Association of vitamin D receptor gene polymorphisms with systemic lupus erythematosus: a meta-analysis

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Abstract

Objectives

Vitamin D receptor gene polymorphisms has been shown to be associated with systemic lupus erythematosus (SLE). Several studies have been published which have investigated the association between VDR gene polymorphisms with SLE risk, but the results have been inconclusive. The study was designed to investigate whether the vitamin D receptor gene polymorphisms are associated with the risk of SLE.

Methods

A meta-analysis was conducted on associations between the vitamin D receptor gene polymorphisms and SLE using (1) allele contrast and (2) the recessive, (3) the dominant, and (4) the additive models.

Results

A total of 11 case–control studies of 1683 patients and 1883 unrelated healthy individuals were included. The results of meta-analysis indicated that the BsmI and FokI polymorphisms are associated with increased risk of SLE. The overall ORs are 2.14 [95%CI (1.20-3.82), p=0.01] (BB + Bb vs. bb) and 1.75 [95%CI(1.03-2.97), P=0.04](FF + Ff vs. ff), respectively, while the ApaI and TaqI polymorphism were not associated. In subgroup analysis by ethnicity, the increased risk of SLE remained in the Asian subgroup for the BsmI and FokI polymorphism, whereas no significant association was found in other populations for other polymorphisms.

Conclusions

The current study suggested that the BsmI and FokI polymorphism are associated with increased risk of SLE, especially in the Asian population, but further studies are needed to confirm our results.

Key words

vitamin D receptor, gene polymorphisms, systemic lupus erythematosus, meta-analysis

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Received on June 8, 2013; accepted in revised form on October 9, 2013.

Competing interests: none declared.

Introduction

Systemic lupus erythematosus (SLE) is a prototypic polygenic autoimmune disease with a diverse array of clinical manifestations in multiple organs. Which is contributed by an aberrant autoimmune response, heritable, hormonal, and environmental factors (1). It is characterised by the formation and deposition of immune complexes autoantibody causing tissue and organ injury (2). The estimated incidence ranges from 20 to 150 individuals per 100,000 population without racial difference worldwide (1). The etiology and pathogenetic mechanisms of SLE are still unclear.

Genetic factors are known to play an important role in the disease, many studies have revealed the important influences of genetic epidemiologic on SLE. The immunologically relevant genes, including certain major histocompatibility complex (MHC) loci, Fcγreceptor, and cytokines are well studied (3).

Recently, complex cytokines networks including type-1 T-helper cell (Th1) and Th2 have been studied and revealed that they played an important role in the pathogenesis of SLE (4). It is reported that 1a, 25-dihydroxyvitamin D3 (1, $25(OH)_2D3$) exerts many of its actions through interaction with a specific intracellular receptor termed as the vitamin D3 receptor (VDR). It inhibited interferon (IFNγ) secretion by Th1 cells in a dose-dependent manner (5). It also inhibits the accumulation of mRNA for interleukin (IL), and granulocyte-macrophage colony-stimulating factor (GM-CSF) and negatively regulates IL12 production by down regulation of nuclear factor-kappa (NF-κB) activation (6). The VDR gene is located on chromosome 12q13.11 (7), there are four polymorphisms, BsmI, ApaI (both in intron 8), TaqI (in exon 9), and FokI (located in the start codon) have been identified (8, 9).

Previous research demonstrated that VDR is associated with regulation of calcium homeostasis but also in the immune system (10, 11). To date, several studies have been published which have investigated the association between VDR gene polymorphisms with SLE risk but the results have been inconclusive (2, 12-16). This disparity may be small sample sizes, low statistical power, and/or clinical heterogeneity. A meta-analysis of an association between VDR polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus has been reported (17), but did not include the data from a number of studies published in the past few years.

The aim of the present study was to determine whether the VDR gene polymorphisms of VDR confer susceptibility to SLE by meta-analysing all the available data on published articles.

Methods

Data sources and search strategy

We performed a search to identify the studies examined the associations between VDR polymorphisms and SLE .Literature were identified by searching MEDLINE via Ovid, EMBASE, PubMed, Google scholar, China National Knowledge Infrastructure (CNKI) database and the Wanfang Database. The last updated search was performed on April 1st, 2013. The searching terms were ''vitamin D receptor gene'', ''VDR'', ''polymorphism'' and ''systemic lupus erythematosus''. The search was carried out without restriction on language, but was limited to studies that had been conducted on human subjects. The included studies met the following criteria: (i) evaluated VDR gene polymorphism and SLE risk; (ii) case–control studies; (iii) supplied the number of individual genotypes in SLE cases and controls; and (iv) indicated that the distribution of genotypes in cases and controls were available for estimating odds ratio (OR) with 95% confidence interval (CI).

Data extraction

Two authors independently extracted the information from all eligible publications using standard data extraction forms. Disagreement was resolved by discussion between the two authors, or the consultation with a third reviewer. The standardised data form was used for data collection, including: first author, year of publication, country of origin, ethnicity of the study population definition of cases, source of controls, genotyping methods, total number of

cases and controls, genotype distribution in cases and controls.

Evaluation of publication bias

Funnel plots are often used to detect publication bias. In order to measure the including individual study size or precision of the estimated intervention effect, we evaluated publication bias using funnel plots generated within RevMan software, which measures funnel plot asymmetry using a natural logarithm scale of odds ratios (ORs).

Evaluations of statistical associations

We performed meta-analysis on: (1) allelic contrast, (2) recessive, (3) dominant, and (4) additive models. Point estimates of risks, ORs, and 95% confidence intervals (CI) were estimated for each study. We also assessed within- and between-study variations and heterogeneities using Cochran's Q-statistic. Heterogeneity was analysed using a chi squared test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (18). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity. The fixed effects model assumes that a genetic factor has a similar effect on SLE susceptibility across all studies investigated, and that observed variations among studies are caused by chance alone. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance. A random-effects model was used if the studies exhibited heterogeneity (I^2 values >30%); otherwise, the fixed-effects model was selected. To evaluate the ethnicity-specific effects, subgroup analysis was performed by ethnicity. Asymmetry funnel plots were used to assess potential publication bias. Hardy-Weinberg equilibrium (HWE) was tested by Pearson's v2 test. All statistical analyses were performed by using the Revman 5.2 software.

Results

Descriptions of studies included in the meta-analysis

Figure 1 shows the selection process of our study. There are 11 relevant studies (8 Asian, 2 European and 1 Latino population studies) on VDR polymorphisms in SLE met our inclusion criteria, eight studies examined the VDR BsmI polymorphism, five studies examined FokI polymorphism, two studies examined ApaI polymorphism, only one study examined the TaqI polymorphism of VDR gene in SLE, Ethnicity-specific meta-analysis in Asian, European and Latin populations was also performed in our study. The characteristics of each case-control study are listed in Table I. Genotype and allele distributions for each case-control study are shown in Table II.

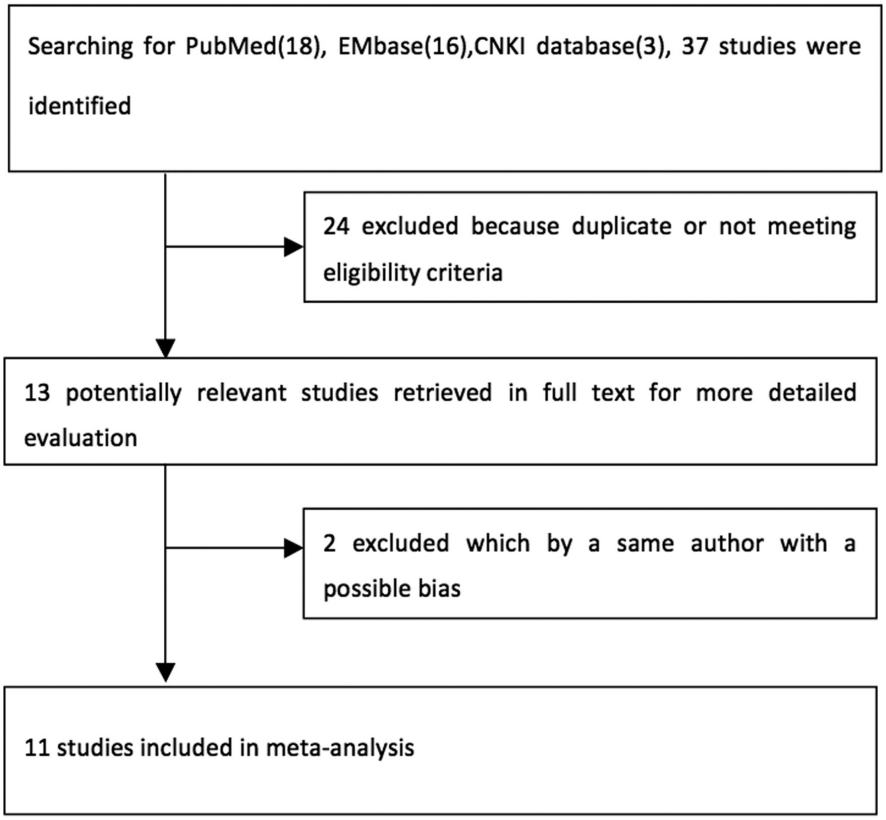

Fig. 1. Flow diagram of included/excluded studies.

Methodological quality of included studies

– Meta-analysis of the VDR BsmI polymorphisms and SLE susceptibility

A total of 1298 SLE cases and 1563 controls in 8 case-control studies were included in the meta-analysis for the relationship between the BsmI polymorphism and the risk of SLE, six case-control studies were from Asians, 1 from European and 1 from Latino, there showed significant association between the BsmI polymorphism and SLE risk (OR=2.14, 95%CI=1.20-3.82, p=0.01 for BB + Bb *vs*. bb) (Fig. 1). In the subgroup meta-analysis by ethnicity, significantly increased risks were found among Asians (OR=2.86, 95%CI=1.35-6.06, p=0.006) but not in Europeans(OR=0.91, 95%CI=0.67–1.23, p=0.55) or Latinos (OR=1.15, 95%CI=0.72–0.86, p=0.54) BB genotype *vs*. bb genotype also showed significant association with SLE, while BB genotype *vs*. bb + Bb genotype and B allies did not show statistical association with SLE, Thus, the Asian variant allele carriers (BB + Bb) may have a higher risk of SLE than European and Latino populations, A summary of the results of other genetic comparisons is shown in Table III.

– Meta-analysis of the VDR FokI polymorphisms and SLE susceptibility

A total of 838 SLE cases and 1066 controls in 5 case-control studies were included in the meta-analysis on the relationship between the FokI polymorphism and the risk of SLE (Table I). 2 case-control studies were from

Table I. Characteristics of the studies included in the meta-analysis.

Author	Year	Country	Ethnicity	Cases/controls	Genotype method	Polymorphism
Yoshio Ozaki *et al*.	2000	Japan	Asian	58/87	PCR–RELP	BsmI
C-M Huang *et al*.	2001	Taiwan	Asian	52/90	PCR–RELP	FokI
C-M Huang *et al*.	2002	Taiwan	Asian	47/90	PCR–RELP	BsmI
Wilaiporn Sakulpipatsin *et al*.	2006	Thailand	Asian	101/194	PCR–RELP	BsmI
Mahnaz Abbasi *et al*.	2010	Iran	Asian	60/45	PCR–RELP	BsmI
X-Y Luo *et al*.	2011	China	Asian	271/130	PCR–RELP	FokI
X-Y Luo *et al*.	2011	China	Asian	242/162	PCR–RELP	BsmI
X-Y Luo *et al*.	2012	China	Asian	337/239	PCR–RELP	ApaI BsmI
OA Monticielo *et al*.	2012	Brazil	Latino	195/201	PCR–RELP	BsmI FokI
Adrianna Mostowska *et al*.	2013	Polish	Europe	258/545	PCR–RELP	ApaI BsmI, FokI, and TaqI
Jaroslaw Bogaczewicz *et al*.	2013	Polish	Europe	62/100	PCR–RELP	FokI

Table II. Distribution of VDR genotype and allele among SLE patients and control.

Author	Case			Control			Case		Control		HWE
	bb	Bb	BB	bb	Bb	BB	b	B	b	B	
Yoshio Ozaki *et al*.	24	25	9	72	10	5	73	43	154	20	YES
C-M Huang *et al*.	12	33	2	78	9	3	57	37	165	15	YES
W Sakulpipatsin *et al*.	77	22	2	161	31	2	176	26	353	35	YES
Mahnaz Abbasi *et al*.	10	36	14	9	21	15	56	64	39	51	YES
OA Monticielo *et al*.	40	61	20	73	97	31	141	101	153	267	YES
X-Y Luo *et al*.	204	35	3	145	15	2	443	41	305	19	YES
X-Y Luo *et al*.	282	47	8	214	22	3	611	63	450	28	YES
A Mostowska *et al*.	109	121	28	218	245	82	339	177	681	409	YES
	ff	Ff	FF	ff	Ff	FF	F	f	F	f	
X-Y Luo *et al*.	57	98	116	36	61	33	330	212	127	133	YES
A Mostowska *et al*.	40	113	105	100	243	202	323	193	647	443	YES
OA Monticielo *et al*.	11	56	64	18	94	86	184	78	266	130	YES
C-M Huang *et al*.	7	34	11	26	43	21	56	48	95	85	YES
J Bogaczewicz *et al*.	17	38	7	29	53	18	72	52	111	89	YES
	aa	Aa	AA	Aa	Aa	AA	A	a	A	a	
X-Y Luo *et al*.	82	95	67	69	36	57	229	259	150	174	YES
A Mostowska *et al*.	62	118	78	136	257	152	274	242	529	561	YES
	tt	Tt	TT	tt	Tt	TT	T	t	T	t	
A Mostowska *et al*.	28	122	108	81	247	217	338	178	681	409	YES

HWE Hardy-Weinberg equilibrium.

Asians, 2 were from Europeans and one from a Latino population. Overall, there was a statistical evidence of an association between the FokI polymorphism and overall SLE risks (OR=1.75, 95%CI=1.03–2.97, p=0.04 for FF + Ff *vs*. ff) (Fig. 3). In the subgroup analysis by ethnicity, significantly increased risks were found among Asians (OR=3.36, 95%CI=2.11–5.34, p<0.00001), no significantly increased risks were found in either Europeans (OR=1.19, 95% CI=0.84–1.68, p=0.33) or in Latinos (OR=1.09, 95%CI=0.50-2.39, p=0.83). Thus, the Asian variant allele carriers (FF+ Ff) may have a higher risk of SLE than European and Latino populations. A summary of the results of other genetic comparisons is shown in Table III.

– Meta-analysis of the VDR ApaI and TaqI polymorphisms and SLE susceptibility

A total of 595 SLE cases and 784 controls in 2 case-control studies were included in the meta-analysis on the relationship between the ApaI polymorphism and the risk of SLE, 1 case-control study was from Asians and 1 was from Europeans. There only one study about TaqI polymorphism included 285 SLE cases and 545 controls from a European population. Overall, there was no statistical evidence of an association between the ApaI and TaqI polymorphism overall SLE, OR=1.22, 95%CI=0.88–1.68], p=0.23 for AA+ Aa *vs*. aa and OR=1.43, 95%CI=0.91–2.27, p=0.12 for TT + Tt *vs*. tt, respectively (Fig. 4-5). In the subgroup analysis by ethnicity, no significantly increased risks were found in any of these populations for both ApaI and TaqI polymorphism with SLE. A summary of the results of other genetic comparisons is shown in Table III.

Discussion

SLE is a multifactorial autoimmune disease with a broad spectrum etiology pathology and clinical manifestation. Genetics indicate that SLE is multiple different diseases and play essential

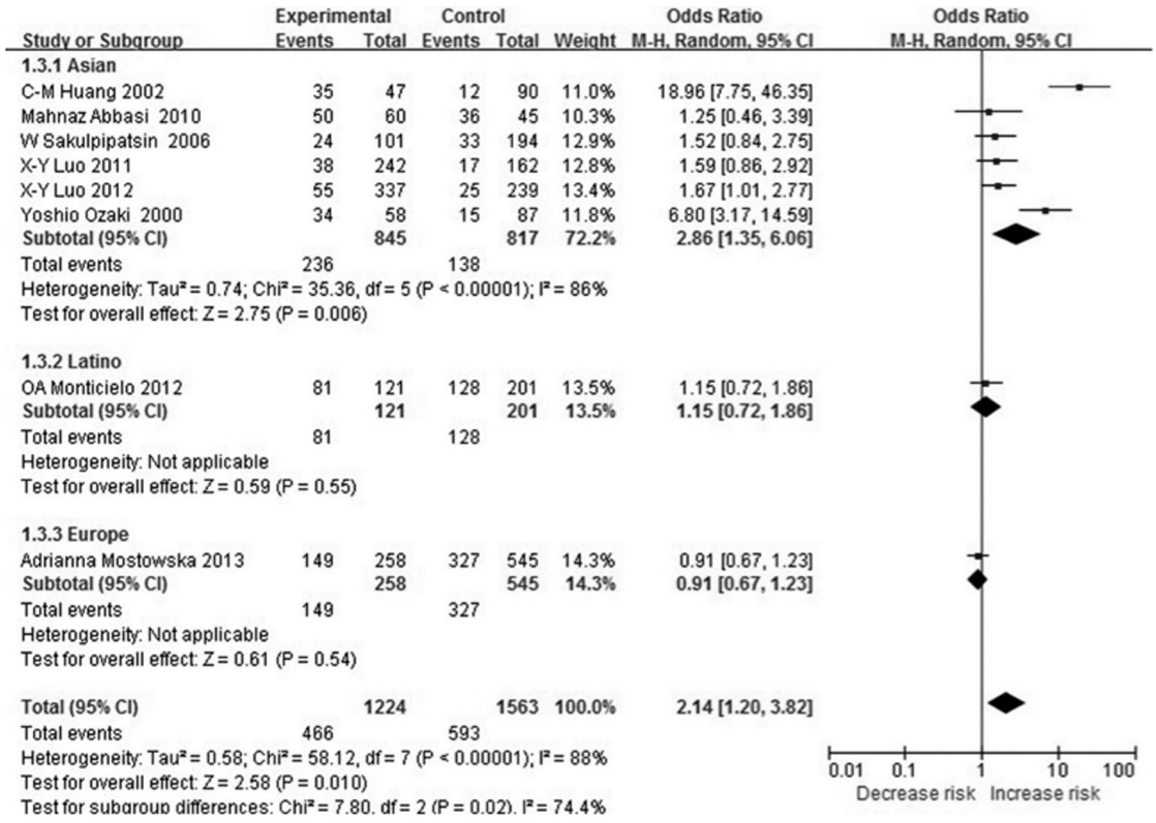

Fig. 2. Meta-analysis with a random-effects model for the association between SLE risk and the VDR BsmI polymorphism (BB+Bb *vs*. bb).

Table III. Meta-analysis of associations between the VDR gene polymorphisms and SLE.

	Number	Cases / controls	B *vs*. b		BB *vs*. bb + Bb		BB + Bb *vs*. bb		BB *vs*. bb	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
BsmI										
Total	8	1298/1563	1.70 [1.09, 2.67]	0.64	0.93 [0.69, 1.25]	0.63	2.14 [1.20, 3.82]	0.01	1.08 [0.78, 1.49]	0.02
Asian	6	845/817	2.13 [1.19, 3.80]	0.31	1.26 [0.75, 2.11]	0.38	2.86 [1.35, 6.06]	0.006	2.00 [1.11, 3.58]	0.01
Latino	1	195/201	1.09 [0.79, 1.51]	0.64	1.09 [0.59, 2.01]	0.79	1.15 [0.72, 1.86]	0.55	1.18 [0.60, 2.33]	0.58
Europe	1	258/545	0.87 [0.70, 1.08]	0.12	0.69 [0.44, 1.09]	0.11	0.91 [0.67, 1.23]	0.54	0.68 [0.42, 1.11]	0.21
FokI										
Total	5	838/1066	0.92 [0.64, 1.32]	0.65	1.23 [0.87, 1.75]	0.25	1.75 [1.03, 2.97]	0.04	1.45 [1.02, 2.04]	0.04
Asian	2	323/220	0.64 [0.25, 1.63]	0.35	1.49 [0.61, 3.61]	0.38	3.36 [2.11, 5.34]	<0.00001	2.16 [1.30, 3.58]	0.003
Latino	1	195/201	1.15 [0.82, 1.62]	0.41	1.24 [0.80, 1.94]	0.33	1.09 [0.50, 2.39]	0.83	1.22 [0.54, 2.76]	0.64
Europe	2	320/645	1.14 [0.94, 1.38]	0.19	0.95 [0.51, 1.77]	0.88	1.19 [0.84, 1.68]	0.33	1.11 [0.64, 1.94]	0.71
ApaI										
Total	2	595/784	1.14 [0.96, 1.34]	0.14	0.90 [0.57, 1.43]	0.67	1.22 [0.88, 1.68]	0.23	1.07 [0.78, 1.45]	0.68
Asian	1	337/239	1.03 [0.77, 1.36]	0.86	0.70 [0.45, 1.07]	0.10	1.47 [0.97, 2.21]	0.07	0.99 [0.61, 1.59]	0.96
Eurpoe	1	258/545	1.20 [0.97, 1.48]	0.09	1.12 [0.81, 1.55]	0.49	1.05 [0.74, 1.48]	0.78	1.13 [0.75, 1.69]	0.57
TaqI										
Total	1	258/545	1.14 [0.92, 1.42]	0.24	1.09 [0.81, 1.47]	0.58	1.43 [0.91, 2.27]	0.12	1.44 [0.88, 2.34]	0.14
Europe	1	258/545	1.14 [0.92, 1.42]	0.24	1.09 [0.81, 1.47]	0.58	1.43 [0.91, 2.27]	0.12	1.44 [0.88, 2.34]	0.14

role in the etiology of SLE (19, 20). VDR gene is one of many genes that have been studied in the context of SLE (21, 22), VDRs were expressed on most cells of the immune system such as lymphocytes and macrophages. Vitamin D is a fat-soluble prohormone that exerts its action by depending on the VDR, which suggests that vitamin D may play an important role in the regulation of the immune response including rheumatoid arthritis (RA) and SLE (22, 23), Vitamin D deficiency has been associated with SLE, previous studies have shown that low levels of vitamin D in SLE patients are associated with more active disease and an increased risk of complications such as osteoporosis, subclinical atherosclerosis, fatigue certain cardiovascular risk factors (22). But administration of 1, $25(OH)_2$ D3 before disease manifestation can prevent lupus (24). VDR gene polymorphisms have been used as ge-

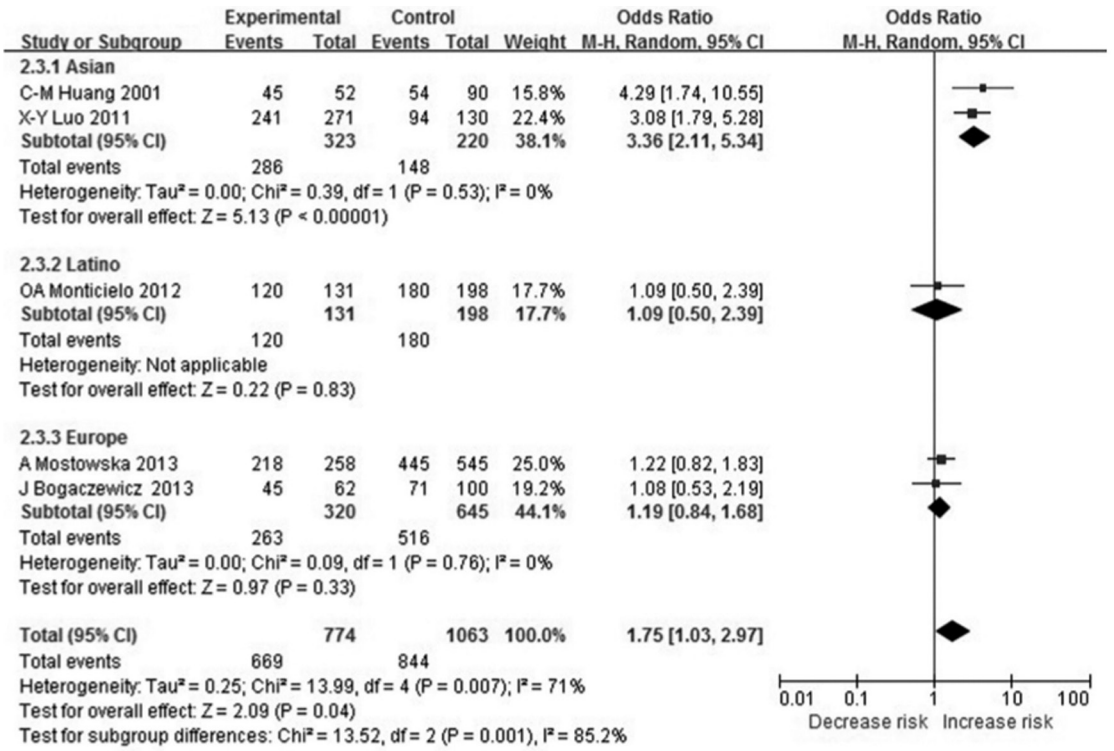

Fig. 3. Meta-analysis with a random-effects model for the association between SLE risk and the VDR FokI polymorphism (FF+Ff *vs*. ff).

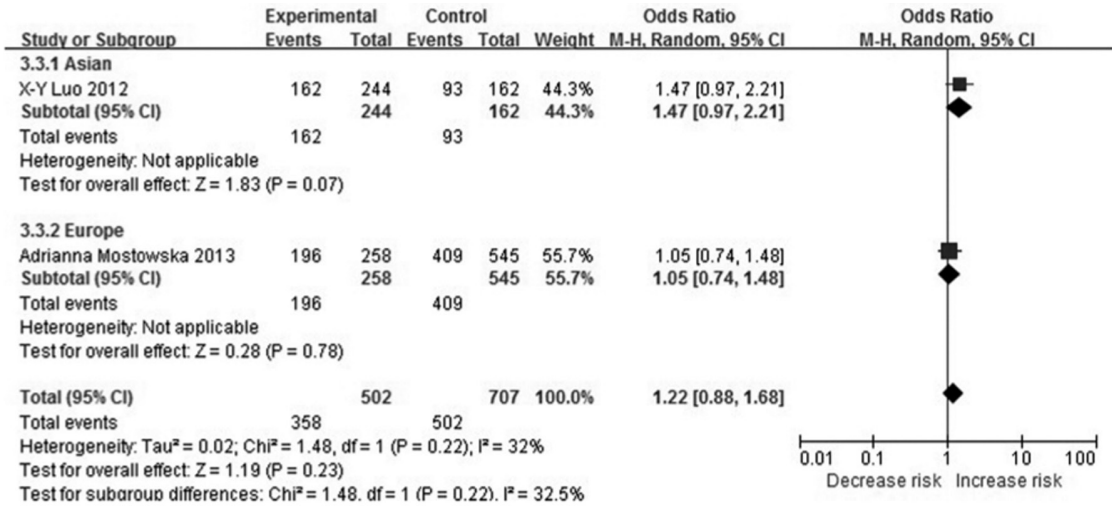

Fig. 4. Meta-analysis with a random-effects model for the association between SLE risk and the VDR ApaI polymorphism (AA+Aa *vs*. aa).

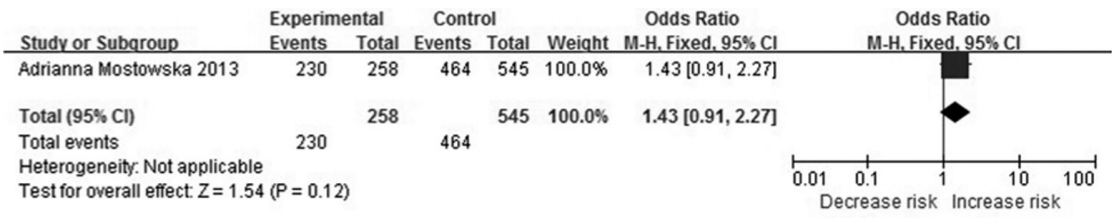

Fig. 5. Meta-analysis with a fixed model for the association between SLE risk and the VDR TaqI polymorphism (TT+Tt *vs*. tt).

netic markers to determine their association with SLE, in 2000, Ozaki *et al*. (12) was first to report the association study of the BsmI polymorphism of VDR gene with SLE, after that, several studies have been undertaken to replicate this association. Thus, VDR activity can be influenced by VDR polymorphisms, we performed a meta-analysis to comprehensively analyse these associations.

In our meta-analysis, the genetic models evaluated for this polymorphism were the dominant model, recessive model, additive model, and we included the Europe and Latino population in the review, a subgroup analysis was also performed to evaluate the genetic relations between the VDR gene polymorphisms and SLE in different ethnicities. Our results indicate that the variant

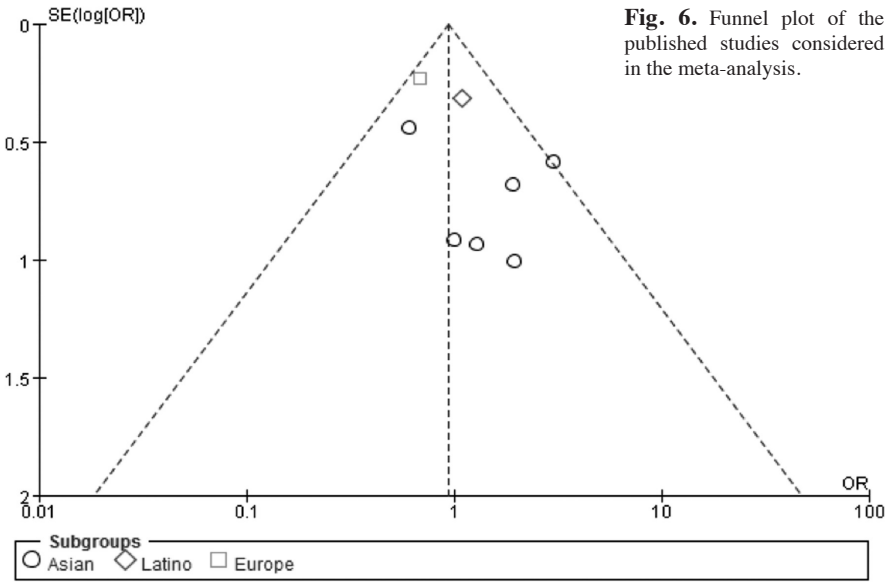

Fig. 6. Funnel plot of the published studies considered in the meta-analysis.

genotype (Bb + BB) of the BsmI is associated with a significantly increased risk for the development of SLE, and also FokI polymorphism is associated with risk of SLE, whereas the ApaI and TaqI polymorphisms do not appear to have a significant association with overall SLE risk. These results suggest that the BsmI and FokI polymorphism might contribute to SLE pathogenesis and might help to explain individual differences in susceptibility to SLE. Because genetic background can influence the results of meta-analysis, we also preformed subgroup analyses by ethnicity for these polymorphisms. Our results indicate that the BsmI and FokI polymorphism is associated with an increased risk of SLE in Asian populations, but not in European or Latino populations. It is possible that different genetic backgrounds may contribute to these differences. However, the other two polymorphisms showed no significant associations in Asians, Europeans or Latinos. Our results is different from the previous meta-analysis which we showed the FokI polymorphism is significantly associated with SLE. Luo et al indicate that the frequency of B allele of the BsmI polymorphism is associated with production of anti-nucleosome antibodies and the mRNA down-regulated in patient with SLE (15).

Our studies has some limitations taken into account. First, the number of studies included in this meta-analysis was small, only including 11 studies, 8 from Asian populations, 2 from European populations and 1 from Latino populations, so there has a significant heterogeneity among the studies in the subgroup analysis, the stratified analysis for Europe and Latino populations might not be reliable. A publication bias may have occurred. The funnel plot shows significant evidence of the bias (Fig. 6). Second, we can only find the ethnicity between the VDR gene polymorphisms and SEL, clinical features such as the age, sex differences and other were not include to analyse the association between VDR gene polymorphisms, because of the limited data. In conclusion, the results of this meta-analysis suggested that the associated between VDR gene polymorphisms BsmI and FokI with SLE susceptibility especially for the Asian population. These findings would prompt further investigation on the associations between the VDR gene polymorphisms and SLE susceptibility with different ethnicities.

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