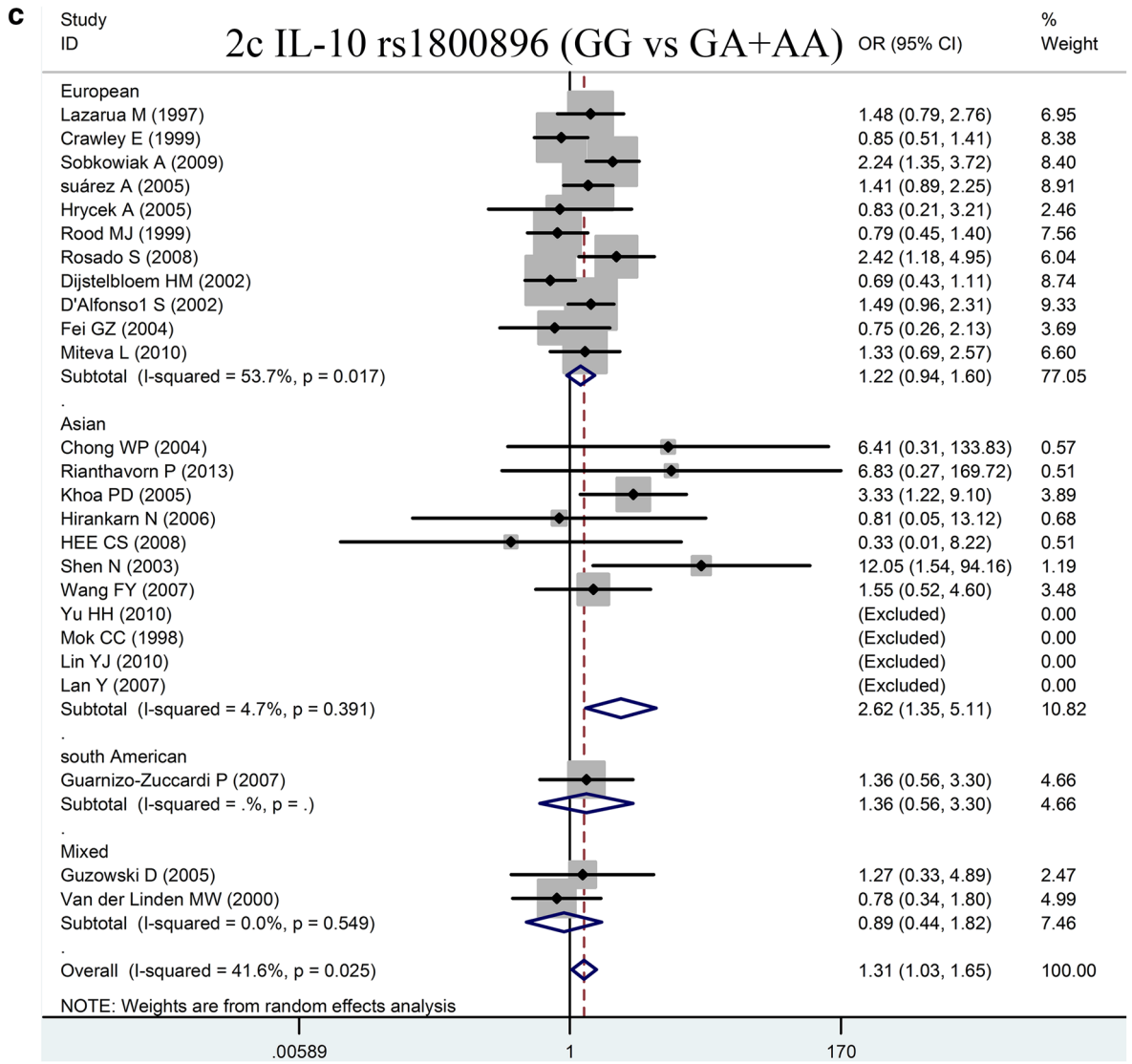


Fig. 2 (continued)

frequency might be the cause of the inconsistent result between the two populations.

Overproduction of the IL-10-receptor complex would lead to more autoantibodies that could damage organs and tissues [78]. Three SNPs (rs1800896, rs1800871, rs1800872) were found in the promoter region of *IL-10* gene. An association was identified between *IL-10* rs1800896 and SLE risk in overall population under allelic and recessive model. To be specific, the previous meta-analysis, including 1788 patients and 2673 controls by Zhou et al., found a trend of association between rs1800896 and SLE risk in the overall population under the allelic model (allelic: OR 1.125, $P = 0.054$) [32], after carefully comparing our study and Zhou et al., we found that we included four additional articles [70–72, 74] of Chinese dataset, and expanded the sample size by approximately 1.8 times, which might have had an effect on the results.

In the subgroup analysis, under the allelic model, we have indicated a suggestive association between rs1800896 and SLE risk in Europeans, but not in Asians. Our result was consistent with other studies [31, 41, 42, 47, 49, 56], which showed rs1800896_G allele did not confer the risk of SLE in Asian. For further exploring the relationship between the rs1800896 polymorphism and SLE risk in Asians, we assessed the association model. We suggested that GG homozygote might make a contribution to increasing the risk of SLE. Besides, it is noteworthy that the frequency of G allele has shown a distinct difference betweens Asian and Europeans in the 1000 Genomes Phase3 (0.052 in Asians vs. 0.453 in Europeans). The frequency of G allele in Asians was low, and a larger sample size was needed to investigate

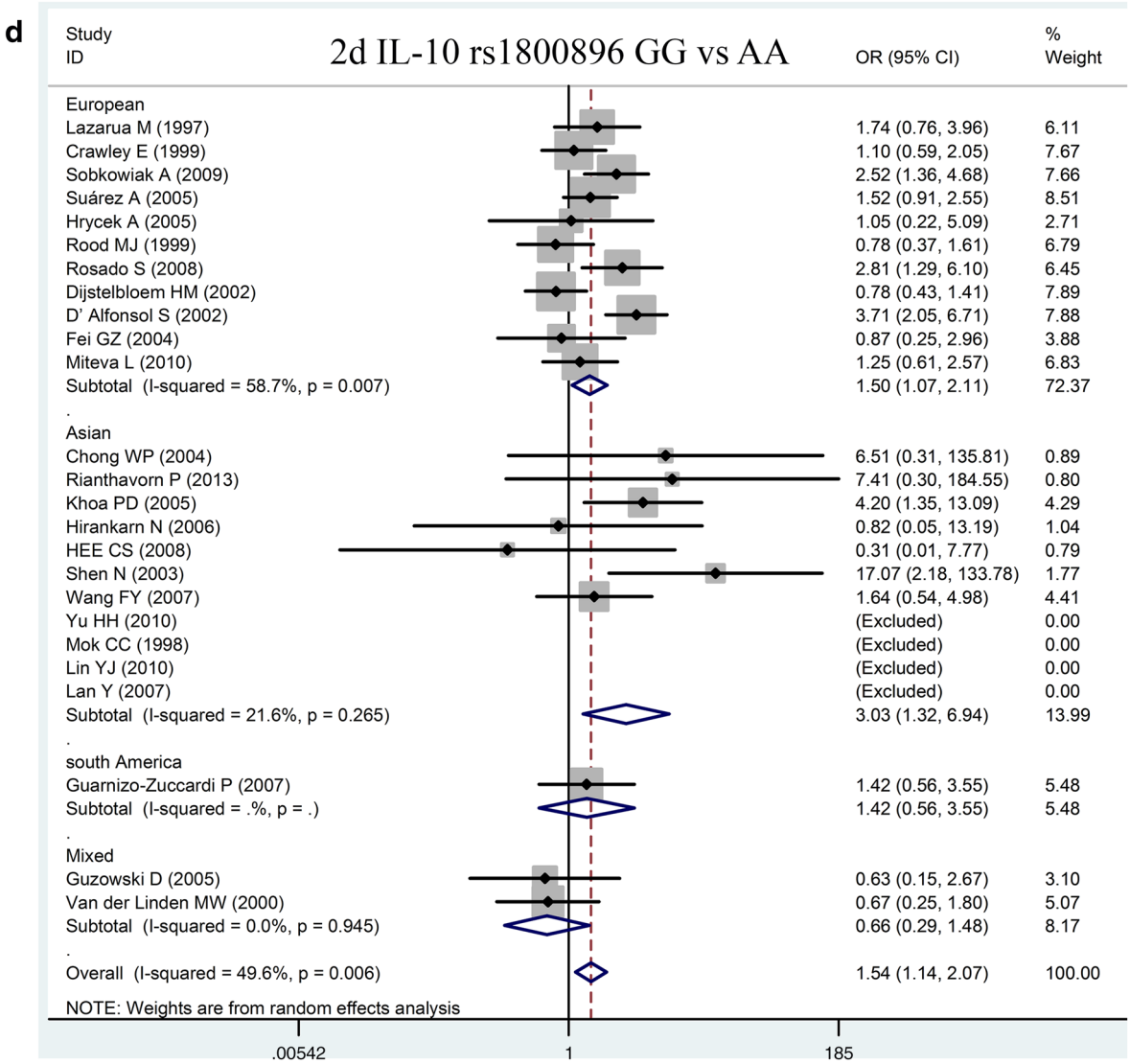


Fig. 2 (continued)

the association between rs1800896_G allele and SLE susceptibility in Asians.

In the previous studies, no association was found between the rs1800871 and SLE risk in Asians [41, 42, 47], which was consistent with our results. But, the study by Song et al. reported an trend of association between rs1800871 and SLE in Asians ($P = 0.027$) [87], after checking carefully, we found that two studies (Lu et al. [75] and Chong et al. [31]), that deviated from HWE, were excluded in our meta-analysis, furthermore, we included three newly published articles [48, 49, 56] in our analysis.

In the JAK-STAT pathway, the combination of IL-10 and IL-10R complex was very important, and it should be noted that TYK2 focused on the tetrameric IL-10 receptor, than creating docking sites for the transcription factor STAT3 [88]. We preformed a meta-analysis to identify the association between *TYK2* rs2304256, rs12720270, rs280519 polymorphisms and SLE, respectively. In terms of *TYK2* rs2304256, a genetic association between rs2304256 and SLE was significantly detected in Europeans [1, 25, 26, 28], but not in Asians [27, 69]. Simultaneously, the previous meta-analysis [30] also reported similar results. These phenomena were consistent with the recent GWAS study [85] which demonstrated a strong association between rs2304256 and SLE ($P = 2.43 \times 10^{-12}$) in Europeans. To identify the relationship between rs2304256 and SLE risk in different ethnicities, we conducted population stratification analyses (Europeans and Asians). A significant association was found in Europeans ($P < 0.0001$), but not in Asians. Though we found no association between the rs2304256 and SLE in Asians, the ethnicity-specific association should be interpreted cautiously because only three articles for Asian

Table 3 Meta-analysis of the association between *TYK2* polymorphism and SLE risk

Polymorphism	Population	No. of studies	A vs. B allele		AA + AB vs. AA (dominant model)		AA vs. AB + BB (recessive model)		Test of heterogeneity
			OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	*P*
rs2304256	Overall	6	1.294 (1.054–1.589)	0.014	1.370 (0.959–1.958)	0.084	1.314 (1.074–1.608)	8.05×10^{-3}	0.000
	Asian	3	1.154 (0.806–1.653)	0.418	1.115 (0.634–1.961)	0.704	1.044 (0.846–1.289)	0.689	0.000
	European	3	1.434 (1.203–1.710)	5.82×10^{-5}	1.599 (1.264–2.022)	8.85×10^{-5}	1.512 (1.233–1.855)	7.19×10^{-5}	0.092
rs12720270	Overall	3	1.052 (0.944–1.172)	0.363	1.054 (0.861–1.290)	0.610	1.075 (0.920–1.255)	0.363	0.854
	Asian	3	1.052 (0.944–1.172)	0.363	1.054 (0.861–1.290)	0.610	1.075 (0.920–1.255)	0.363	0.854
rs280519	Overall	3	1.055 (0.879–1.267)	0.562	1.107 (0.965–1.270)	0.575	1.089 (0.808–1.468)	0.147	0.023
	Asian	2	0.962 (0.852–1.086)	0.529	0.948 (0.742–1.210)	0.562	0.951 (0.804–1.125)	0.667	0.803
	European	1	1.196 (1.079–1.325)	6.26×10^{-4}	1.193 (1.011–1.408)	6.04×10^{-4}	1.350 (1.137–1.602)	0.037	–

OR odd ratio, *95% CI* confidence interval, *P* value for the test of association, P_{hetero} *P* value for heterogeneity analysis
SNP rs2304256 A vs. B (C vs. A), rs12720270 A vs. B (T vs. C), rs280519 A vs. B (A vs. G)

Table 4 Meta-analysis of the association between *IL-10* polymorphism and SLE risk

Polymorphism	Population	No. of studies	A vs. B allele		AA + AB vs. AA (dominant model)		AA vs. AB + BB (recessive model)		Test of heterogeneity
			OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	*P*
rs1800896	Overall	25	1.211 (1.028–1.427)	0.021	1.269 (1.013–1.590)	0.038	1.308 (1.035–1.653)	0.024	0.000
	Asian	11	1.329 (0.903–1.954)	0.150	1.335 (0.872–2.042)	0.184	2.623 (1.346–5.115)	4.65×10^{-3}	0.000
	European	11	1.211 (1.028–1.427)	0.022	1.375 (1.072–1.764)	0.012	1.224 (0.938–1.596)	0.136	0.007
	South American	1	1.156 (0.771–1.732)	0.484	1.143 (0.674–1.939)	0.617	1.365 (0.565–3.299)	0.490	–
	Mixed	2	0.705 (0.451–1.102)	0.126	0.462 (0.157–1.364)	0.162	0.892 (0.438–1.818)	0.757	0.002
rs1800871	Overall	18	1.128 (0.923–1.377)	0.238	1.091 (0.837–1.421)	0.522	1.149 (0.872–1.516)	0.322	0.000
	Asian	9	1.037 (0.755–1.424)	0.818	1.021 (0.621–1.780)	0.936	1.008 (0.702–1.447)	0.968	0.000
	European	6	1.097 (0.921–1.306)	0.298	0.986 (0.794–1.224)	0.897	1.463 (0.864–2.479)	0.156	0.729
	Mixed	2	1.371 (0.398–4.723)	0.617	1.422 (0.349–5.787)	0.624	1.534 (0.198–11.881)	0.682	0.012
	Africa	1	2.008 (1.346–2.994)	6.26×10^{-4}	13.22 (1.646–106.167)	0.015	1.398 (0.938–2.082)	0.099	–
rs1800872	Overall	23	1.112 (0.939–1.316)	0.219	1.106 (0.872–1.403)	0.407	1.205 (0.940–1.545)	0.142	0.000
	Asian	12	1.211 (0.912–1.610)	0.187	1.272 (0.749–2.163)	0.373	1.289 (0.943–1.762)	0.112	0.000
	European	8	0.988 (0.863–1.131)	0.865	0.939 (0.800–1.103)	0.447	1.197 (0.793–1.805)	0.390	0.377
	Mixed	2	1.056 (0.508–2.195)	0.881	0.984 (0.477–2.033)	0.968	1.215 (0.311–4.743)	0.779	0.117
	South American	1	0.795 (0.530–1.192)	0.267	0.984 (0.770–1.246)	0.952	0.265 (0.086–0.821)	0.021	–

OR odd ratio, *95% CI* confidence interval, *P* value for the test of association, P_{hetero} *P* value for heterogeneity analysis
SNP rs1800896 A vs. B (G vs. A), rs1800871 A vs. B (T vs. C), rs1800872 A vs. B (A vs. C)

Table 5 The allele frequency comparison between the meta-analysis and 1000 Genomes Project

Polymorphism	Population	Meta-analysis (alleles' frequencies)				1000 Genomes (alleles' frequencies)	
		Case		Ctrl			
IFIH1 rs1990760		T	C	T	C	T	C
	European	0.640	0.360	0.607	0.393	0.610 (EUR)	0.390 (EUR)
	Asian	0.340	0.660	0.316	0.684	0.190 (EAS)	0.810 (EAS)
	European-Americans	0.625	0.375	0.600	0.400	0.610 (EUR)	0.390 (EUR)
	African-Americans	0.201	0.799	0.171	0.829	0.130 (AFR)	0.870 (AFR)
	All	0.521	0.479	0.509	0.491	0.360 (All)	0.640 (All)
TYK2 rs2304256		C	A	C	A	C	A
	European	0.769	0.231	0.712	0.288	0.738 (EUR)	0.262 (EUR)
	Asian	0.393	0.607	0.401	0.599	0.476 (EAS)	0.524 (EAS)
	All	0.610	0.390	0.523	0.477	0.734 (All)	0.266 (All)
IL-10 rs1800896		G	A	G	A	G	A
	European	0.484	0.516	0.432	0.568	0.453 (EUR)	0.547 (EUR)
	Asian	0.109	0.890	0.074	0.926	0.052 (EAS)	0.948 (EAS)
	South American	0.325	0.675	0.294	0.706	0.295 (AMR)	0.705 (AMR)
	Mixed	0.363	0.638	0.487	0.513		
	All	0.274	0.726	0.273	0.727	0.272 (All)	0.728 (All)

population were included in our study. According to the data from 1000 Genomes Phase3, the frequency of C allele was almost threefold than A allele in Europeans (C: 0.738, A: 0.262), while the frequency of the two alleles had no big difference in Asians. The discrepancy of frequency led to the difference of results; therefore, a more larger sample size is needed to investigate the relationship between rs2304256_C allele and SLE susceptibility in Asians. In our study, *TYK2* rs12720270 and *TKY2* rs280519 did not confer a significant risk for the development of SLE in any of the racial subgroups.

The current meta-analysis had some inevitable limitations to be taken into account. On the one hand, although our overall sample size was large, the participant number in the specific ethnic population was relatively small, with the smallest sample size of 738 patients and 2632 controls [43]. On the other hand, it was universally acknowledged that the mechanism of SLE was sophisticated. A more precise analysis could be performed because of potential confounding factors such as gene–gene and gene–environment interaction, and other life style factors.

In summary, *IFIH1* rs1990760_T and *TYK2* rs2304256_C alleles had a significant association with SLE susceptibility in Europeans, but not in Asians; however, the ethnicity-specific association should be interpreted cautiously because of the different sample sizes in different ethnicities. For *IL-10* rs1800896, GG homozygous might contribute to SLE in Asians. Considering the limited samples in Africans and African-Americans in this analysis, further studies are still required in a larger number of samples and diverse ethnic populations.

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Compliance with ethical standards

Conflict of interest The authors have no competing interests that might be perceived to influence the results and/or discussion reported in this paper. This study re-analyzed the previous published data, therefore, this study did not involve origin human participants.

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