Pooling analysis regarding the impact of human vitamin D receptor variants on the odds of psoriasis

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Abstract

Background: The study aims at scientifically investigating the genetic effect of four polymorphisms (rs7975232, rs1544410, rs2228570, and rs731236) within the human Vitamin D Receptor (VDR) gene on the odds of psoriasis through an updated meta-analysis.

Methods: We searched eight databases and screened the studies for pooling. Finally, a total of eighteen eligible case-control studies were included. BH (Benjamini & Hochberg) adjusted P-values of association (P_assoc) and odd ratios (ORs) with the corresponding 95% confidence intervals (CIs) were calculated under the allele, homozygote, heterozygote, dominant, recessive, and carrier models.

Results: Compared with the negative controls, no statistically significant difference in the odds of psoriasis was detected for the cases under any genetic models (BH adjusted P_assoc > 0.05). We also performed subgroup meta-analyses by the source of controls, ethnicity, country, Hardy-Weinberg equilibrium, and genotyping method. Similar results were observed in most subgroup meta-analyses (BH adjusted P_assoc > 0.05). Besides, data of Begg’s and Egger’s tests excluded the significant publication bias; while the sensitivity analysis data further indicated the statistical reliability of our pooling results.

Conclusion: The currently available data fails to support a robust association between VDR rs7975232, rs1544410, rs2228570 and rs731236 polymorphisms and psoriasis susceptibility, which still required the support of more case-control studies.

Keywords: VDR, Psoriasis, Polymorphism, Meta-analysis

Background

Vitamin D Receptor (VDR) protein, a member of the nuclear receptor superfamily of ligand-activated transcription factors, is thought to be implicated in several cell biological events (e.g., calcium and phosphate homeostasis, cell differentiation and apoptosis) [1, 2]. The human VDR gene is mapped on chromosome 12 and contains four common polymorphisms, namely rs7975232 A/C in intron eight (ApaI) rs1544410 G/A in intron eight (BsmI), rs2228570 T/C in exon two (FokI), and rs731236 T/C in exon nine (TaqI) [3–5]. In addition, linkage disequilibrium exists among the rs7975232, rs1544410, and rs731236 polymorphisms [6, 7]. Here, we investigated the possible role of VDR rs7975232, rs1544410, rs2228570, and rs731236 polymorphisms in the susceptibility to psoriasis disease.

Psoriasis is a type of chronic inflammatory immune-mediated disease with discrete, erythematous scaly plaques on the skin, and is characterized by the abnormal proliferation of keratinocytes and disordered maturation of the epidermis [8–10]. Genetic factors are potentially linked to the occurrence or pathogenesis of psoriasis [11, 12]. We observed the open questions of the association between the VDR polymorphisms and psoriasis susceptibility among different populations. For instance, the rs7975232 polymorphism of VDR was reportedly associated with the psoriasis risks in the Korean population [13, 14], Chinese population [15], or Turkish population [16, 17]. However, the VDR rs7975232 polymorphism was not considered a
risk factor for psoriasis cases in Japan [18], Italy [19], Croatia [20], or Egypt [21]. Therefore, it is meaningful to conduct a meta-analysis to pool the relevant data for a comprehensive assessment of this issue. Even though a recent meta-analysis was conducted by searching three databases in February 2018 [3], the publication of possible new data, different database retrieval, data collection and analysis strategies led us to perform another updated comprehensive pooling analysis and a series of followed stratification analysis of gene-disease association up to August 18, 2019.

Methods

Database retrieval
Referring to the HuGENet™ HuGE Review Handbook, version 1.0, we retrieved the relevant publications from eight online databases, including PubMed, Web of Science (WOS), Excerpta Medica Database (EMBASE), China National Knowledge Infrastructure (CNKI), WANFANG, OVID, Scopus and Cochrane, up to August 18, 2019, without any restrictions regarding geographical, language or publication time. We provided the searching terms in Additional file 1: Table S1.

Inclusion and exclusion criteria
Three investigators (J. Li, L. Sun, and J. Sun) designed the inclusion and exclusion criteria, independently screened the above articles, and evaluated the eligibility. Inclusion criteria: (1) comparing psoriasis cases versus negative controls; (2) detecting the VDR polymorphisms; (3) containing the major/minor allele frequency or completed genotype distribution. Exclusion criteria: (1) non-human studies; (2) reviews; (3) meeting or conference abstracts; (4) meta-analyses; (5) other diseases; (6) other genes; (7) expression or non-SNP; (8) duplicate or overlapped data.

Data collecting
Two investigators (J. Li and L. Sun) designed a form and independently collected the information, including the first author, publication year, ethnicity, source of controls, gender, age, calcipotriol response, family
| First author | Year | Ethnicity | case polymorphism | Control polymorphism | Source of controls | P_{HWE} | Genotyping method |
|--------------|------|-----------|-------------------|---------------------|-------------------|---------|------------------|
| Dayangac     | 2007 | Caucasian | rs7975232         | rs7975232            | PB                | 0.21    | PCR-RFLP         |
| Kaya         | 2002 | Caucasian | rs7975232         | rs7975232            | PB                | 0.54    | PCR-RFLP         |
| Lee          | 2002 | Asian     | rs7975232         | rs7975232            | PB                | 0.97    | PCR-RFLP         |
| Liu          | 2017 | Asian     | rs7975232         | rs7975232            | PB                | 0.33    | LDR              |
| Okita        | 2002 | Asian     | rs7975232         | rs7975232            | PB                | 0.59    | PCR-RFLP         |
| Park         | 1999 | Asian     | rs7975232         | rs7975232            | PB                | 0.97    | PCR-RFLP         |
| Richetta     | 2014 | Caucasian | rs7975232         | rs7975232            | PB                | 0.48    | Taqman assay     |
| Rucevic      | 2012 | Caucasian | rs7975232         | rs7975232            | PB                | 0.17    | PCR-RFLP         |
| Saeki        | 2002 | Asian     | rs7975232         | rs7975232            | PB                | 0.21    | PCR-RFLP         |
| Zhao         | 2015 | Asian     | rs7975232         | rs7975232            | PB                | 0.31    | gene sequencing  |
| Zhou         | 2014 | Asian     | rs7975232         | rs7975232            | HB                | 0.47    | Multiplex SNapSHOT |
| Zhu          | 2002 | Asian     | rs7975232         | rs7975232            | PB                | 0.49    | PCR-RFLP         |
| Zuel         | 2011 | African   | rs7975232         | rs7975232            | PB                | 0.02    | PCR-RFLP         |
| Kaya         | 2002 | Caucasian | rs1544410         | rs1544410            | PB                | 0.25    | PCR-RFLP         |
| Kontula      | 1997 | Caucasian | rs1544410         | rs1544410            | PB                | 0.29    | PCR-RFLP         |
| Lee          | 2002 | Asian     | rs1544410         | rs1544410            | PB                | 0.49    | PCR-RFLP         |
| Liu          | 2017 | Asian     | rs1544410         | rs1544410            | PB                | 0.08    | LDR              |
| Mee          | 1998 | Caucasian | rs1544410         | rs1544410            | NA                | >0.05   | PCR-RFLP         |
| Okita        | 2002 | Asian     | rs1544410         | rs1544410            | PB                | 0.00    | PCR-RFLP         |
| Richetta     | 2014 | Caucasian | rs1544410         | rs1544410            | PB                | 0.30    | Taqman assay     |
| Rucevic      | 2012 | Caucasian | rs1544410         | rs1544410            | PB                | 0.68    | PCR-RFLP         |
| Ruggiero     | 2004 | Caucasian | rs1544410         | rs1544410            | PB                | 0.63    | PCR-RFLP         |
| Saeki        | 2002 | Asian     | rs1544410         | rs1544410            | PB                | 0.00    | PCR-RFLP         |
| Zhao         | 2015 | Asian     | rs1544410         | rs1544410            | PB                | 0.50    | gene sequencing  |
| Zhou         | 2014 | Asian     | rs1544410         | rs1544410            | HB                | 0.41    | PCR-RFLP         |
| Zhu          | 2002 | Asian     | rs1544410         | rs1544410            | HB                | 0.39    | PCR-RFLP         |
| Dayangac     | 2007 | Caucasian | rs2228570         | rs2228570            | PB                | >0.05   | PCR-RFLP         |
| Halsall      | 2005 | Caucasian | rs2228570         | rs2228570            | PB                | 0.06    | PCR-RFLP         |
| Kaya         | 2002 | Caucasian | rs2228570         | rs2228570            | PB                | 0.37    | LDR              |
| Liu          | 2017 | Asian     | rs2228570         | rs2228570            | PB                | 0.28    | Taqman assay     |
| Richetta     | 2014 | Caucasian | rs2228570         | rs2228570            | PB                | 0.87    | PCR-RFLP         |
| Saeki        | 2002 | Asian     | rs2228570         | rs2228570            | PB                | 0.31    | gene sequencing  |
| Zhou         | 2014 | Asian     | rs2228570         | rs2228570            | HB                | 0.86    | Multiplex SNapSHOT |
| Acikbas      | 2012 | Caucasian | rs731236          | rs731236             | PB                | <0.05   | PCR-RFLP         |
| Dayangac     | 2007 | Caucasian | rs731236          | rs731236             | PB                | 0.87    | PCR-RFLP         |
| Halsall      | 2005 | Caucasian | rs731236          | rs731236             | HB                | >0.05   | PCR-RFLP         |
| Kaya         | 2002 | Caucasian | rs731236          | rs731236             | PB                | 0.73    | PCR-RFLP         |
| Liu          | 2017 | Asian     | rs731236          | rs731236             | PB                | 0.65    | LDR              |
| Okita        | 2002 | Asian     | rs731236          | rs731236             | PB                | 0.41    | PCR-RFLP         |
| Richetta     | 2014 | Caucasian | rs731236          | rs731236             | PB                | 0.99    | Taqman assay     |
| Rucevic      | 2012 | Caucasian | rs731236          | rs731236             | PB                | 0.80    | PCR-RFLP         |
| Saeki        | 2002 | Asian     | rs731236          | rs731236             | PB                | 0.59    | PCR-RFLP         |
history, genotyping method and genotype frequency. Based on the genotype frequency distribution, we utilized the chi-square test to calculate the \( P \)-value of HWE. The summarized data were assessed together for errors. When the frequency data were missing, the investigator (M. Yan) sent an email to the corresponding author. In addition, two investigators (J. Li and L. Sun) assessed the study quality using the Newcastle-Ottawa quality assessment scale (NOS) where scores range between 1 and 9. When a disagreement was encountered, we discussed with the third investigator (M. Yan) to obtain consensus. We considered studies high quality when the NOS score \( \geq 5 \).

**Tests for association, heterogeneity**

After data sorting via Microsoft Excel 2016, STATA 12.0 software (StataCorp, USA) was applied to obtain the \( P \)-value of association, ORs and 95% CI under the allele (al- lene C vs. A for \( VDR \) rs7975232 polymorphism; allele A vs. G for rs1544410 polymorphism; allele C vs. T for rs2228570 polymorphism; allele C vs. T for rs731236 polymorphism), homozygote (CC vs. AA; AA vs. GG; CC vs. TT; CC vs. TT), heterozygote (AC vs. AA; GA vs. GG; TC vs. CC; TC vs. TT), dominant (AC + CC vs AA; GA + AA vs. GG; TC + CC vs. TT; TC + CC vs. TT), recessive (CC vs. AA+AC; AA vs. GG + GA; CC vs. TT + CC; CC vs. TT + TC) and carrier (carrier C vs. A; carrier A vs. G; carrier C vs. T) models. We utilized the BH (Benjamini & Hochberg) correction method to adjust the \( P_{\text{association}} \) value through the \( p\text{-adjust}() \) function of R software version 3.4.4. BH-corrected \( P_{\text{association}} \) \(< 0.05 \) from the association test was considered statistically significant.

> Based on the “meta-analysis of binary data” function of STATA 12.0 software, we obtained the \( I^2 \) value (variation in ORs attributable to heterogeneity) and \( P \)-value of heterogeneity. When \( P \)-value \(< 0.05 \) or the \( I^2 \) value \( > 50% \), we utilized the random-effect pooling model (DerSimonian and Laird method); Otherwise, we used a fixed-effect model (Mantel-Haenszel method). To assess data stability and the source of potential heterogeneity, we conducted a series of subgroup analyses based on the factors of the control source, ethnicity, country, HWE, and genotyping method.

We performed the sensitivity analyses under all the genetic models, through the “influence analysis, meta- based (metaninf)” function of STATA 12.0 software. Upon the exclusion of each study one by one, the lack of largely affected meta-analysis estimates in figures suggested the statistical stability of data. If not, the omitted studies are deemed as the source of heterogeneity.

**Tests for publication bias**

We also performed the Begg’s test and Egger’s test to evaluate the potential publication bias through the “Publication Bias (metabias)” function of STATA 12.0 software. Begg’s funnel plot and Egger’s publication bias plot were generated, respectively. The basically symmetrical funnel plot, \( P \)-values for Begg’s test and Egger’s test greater than 0.05 indicate the absence of larger publication bias.

**Results**

**Case-control study identification**

Figure 1 presents the flow chart of study identification. We first retrieved 1955 records from eight on-line databases [PubMed \( (n = 251) \), EMBASE \( (n = 342) \), WOS \( (n = 451) \), CNKI \( (n = 54) \), WANGFANG \( (n = 6) \), OVID \( (n = 684) \), Scopus \( (n = 141) \) and Cochrane \( (n = 26) \)]. We then screened a total of 705 records after removing duplicate records from different databases. Next, we excluded an additional 620 records per the exclusion criteria. The detailed information was shown in Fig. 1. After assessing the eligibility of 85 full-text articles, we removed an additional 67 articles with “expression or non-SNP” data. Finally, we included a total of 18 case-control studies [13–30] for our meta-analysis. We also summarized and listed the genotypic distribution (Table 1) and clinical characteristics, (Additional file 2: Table S2). No low-quality studies with a NOS quality score \( \geq 5 \) were included in this analysis (Additional file 3: Table S3).

**VDR rs7975232 polymorphism**

There are a total of thirteen case-control studies with 1654 cases and 1991 controls for the meta-analysis of the VDR rs7975232 polymorphism and psoriasis susceptibility.

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**Table 1** Genotype distributions of included case-control studies (Continued)

| First author | Year | Ethnicity | case polymorphism | Control polymorphism | Source of controls | \( P_{\text{HWE}} \) | Genotyping method |
|-------------|------|-----------|-------------------|---------------------|------------------|-----------------|-----------------|
| Zhao        | 2015 | Asian     | 283 37 4          | rs731236            | PB               | 0.67            | gene sequencing |
| Zhou        | 2014 | Asian     | 308 33 1          | rs731236            | HB               | 0.46            | Multiplex SNapSHOT |
| Zuel        | 2011 | African   | 16 25 9           | rs731236            | PB               | 0.36            | PCR-RFLP        |

\( X \) major allele, \( Y \) minor allele, \( PB \) population-based controls, \( HB \) hospital-based controls, \( NA \) not available data, \( PCR-RFLP \) polymerase chain reaction-restriction fragment length polymorphism, \( P_{\text{HWE}} \) \( P \)-value of Hardy-Weinberg equilibrium, \( LDR \) ligase detection reactions

* The frequency of major allele and minor allele
Table 2: Pooled analyses of the association between VDR rs7975232 polymorphism and susceptibility to psoriasis

| Models          | M         | $\phi^2$ | $P_{\text{heterogeneity}}$ | Stratification | case/control (N) | OR [95% CI] | $P_{\text{association}}$ | BH      |
|-----------------|-----------|----------|-----------------------------|----------------|------------------|-------------|--------------------------|---------|
| allele C vs. A  | R         | < 0.001  | overall                      | 1654/1991 (13) | 1.05 [0.85–1.30] | 0.640       | 0.960                    |         |
|                 |           |          | Asian                        | 1212/1153 (8)  | 0.980 [0.70–1.38] | 0.921       | 0.921                    |         |
|                 |           |          | Caucasian                    | 392/788 (4)    | 1.16 [0.96–1.39] | 0.123       | 0.346                    |         |
|                 |           |          | PB                           | 1312/1650 (12) | 1.02 [0.81–1.30] | 0.849       | 0.856                    |         |
|                 |           |          | China                        | 888/790 (4)    | 1.26 [0.99–1.61] | 0.065       | 0.195                    |         |
|                 |           |          | $P_{\text{HWE} > 0.05}$     | 1604/1941 (12) | 1.07 [0.85–1.33] | 0.567       | 0.740                    |         |
|                 |           |          | PCR-RFLP                     | 770/1041 (9)   | 0.93 [0.69–1.27] | 0.668       | 0.819                    |         |
| CC vs. AA       | R         | 0.008    | overall                      | 1654/1991 (13) | 1.11 [0.76–1.64] | 0.585       | 0.960                    |         |
|                 |           |          | Asian                        | 1212/1153 (8)  | 0.91 [0.48–1.71] | 0.761       | 0.921                    |         |
|                 |           |          | Caucasian                    | 392/788 (4)    | 1.31 [0.91–1.90] | 0.147       | 0.346                    |         |
|                 |           |          | PB                           | 1312/1650 (12) | 1.04 [0.69–1.59] | 0.838       | 0.856                    |         |
|                 |           |          | China                        | 888/790 (4)    | 1.11 [0.76–1.64] | 0.718       | 0.718                    |         |
|                 |           |          | $P_{\text{HWE} > 0.05}$     | 1604/1941 (12) | 1.11 [0.74–1.65] | 0.617       | 0.740                    |         |
|                 |           |          | PCR-RFLP                     | 770/1041 (9)   | 0.93 [0.52–1.66] | 0.803       | 0.819                    |         |
| AC vs. AA       | R         | 0.002    | overall                      | 1654/1991 (13) | 1.15 [0.85–1.54] | 0.370       | 0.960                    |         |
|                 |           |          | Asian                        | 1212/1153 (8)  | 1.10 [0.70–1.72] | 0.683       | 0.921                    |         |
|                 |           |          | Caucasian                    | 392/788 (4)    | 1.27 [0.84–1.91] | 0.257       | 0.346                    |         |
|                 |           |          | PB                           | 1312/1650 (12) | 1.11 [0.78–1.57] | 0.578       | 0.856                    |         |
|                 |           |          | China                        | 888/790 (4)    | 1.15 [0.64–2.07] | 0.638       | 0.718                    |         |
|                 |           |          | $P_{\text{HWE} > 0.05}$     | 1604/1941 (12) | 1.20 [0.89–1.63] | 0.235       | 0.478                    |         |
|                 |           |          | PCR-RFLP                     | 770/1041 (9)   | 0.94 [0.58–1.54] | 0.819       | 0.819                    |         |
| AC + CC vs. AA  | R         | 0.001    | overall                      | 1654/1991 (13) | 1.15 [0.86–1.54] | 0.356       | 0.960                    |         |
|                 |           |          | Asian                        | 1212/1153 (8)  | 1.06 [0.68–1.66] | 0.800       | 0.921                    |         |
|                 |           |          | Caucasian                    | 392/788 (4)    | 1.30 [0.89–1.90] | 0.179       | 0.346                    |         |
|                 |           |          | PB                           | 1312/1650 (12) | 1.10 [0.78–1.55] | 0.595       | 0.856                    |         |
|                 |           |          | China                        | 888/790 (4)    | 1.24 [0.75–2.04] | 0.402       | 0.603                    |         |
|                 |           |          | $P_{\text{HWE} > 0.05}$     | 1604/1941 (12) | 1.20 [0.89–1.62] | 0.239       | 0.478                    |         |
|                 |           |          | PCR-RFLP                     | 770/1041 (9)   | 0.93 [0.57–1.52] | 0.771       | 0.819                    |         |
| CC vs. AA+AC    | R         | 0.001    | overall                      | 1654/1991 (13) | 1.01 [0.74–1.39] | 0.928       | 0.977                    |         |
|                 |           |          | Asian                        | 1212/1153 (8)  | 0.91 [0.57–1.47] | 0.712       | 0.921                    |         |
|                 |           |          | Caucasian                    | 392/788 (4)    | 1.19 [0.86–1.64] | 0.295       | 0.346                    |         |
|                 |           |          | PB                           | 1312/1650 (12) | 0.97 [0.69–1.35] | 0.856       | 0.856                    |         |
|                 |           |          | China                        | 888/790 (4)    | 1.26 [0.88–2.14] | 0.205       | 0.410                    |         |
|                 |           |          | $P_{\text{HWE} > 0.05}$     | 1604/1941 (12) | 1.00 [0.72–1.39] | 0.977       | 0.977                    |         |
|                 |           |          | PCR-RFLP                     | 770/1041 (9)   | 0.93 [0.60–1.42] | 0.727       | 0.819                    |         |
| carrier C vs. A | F         | 0.053    | overall                      | 1654/1991 (13) | 1.08 [0.96–1.21] | 0.977       | 0.977                    |         |
|                 |           |          | Asian                        | 1212/1153 (8)  | 1.08 [0.93–1.25] | 0.313       | 0.921                    |         |
|                 |           |          | Caucasian                    | 392/788 (4)    | 1.10 [0.90–1.34] | 0.346       | 0.346                    |         |
|                 |           |          | PB                           | 1312/1650 (12) | 1.04 [0.92–1.19] | 0.507       | 0.856                    |         |
|                 |           |          | China                        | 888/790 (4)    | 1.23 [1.03–1.47] | 0.020       | 0.120                    |         |
|                 |           |          | $P_{\text{HWE} > 0.05}$     | 1604/1941 (12) | 1.09 [0.96–1.22] | 0.170       | 0.478                    |         |
|                 |           |          | PCR-RFLP                     | 770/1041 (9)   | 0.96 [0.82–1.13] | 0.650       | 0.819                    |         |

$M$ statistical model, $R$ random effect, $F$ fixed effect, $P_{\text{HWE}}$ $P$-value of Hardy-Weinberg equilibrium, $P_{\text{heterogeneity}}$ $P$-value of Cochrane’s Q statistic for the assessment of heterogeneity, $N$ Number of included case-control studies, OR odds ratio, CI confidence interval, $P_{\text{association}}$ $P$-value of association

$BH$ Benjamini & Hochberg-adjusted $P_{\text{association}}$
The heterogeneity under the carrier C vs. A model (Table 2, $I^2 = 42.3\%$, $P_{\text{heterogeneity}} = 0.053$) led to the utilization of a random-effects pooling model, and a fixed-effects pooling model was utilized for the other genetic models. Pooling results of Table 2 showed no statistically significant difference in the odds of psoriasis between cases and controls under the following six genetic models: allele C vs. A ($P_{\text{association}} = 0.640$, BH-adjusted $P_{\text{association}} = 0.960$), homozygote CC vs. AA ($P_{\text{association}} = 0.585$, BH-adjusted $P_{\text{association}} = 0.960$), heterozygote AC vs. AA ($P_{\text{association}} = 0.370$, BH-adjusted $P_{\text{association}} = 0.960$), dominant AC + CC vs. AA ($P_{\text{association}} = 0.356$, BH-adjusted $P_{\text{association}} = 0.960$), recessive CC vs. AA + AC ($P_{\text{association}} = 0.928$, BH-adjusted $P_{\text{association}} = 0.977$), and carrier C vs. A ($P_{\text{association}} = 0.977$, BH-adjusted $P_{\text{association}} = 0.977$). Figure 2 presents the forest plot under the allele model.

We also performed subgroup meta-analyses based on the factors of control source, ethnicity, country, HWE, and genotyping method. We observed no significant differences between cases and controls in any subgroup (Table 2, all $P_{\text{association}} > 0.05$, BH-adjusted $P_{\text{association}} > 0.05$ except the subgroup of “China” under the carrier model ($P_{\text{association}} = 0.020$, BH-adjusted $P_{\text{association}} = 0.120$, OR = 1.23). Additional file 4: Figure S1 and Additional file 5: Figure S2 show the forest plots in the subgroup analysis by the factors of ethnicity and the source of controls (allele model). These results suggested that the VDR rs7975232 polymorphism has no significant influence on the susceptibility to psoriasis.

### VDR rs1544410 polymorphism

For VDR rs1544410, thirteen studies containing 1620 cases/2001 controls were included. A random-effects pooling model was used for the allele A vs. G (Table 3, $I^2 = 54.9\%$, $P_{\text{heterogeneity}} = 0.009$), whereas a fixed-effects pooling model was utilized for the others (all $I^2 < 50.0\%$, $P_{\text{heterogeneity}} > 0.05$). We did not observe the statistical differences between cases and controls under any genetic model during the overall meta-analysis and subsequent

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**Table 2: VDR rs7975232 Polymorphism**

| Study         | VDR rs7975232 Polymorphism | OR (95% CI) | Weight |
|---------------|----------------------------|-------------|--------|
| Dayangac (2007)|                            | 1.25 (0.77, 2.02) | 7.08   |
| Kaya (2002)   |                            | 1.61 (1.03, 3.17) | 6.26   |
| Lee (2002)    |                            | 0.38 (0.22, 0.65) | 6.51   |
| Liu (2017)    |                            | 1.73 (1.21, 2.47) | 8.43   |
| Okita (2002)  |                            | 1.41 (0.82, 2.43) | 6.44   |
| Park (1999)   |                            | 0.44 (0.27, 0.69) | 7.22   |
| Richetta (2014)|                           | 1.03 (0.75, 1.42) | 8.83   |
| Rucevic (2012)|                            | 1.10 (0.85, 1.41) | 9.53   |
| Saeki (2002)  |                            | 1.30 (0.82, 2.05) | 7.32   |
| Zhao (2015)   |                            | 1.19 (0.88, 1.62) | 8.96   |
| Zhou (2014)   |                            | 1.35 (1.06, 1.73) | 9.60   |
| Zhu (2002)    |                            | 0.85 (0.57, 1.28) | 7.90   |
| Zuel (2011)   |                            | 0.83 (0.46, 1.51) | 5.93   |
| Overall       |                            | 1.05 (0.85, 1.30) | 100.00 |

**Note:** Weights are from random effects analysis.
| Models          | M    | $I^2$ | $P_{\text{heterogeneity}}$ | Stratification | case/control (N) | OR [95% CI] | $P_{\text{association}}$ | BH  |
|----------------|------|-------|---------------------------|----------------|------------------|-------------|--------------------------|-----|
| allele A vs. G | R    | 54.9% | 0.009                     | overall        | 1620/2001 (13)  | 1.01 [0.82~1.26] | 0.898                    | 0.925 |
|                |      |       |                           | Asian          | 1108/1046 (7)   | 1.04 [0.63~1.69] | 0.889                    | 0.973 |
|                |      |       |                           | Caucasian      | 512/955 (6)     | 1.05 [0.89~1.24] | 0.547                    | 0.821 |
|                |      |       |                           | PB             | 1186/1536 (11)  | 0.95 [0.74~1.23] | 0.711                    | 0.971 |
|                |      |       |                           | China          | 888/790 (4)     | 0.82 [0.43~1.54] | 0.533                    | 1.000 |
|                |      |       |                           | $P_{\text{HWE}} > 0.05$ | 1478/1791 (11)  | 1.00 [0.78~1.30] | 0.973                    | 0.973 |
|                |      |       |                           | PCR-RFLP       | 736/1051 (9)    | 1.02 [0.77~1.36] | 0.898                    | 0.898 |
| AA vs. GG      | F    | 0.0%  | 0.452                     | overall        | 1416/1769 (11)  | 1.26 [0.93~1.73] | 0.151                    | 0.925 |
|                |      |       |                           | Asian          | 996/938 (6)     | 1.65 [0.79~3.46] | 0.186                    | 0.973 |
|                |      |       |                           | Caucasian      | 420/831 (5)     | 1.19 [0.84~1.68] | 0.339                    | 0.821 |
|                |      |       |                           | PB             | 1074/1428 (10)  | 1.25 [0.91~1.71] | 0.172                    | 0.971 |
|                |      |       |                           | China          | 776/682 (3)     | 1.74 [0.44~6.92] | 0.433                    | 1.000 |
|                |      |       |                           | $P_{\text{HWE}} > 0.05$ | 1366/1683 (10)  | 1.29 [0.93~1.77] | 0.125                    | 0.375 |
|                |      |       |                           | PCR-RFLP       | 532/819 (7)     | 1.43 [0.97~2.10] | 0.072                    | 0.144 |
| GA vs. GG      | F    | 41.6% | 0.071                     | overall        | 1416/1769 (11)  | 1.08 [0.85~1.37] | 0.524                    | 0.925 |
|                |      |       |                           | Asian          | 996/938 (6)     | 1.01 [0.70~1.46] | 0.945                    | 0.973 |
|                |      |       |                           | Caucasian      | 420/831 (5)     | 1.13 [0.83~1.55] | 0.437                    | 0.821 |
|                |      |       |                           | PB             | 1074/1428 (10)  | 1.00 [0.78~1.30] | 0.971                    | 0.971 |
|                |      |       |                           | China          | 776/682 (3)     | 1.00 [0.68~1.48] | 1.000                    | 1.000 |
|                |      |       |                           | $P_{\text{HWE}} > 0.05$ | 1366/1683 (10)  | 1.09 [0.86~1.38] | 0.496                    | 0.744 |
|                |      |       |                           | PCR-RFLP       | 532/819 (7)     | 1.45 [0.99~2.14] | 0.050                    | 0.144 |
| GA + AA vs. GG | F    | 44.1% | 0.057                     | overall        | 1416/1769 (11)  | 1.12 [0.89~1.40] | 0.335                    | 0.925 |
|                |      |       |                           | Asian          | 996/938 (6)     | 1.12 [0.79~1.58] | 0.535                    | 0.973 |
|                |      |       |                           | Caucasian      | 420/831 (5)     | 1.12 [0.83~1.50] | 0.462                    | 0.821 |
|                |      |       |                           | PB             | 1074/1428 (10)  | 1.05 [0.82~1.34] | 0.710                    | 0.971 |
|                |      |       |                           | China          | 776/682 (3)     | 1.05 [0.72~1.53] | 0.813                    | 1.000 |
|                |      |       |                           | $P_{\text{HWE}} > 0.05$ | 1366/1683 (10)  | 1.13 [0.90~1.41] | 0.307                    | 0.614 |
|                |      |       |                           | PCR-RFLP       | 532/819 (7)     | 1.46 [1.03~2.08] | 0.035                    | 0.144 |
| AA vs. GG + GA | F    | 40.7% | 0.070                     | overall        | 1528/1877 (12)  | 0.98 [0.79~1.22] | 0.866                    | 0.925 |
|                |      |       |                           | Asian          | 1108/1046 (7)   | 0.94 [0.65~1.37] | 0.765                    | 0.973 |
|                |      |       |                           | Caucasian      | 420/831 (5)     | 1.00 [0.77~1.30] | 0.998                    | 0.998 |
|                |      |       |                           | PB             | 1186/1536 (11)  | 0.98 [0.79~1.21] | 0.823                    | 0.971 |
|                |      |       |                           | China          | 888/790 (4)     | 0.50 [0.28~0.88] | 0.901                    | 1.000 |
|                |      |       |                           | $P_{\text{HWE}} > 0.05$ | 1478/1791 (11)  | 0.99 [0.79~1.23] | 0.018                    | 0.108 |
|                |      |       |                           | PCR-RFLP       | 644/927 (8)     | 0.95 [0.75~1.20] | 0.680                    | 0.898 |
| carrier A vs. G| F    | 34.8% | 0.112                     | overall        | 1528/1877 (12)  | 1.01 [0.86~1.18] | 0.925                    | 0.925 |
|                |      |       |                           | Asian          | 1108/1046 (7)   | 1.00 [0.76~1.30] | 0.973                    | 0.973 |
|                |      |       |                           | Caucasian      | 420/831 (5)     | 1.01 [0.83~1.24] | 0.887                    | 0.998 |
|                |      |       |                           | PB             | 1186/1536 (11)  | 0.97 [0.82~1.15] | 0.737                    | 0.971 |
|                |      |       |                           | China          | 888/790 (4)     | 0.84 [0.61~1.16] | 0.285                    | 1.000 |
|                |      |       |                           | $P_{\text{HWE}} > 0.05$ | 1478/1791 (11)  | 1.01 [0.86~1.19] | 0.895                    | 0.973 |
|                |      |       |                           | PCR-RFLP       | 644/927 (8)     | 1.02 [0.84~1.25] | 0.815                    | 0.898 |

$M$ statistical model, $R$ random effect, $F$ fixed effect, $P_{\text{HWE}}$ $P$-value of Hardy-Weinberg equilibrium, $P_{\text{heterogeneity}}$ $P$-value of Cochrane’s Q statistic for the assessment of heterogeneity, $N$ Number of included case-control studies, OR odds ratio, CI confidence interval, $P_{\text{association}}$ $P$-value of association

$BH$ Benjamini & Hochberg-adjusted $P_{\text{association}}$
subgroup analysis (Table 3, all $P_{association} > 0.05$, BH-adjusted $P_{association} > 0.05$) with the exception of the "$P_{HW} > 0.05$" subgroup under the AA vs. GG + GA model ($P_{association} = 0.018$, BH-adjusted $P_{association} = 0.108$, OR = 0.99) and "PCR-RFLP" subgroup under the GG + GA vs. GG model ($P_{association} = 0.035$, BH-adjusted $P_{association} = 0.144$, OR = 1.46). Figure 3 presents a forest plot of the allele model in the overall meta-analysis, and Additional file 6: Figure S3 and Additional file 7: Figure S4 show the forest plots in the subgroup analysis by the factors of ethnicity and source of controls (allele model). These data suggested that the VDR rs1544410 polymorphism seems not to be linked to the psoriasis susceptibility.

VDR rs2228570 polymorphism

A total of eight studies involving 1308 cases/1253 controls were enrolled for meta-analysis of VDR rs2228570. A fixed-effect pooling model was utilized for the TC vs. TT (Table 4, $I^2 = 46.2\%$, $P_{heterogeneity} = 0.84$), whereas a random-effects pooling model was used for the others (all $I^2 > 50.0\%$, $P_{heterogeneity} < 0.05$). As shown in Table 4, no statistically significant association was detected in the overall meta-analysis and subsequent subgroup analysis ($P_{association} > 0.05$, BH-adjusted $P_{association} > 0.05$). Figure 4 shows the forest plot under the allele model, and Additional file 8: Figure S5 and Additional file 9: Figure S6 show the forest plots in the subgroup analysis by the factors of ethnicity and source of controls (allele model). These findings indicated that VDR rs2228570 might not be associated with the risk of psoriasis.

VDR rs731236 polymorphism

During the meta-analysis of VDR rs731236 containing 1690 cases/1857 controls, a random-effect model was used for the allele C vs. T ($P_{heterogeneity} = 0.034$), TC vs. TT ($P_{heterogeneity} = 0.043$) and TC + CC vs. TT ($I^2 = 50.7\%$, $P_{heterogeneity} = 0.027$), and a fix-effect model was applied for others (all $I^2 < 50.0\%$, $P_{heterogeneity} > 0.05$). As shown in Table 5, no
| Models          | M | i²| P_{heterogeneity} | Stratification | case/control (N) | OR [95% CI] | P_{association} | BH |
|-----------------|---|---|-------------------|----------------|------------------|-------------|-----------------|----|
| allele C vs. T  | R | 84.7% | < 0.001 | overall | 1308/1253 (8) | 1.00 [0.73~1.38] | 0.989 | 0.989 |
|                 | 92.2% | < 0.001 | Asian | 891/751 (4) | 0.89 [0.52~1.53] | 0.681 | 0.760 |
|                 | 0.0% | 0.766 | Caucasian | 417/502 (4) | 1.16 [0.93~1.43] | 0.681 | 0.681 |
|                 | 88.4% | < 0.001 | PB | 761/832 (6) | 0.99 [0.62~1.58] | 0.964 | 0.987 |
|                 | 93.8% | < 0.001 | China | 776/682 (3) | 0.78 [0.41~1.46] | 0.429 | 0.521 |
|                 | 86.6% | < 0.001 | P_{heterogeneity} > 0.05 | 1103/1173 (7) | 0.99 [0.69~1.42] | 0.946 | 0.955 |
|                 | 0.0% | 0.603 | PCR-RFLP | 424/303 (4) | 1.20 [0.95~1.52] | 0.121 | 0.348 |
| CC vs. TT       | R | 84.4% | < 0.001 | overall | 1103/1173 (7) | 0.96 [0.47~1.97] | 0.914 | 0.989 |
|                 | 90.9% | < 0.001 | Asian | 891/751 (4) | 0.81 [0.29~2.28] | 0.695 | 0.760 |
|                 | 0.0% | 0.440 | Caucasian | 212/422 (3) | 1.33 [0.76~2.32] | 0.317 | 0.560 |
|                 | 86.5% | < 0.001 | PB | 761/832 (6) | 0.97 [0.38~2.47] | 0.947 | 0.987 |
|                 | 92.8% | < 0.001 | China | 776/682 (3) | 0.62 [0.19~2.06] | 0.438 | 0.521 |
|                 | 88.4% | < 0.001 | P_{heterogeneity} > 0.05 | 1103/1173 (7) | 0.96 [0.47~1.97] | 0.914 | 0.955 |
|                 | 6.2% | 0.344 | PCR-RFLP | 219/223 (3) | 1.58 [0.78~3.21] | 0.204 | 0.348 |
| TC vs. TT       | F | 46.2% | 0.084 | overall | 1103/1173 (7) | 1.02 [0.84~1.25] | 0.810 | 0.989 |
|                 | 70.4% | 0.017 | Asian | 891/751 (4) | 0.96 [0.75~1.21] | 0.717 | 0.760 |
|                 | 0.0% | 0.955 | Caucasian | 212/422 (3) | 1.20 [0.84~1.72] | 0.325 | 0.560 |
|                 | 54.3% | 0.053 | PB | 761/832 (6) | 0.99 [0.78~1.25] | 0.919 | 0.987 |
|                 | 77.2% | 0.012 | China | 776/682 (3) | 0.90 [0.70~1.17] | 0.440 | 0.521 |
|                 | 46.2% | 0.084 | P_{heterogeneity} > 0.05 | 1103/1173 (7) | 1.02 [0.84~1.25] | 0.810 | 0.955 |
|                 | 0.0% | 0.886 | PCR-RFLP | 219/223 (3) | 1.25 [0.83~1.89] | 0.290 | 0.348 |
| TC + CC vs. TT  | R | 76.0% | < 0.001 | overall | 1103/1173 (7) | 1.01 [0.67~1.52] | 0.955 | 0.989 |
|                 | 86.6% | < 0.001 | Asian | 891/751 (4) | 0.90 [0.47~1.74] | 0.760 | 0.760 |
|                 | 0.0% | 0.790 | Caucasian | 212/422 (3) | 1.22 [0.87~1.71] | 0.253 | 0.560 |
|                 | 79.7% | < 0.001 | PB | 761/832 (6) | 1.00 [0.60~1.69] | 0.987 | 0.987 |
|                 | 89.5% | < 0.001 | China | 776/682 (3) | 0.77 [0.35~1.71] | 0.521 | 0.521 |
|                 | 76.0% | < 0.001 | P_{heterogeneity} > 0.05 | 1103/1173 (7) | 1.01 [0.67~1.52] | 0.955 | 0.955 |
|                 | 0.0% | 0.651 | PCR-RFLP | 219/223 (3) | 1.30 [0.88~1.92] | 0.191 | 0.348 |
| CC vs. TT + TC  | R | 79.6% | < 0.001 | overall | 1103/1173 (7) | 0.93 [0.54~1.60] | 0.782 | 0.989 |
|                 | 87.7% | < 0.001 | Asian | 891/751 (4) | 0.82 [0.39~1.71] | 0.600 | 0.760 |
|                 | 0.0% | 0.466 | Caucasian | 212/422 (3) | 1.21 [0.72~2.04] | 0.467 | 0.560 |
|                 | 82.0% | < 0.001 | PB | 761/832 (6) | 0.94 [0.46~1.92] | 0.869 | 0.987 |
|                 | 90.0% | < 0.001 | China | 776/682 (3) | 0.68 [0.30~1.55] | 0.358 | 0.521 |
|                 | 79.6% | < 0.001 | P_{heterogeneity} > 0.05 | 1103/1173 (7) | 0.93 [0.54~1.60] | 0.782 | 0.955 |
|                 | 0.0% | 0.396 | PCR-RFLP | 219/223 (3) | 1.41 [0.75~2.68] | 0.287 | 0.348 |
| carrier C vs. T | R | 61.8% | 0.015 | overall | 1103/1173 (7) | 0.97 [0.76~1.25] | 0.840 | 0.989 |
|                 | 77.9% | 0.004 | Asian | 891/751 (4) | 0.91 [0.63~1.32] | 0.632 | 0.760 |
|                 | 0.0% | 0.843 | Caucasian | 212/422 (3) | 1.12 [0.84~1.49] | 0.444 | 0.560 |
|                 | 67.2% | 0.009 | PB | 761/832 (6) | 0.98 [0.71~1.35] | 0.883 | 0.987 |
|                 | 82.5% | 0.003 | China | 776/682 (3) | 0.84 [0.53~1.29] | 0.425 | 0.521 |
|                 | 61.8% | 0.015 | P_{heterogeneity} > 0.05 | 1103/1173 (7) | 0.97 [0.76~1.25] | 0.840 | 0.955 |
|                 | 0.0% | 0.772 | PCR-RFLP | 219/223 (3) | 1.17 [0.84~1.63] | 0.360 | 0.360 |

* M statistical model, R random effect, F fixed effect, P_{heterogeneity} P-value of Hardy-Weinberg equilibrium, P_{heterogeneity} P-value of Cochrane’s Q statistic for the assessment of heterogeneity, N Number of included case-control studies, OR odds ratio, CI confidence interval, BH Benjamini & Hochberg-adjusted P_{association}
differences between cases and controls were detected in all analyses (Table 5, all \( P_{\text{association}} > 0.05 \), BH-adjusted \( P_{\text{association}} > 0.05 \)). Figure 5 presents the forest plot of the allele model, and Additional file 10: Figure S7 and Additional file 11: Figure S8 show the forest plot in the subgroup analysis by the factors of ethnicity and source of controls (allele model). As a result, \( VDR \) rs731236 polymorphism is not significantly associated with the odds of psoriasis disease.

**Sensitivity analysis and publication bias**

We did not observe largely altered meta-analysis estimates in the results of our sensitivity analysis (Fig. 6 for the allele model; and other data not shown), suggesting the statistical reliability of pooling results. We also conducted the Begg’s and Egger’s tests to assess the potential publication bias. As shown in Table 6, the \( P \)-value of Begg’s and Egger’s test was greater than 0.05 under all the above genetic models. Additional file 12: Figure S9 and Additional file 13: Figure S10 show the Begg’s funnel plots and Egger’s publication bias plots under the allele model. We observed basically symmetrical funnel plots. Therefore, there is no large publication bias in our study.

**Discussion**

In the current study, we searched eight online electronic databases, including PubMed, EMBASE, WOS, CNKI, WANFANG, OVID, Scopus and Cochrane (up to August 18, 2019), to enroll a total of 18 case-control studies. Based on the currently available data, we conducted a series of overall meta-analysis and subgroup analysis to evaluate the genetic relationship regarding \( VDR \) rs7975232, rs1544410, rs2228570, and rs731236 polymorphisms and psoriasis susceptibility. Here, we used the “RS” naming, the most common polymorphism nomenclature in the single nucleotide polymorphism database (dbSNP), rather than the name of restriction enzymes in polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay, namely Apal, BsmI, FokI, and TaqI. Moreover, six genetic models, including allele, homozygote, heterozygote, dominant, recessive, and carrier models, were employed. BH correction method was also utilized to adjust the \( P \)-values obtained from the multiple comparisons.

In our updated meta-analysis of \( VDR \) rs7975232, we enrolled thirteen case-control studies for pooling and did
| Models | M | I² | \( P_{\text{heterogeneity}} \) | Stratification | case/control (N) | OR [95% CI] | \( P_{\text{association}} \) | BH |
|-------|---|----|-----------------|----------------|-----------------|-------------|-----------------|-----|
| allele C vs. T | R | 47.5% | 0.034 | overall | 1690/1857 (12) | 0.91 [0.75–1.10] | 0.325 | 0.690 |
| 57.2% | 0.053 | Asian | 941/837 (5) | 0.91 [0.58–1.43] | 0.689 | 0.798 |
| 47.4% | 0.090 | Caucasian | 699/970 (6) | 0.87 [0.70–1.08] | 0.216 | 0.629 |
| 47.7% | 0.045 | PB | 1143/1436 (10) | 0.90 [0.73–1.12] | 0.341 | 0.524 |
| 47.7% | 0.137 | China | 776/682 (3) | 1.01 [0.62–1.64] | 0.962 | 0.974 |
| 73.1% | 0.024 | Turkey | 206/256 (3) | 0.93 [0.54–1.61] | 0.806 | 0.824 |
| 45.7% | 0.056 | \( r_{\text{HWE}} > 0.05 \) | 1383/1675 (10) | 0.90 [0.72–1.11] | 0.324 | 0.389 |
| 57.4% | 0.021 | PCR-RFLP | 806/907 (8) | 0.88 [0.68–1.14] | 0.360 | 0.744 |
| CC vs. TT | F | 38.2% | 0.114 | overall | 1325/1508 (9) | 0.92 [0.67–1.25] | 0.581 | 0.690 |
| 0.0% | 0.460 | Asian | 781/568 (3) | 0.80 [0.24–2.66] | 0.717 | 0.798 |
| 58.7% | 0.046 | Caucasian | 494/890 (5) | 0.87 [0.62–1.22] | 0.419 | 0.629 |
| 43.7% | 0.087 | PB | 983/1167 (8) | 0.90 [0.66–1.24] | 0.524 | 0.524 |
| 73.8% | 0.022 | Turkey | 206/256 (3) | 1.05 [0.68–1.81] | 0.868 | 0.974 |
| 0.0% | 0.511 | China | 666/499 (2) | 1.24 [0.28–5.53] | 0.775 | 0.824 |
| 24.8% | 0.231 | \( r_{\text{HWE}} > 0.05 \) | 1223/1406 (8) | 0.79 [0.56–1.28] | 0.183 | 0.386 |
| 59.8% | 0.029 | PCR-RFLP | 551/741 (6) | 0.88 [0.61–1.28] | 0.499 | 0.749 |
| TC vs. TT | R | 46.8% | 0.043 | overall | 1485/1777 (11) | 0.95 [0.72–1.24] | 0.690 | 0.690 |
| 51.5% | 0.083 | Asian | 941/837 (5) | 0.90 [0.58–1.42] | 0.658 | 0.798 |
| 61.0% | 0.036 | Caucasian | 494/890 (5) | 0.98 [0.63–1.51] | 0.918 | 0.918 |
| 46.6% | 0.051 | PB | 1143/1436 (10) | 0.91 [0.68–1.22] | 0.523 | 0.524 |
| 50.4% | 0.133 | China | 776/682 (3) | 0.97 [0.58–1.63] | 0.915 | 0.974 |
| 73.1% | 0.024 | Turkey | 206/256 (3) | 1.26 [0.53–2.99] | 0.593 | 0.824 |
| 15.7% | 0.299 | \( r_{\text{HWE}} > 0.05 \) | 1383/1675 (10) | 0.85 [0.69–1.06] | 0.155 | 0.386 |
| 56.3% | 0.033 | PCR-RFLP | 601/827 (7) | 0.88 [0.61–1.28] | 0.988 | 0.988 |
| TC + CC vs. TT | R | 50.7% | 0.027 | overall | 1485/1777 (11) | 0.94 [0.71–1.23] | 0.636 | 0.690 |
| 56.0% | 0.059 | Asian | 941/837 (5) | 0.90 [0.57–1.44] | 0.671 | 0.798 |
| 61.4% | 0.035 | Caucasian | 494/890 (5) | 0.93 [0.62–1.40] | 0.733 | 0.880 |
| 49.6% | 0.037 | PB | 1143/1436 (10) | 0.90 [0.67–1.19] | 0.453 | 0.524 |
| 51.4% | 0.128 | China | 776/682 (3) | 0.99 [0.59–1.66] | 0.974 | 0.974 |
| 76.8% | 0.013 | Turkey | 206/256 (3) | 1.12 [0.47–2.68] | 0.794 | 0.824 |
| 32.9% | 0.145 | \( r_{\text{HWE}} > 0.05 \) | 1383/1675 (10) | 0.86 [0.67–1.09] | 0.205 | 0.386 |
| 61.7% | 0.016 | PCR-RFLP | 601/827 (7) | 0.96 [0.63–1.45] | 0.843 | 0.988 |
| CC vs. TT + TC | F | 4.4% | 0.398 | overall | 1325/1508 (9) | 0.91 [0.69–1.20] | 0.487 | 0.690 |
| 0.0% | 0.506 | Asian | 781/568 (3) | 0.85 [0.26–2.85] | 0.798 | 0.798 |
| 25.0% | 0.254 | Caucasian | 494/890 (5) | 0.86 [0.64–1.16] | 0.330 | 0.629 |
| 10.9% | 0.345 | PB | 983/1167 (8) | 0.90 [0.68–1.19] | 0.442 | 0.524 |
| 0.0% | 0.543 | China | 666/499 (2) | 1.30 [0.29–5.76] | 0.734 | 0.974 |
| 47.7% | 0.148 | Turkey | 206/256 (3) | 0.81 [0.52–1.27] | 0.361 | 0.824 |
| 16.3% | 0.301 | \( r_{\text{HWE}} > 0.05 \) | 1223/1406 (8) | 0.89 [0.64–1.23] | 0.472 | 0.472 |
| 27.6% | 0.228 | PCR-RFLP | 551/741 (6) | 0.82 [0.59–1.41] | 0.228 | 0.744 |
| carrier C vs. T | F | 1.1% | 0.430 | overall | 1485/1777 (11) | 0.93 [0.80–1.09] | 0.380 | 0.690 |
| 41.4% | 0.145 | Asian | 941/837 (5) | 0.92 [0.68–1.23] | 0.558 | 0.798 |
| 0.0% | 0.617 | Caucasian | 494/890 (5) | 0.92 [0.76–1.11] | 0.388 | 0.629 |
| 0.0% | 0.492 | PB | 1143/1436 (10) | 0.90 [0.77–1.06] | 0.223 | 0.524 |
not detect any significant statistical association between the VDR rs7975232 polymorphism and the odds of psoriasis. In 2012, Lee, YH et al. included six case-control studies [14, 16–18, 21, 24] for a meta-analysis regarding the association between the VDR rs7975232 polymorphism and psoriasis susceptibility [31]. Data from the “Turkish” subgroup containing two case-control studies [16, 17] indicated a potential genetic correlation between the VDR rs7975232 polymorphism and psoriasis susceptibility [31]. In 2013, Liu, J. L. et al. included eight case-control studies [14, 16–18, 20, 21, 24, 25] for an updated meta-analysis and only found a positive result under the dominant model ($P_{\text{association}} = 0.043$) but not other genetic models [5]. In 2013, Stefanic, M. et al. performed another meta-analysis, which did not include one study [14] but added another study [13], and reported no robust correlation between the VDR rs7975232 polymorphism and psoriasis risk [4]. In the present meta-analysis, we added four new studies [15, 19, 29, 30] in the overall population and subgroup meta-analyses based on the factors of the

### Table 5: Pooled analyses of the association between VDR rs731236 polymorphism and susceptibility to psoriasis (Continued)

| Models | $M$ | $i^2$ | $P_{\text{heterogeneity}}$ | Stratification | case/control (N) | OR [95% CI] | $P_{\text{association}}$ | BH |
|--------|-----|-------|----------------------------|----------------|------------------|-------------|--------------------------|----|
|        | 37.9% | 0.200 | China                      | 776/682 (3)    | 0.98[0.70~1.38]  | 0.922       | 0.974                    |    |
|        | 16.6% | 0.302 | Turkey                     | 206/256 (3)    | 0.96[0.70~1.32]  | 0.824       | 0.824                    |    |
|        | 2.6%  | 0.415 | $P_{\text{het}} > 0.05$   | 1383/1675 (10) | 0.91[0.77~1.07]  | 0.257       | 0.386                    |    |
|        | 11.6% | 0.341 | PCR-RFLP                  | 601/827 (7)    | 0.92[0.75~1.11]  | 0.372       | 0.744                    |    |

$M$ statistical model, $R$ random effect, $F$ fixed effect, $P_{\text{HWE}}$ $P$-value of Hardy-Weinberg equilibrium, $P_{\text{heterogeneity}}$ $P$-value of Cochrane’s $Q$ statistic for the assessment of heterogeneity, $N$ Number of included case-control studies, OR odds ratio, CI confidence interval, $P_{\text{association}}$ $P$-value of association, BH Benjamini & Hochberg-adjusted $P_{\text{association}}$. 

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**Fig. 5** The forest plot for VDR rs731236 polymorphism under the allele model.
control source, ethnicity, country, HWE and genotyping method under six genetic models. Our data failed to support the essential role of the VDR rs7975232 polymorphism in the odds of psoriasis, which is in line with the data of Lee, YH [3].

For rs1544410, rs2228570, and rs731236 polymorphisms, compared with three previous meta-analyses [4, 5, 31], we added four new eligible studies [15, 19, 29, 30] in our updated meta-analysis. Nevertheless, no statistically significant conclusions between VDR rs1544410, rs2228570 and VDR rs731236 polymorphisms and psoriasis susceptibility were observed. The conclusions regarding the genetic effect of VDR rs1544410, rs2228570, but not VDR rs731236 polymorphisms on the odds of psoriasis disease were consistent with the pooling results of Lee, YH [3]. Nevertheless, the subgroup analysis of “Caucasian” suggested that the VDR rs731236 polymorphism is linked to the risk of psoriasis in the Caucasian population under the recessive model, but not the allele, homozygote and dominant models [3]. In our updated study, we added another two new studies [15, 23], and applied two more models, including heterozygote and carrier models. Apart from ethnicity, we also considered the factors of control source, country, and HWE in the subgroup analyses. However, no positive conclusion was observed in any comparison of VDR rs731236. The potential slight genetic effect of VDR rs731236 polymorphism in the high susceptibility to psoriasis in the Caucasian population was masked by the adding of more sample size, and the utilization of BH correction of P-value. Despite of this, we cannot exclude the VDR rs731236 polymorphism in the odds of psoriasis in the Caucasian population, the support of more case-control studies is required.

In this study, three investigators tried the best to reduce the potential bias during database retrieval, study selection, data extraction, and statistical analysis. However, some limitations should be addressed. First, less than ten case-control studies were included in the meta-analysis of the VDR rs2228570 in the overall population. In addition, only one case-control study of the African population [21] is included in the subgroup analysis of VDR rs7975232 and rs731236 by the factor of ethnicity. Given the lack of sufficient genotype data, we did not detect the potential genetic

Fig. 6 Sensitivity analysis result under the allele model. a rs7975232 polymorphism; b rs1544410 polymorphism; c rs2228570 polymorphism; d rs731236 polymorphism
Table 6 Publication bias assessments

| polymorphism | Models          | Begg's test | Egger's test |
|--------------|-----------------|-------------|--------------|
| rs7975232    | allele C vs. A  | 0.43        | 0.669        |
|              | CC vs. AA       | 1.16        | 0.246        |
|              | AC vs. AA       | 1.04        | 0.300        |
|              | AC + CC vs. AA  | 1.40        | 0.161        |
|              | CC vs. AA+AC    | 0.18        | 0.855        |
|              | carrier C vs. A | 0.67        | 0.502        |
| rs1544410    | allele A vs. G  | 0.31        | 0.760        |
|              | AA vs. GG       | 0.00        | 1.000        |
|              | GA vs. GG       | 0.47        | 0.640        |
|              | GA + AA vs GG   | 0.00        | 1.000        |
|              | AA vs. GG+GA    | 0.07        | 0.945        |
|              | carrier A vs. G | −0.07       | 1.000        |
| rs2228570    | allele C vs. T  | 0.62        | 0.536        |
|              | CC vs. TT       | 0.30        | 0.764        |
|              | TC vs. TT       | 0.00        | 1.000        |
|              | TC + CC vs. TT  | 0.00        | 1.000        |
|              | CC vs. TT+TC    | 0.90        | 0.368        |
|              | carrier C vs. T | 0.60        | 0.548        |
| rs731236     | allele C vs. T  | 0.07        | 0.945        |
|              | CC vs. TT       | −0.10       | 1.000        |
|              | TC vs. TT       | 0.62        | 0.533        |
|              | TC + CC vs. TT  | 0.62        | 0.533        |
|              | CC vs. TT+TC    | 0.10        | 0.917        |
|              | carrier C vs. T | 0.16        | 0.876        |

\(P_{\text{Begg}}\) P-value of Begg’s test, \(P_{\text{Egger}}\) P-value of Egger’s test

influence of the other VDR variants (such as rs4516035) or the combined variants of VDR and other relevant genes. Second, high heterogeneity between studies was detected in some analyses of VDR polymorphisms and psoriasis susceptibility. We observed a decreased level of between-study heterogeneity in some subgroups of ‘Asian’ or ‘Caucasian’, indicating that the factor of ethnicity may be implicated in the source of heterogeneity. Third, conflicting conclusions regarding the potential role of VDR polymorphisms in the partial resistance of psoriasis patients to calcipotriol therapy were reported [15, 16, 23, 26, 27]. We extracted the basic information regarding the gender, age, calcipotriol response, and family history within the included case-control studies; nevertheless, the lack of sufficient data did not support the preformation of the relevant stratification analysis or adjusted effect estimates. Increased sample sizes are still needed to investigate the genetic relationship between different VDR polymorphisms and the response of psoriasis patients to drug treatments.

Table 6: Publication bias assessments

| Polymorphism | Models | Begg’s Test z | P_{Begg} | Egger’s Test t | P_{Egger} |
|--------------|--------|---------------|----------|----------------|----------|
| rs7975232    | allele C vs. A | 0.43 | 0.669 | −1.10 | 0.296 |
|              | CC vs. AA | 1.16 | 0.246 | −1.02 | 0.331 |
|              | AC vs. AA | 1.04 | 0.300 | −1.24 | 0.241 |
|              | AC + CC vs. AA | 1.40 | 0.161 | −1.48 | 0.167 |
|              | CC vs. AA+AC | 0.18 | 0.855 | 0.35 | 0.736 |
|              | carrier C vs. A | 0.67 | 0.502 | −1.11 | 0.291 |
| rs1544410    | allele A vs. G | 0.31 | 0.760 | −0.72 | 0.487 |
|              | AA vs. GG | 0.00 | 1.000 | −0.44 | 0.669 |
|              | GA vs. GG | 0.47 | 0.640 | −0.22 | 0.832 |
|              | GA + AA vs GG | 0.00 | 1.000 | −0.13 | 0.896 |
|              | AA vs. GG+GA | 0.07 | 0.945 | 0.04 | 0.966 |
|              | carrier A vs. G | −0.07 | 1.000 | −0.35 | 0.735 |
| rs2228570    | allele C vs. T | 0.62 | 0.536 | 0.83 | 0.437 |
|              | CC vs. TT | 0.30 | 0.764 | 0.66 | 0.539 |
|              | TC vs. TT | 0.00 | 1.000 | 0.24 | 0.823 |
|              | TC + CC vs. TT | 0.00 | 1.000 | 0.30 | 0.777 |
|              | CC vs. TT+TC | 0.90 | 0.368 | 0.95 | 0.387 |
|              | carrier C vs. T | 0.60 | 0.548 | 0.70 | 0.515 |
| rs731236     | allele C vs. T | 0.07 | 0.945 | 0.53 | 0.611 |
|              | CC vs. TT | −0.10 | 1.000 | −0.14 | 0.895 |
|              | TC vs. TT | 0.62 | 0.533 | 1.13 | 0.286 |
|              | TC + CC vs. TT | 0.62 | 0.533 | 1.08 | 0.310 |
|              | CC vs. TT+TC | 0.10 | 0.917 | −0.27 | 0.795 |
|              | carrier C vs. T | 0.16 | 0.876 | 0.43 | 0.675 |

\(P_{\text{Begg}}\) P-value of Begg’s test, \(P_{\text{Egger}}\) P-value of Egger’s test

Conclusions

Above all, based on the presently available case-control studies, our pooling analysis data and previous reports do not provide the robust statistical evidence linking VDR rs7975232, rs1544410, and rs2228570 polymorphisms with the odds of psoriasis. More case-control studies will be of assistance to us to further confirm the effect of the VDR polymorphisms on the psoriasis susceptibility in the Caucasian population.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12881-019-0896-6.

Additional file 1: Table S1. Searching terms for our meta-analysis (up to August 18, 2019).
Additional file 2: Table S2. The clinical characteristics of included case-control studies.
Additional file 3: Table S3. Quality assessment of included case-control studies.
Additional file 4: Figure S1. The forest plot for VDR rs7975232 polymorphism in the subgroup analysis by ethnicity under the allele model.
Additional file 5: Figure S2. The forest plot for VDR rs7975232 polymorphism in the subgroup analysis by the source of controls under the allele model.
Additional file 6: Figure S3. The forest plot for VDR rs1544410 polymorphism in the subgroup analysis by ethnicity under the allele model.
Additional file 7: Figure S4. The forest plot for VDR rs1544410 polymorphism in the subgroup analysis by the source of controls under the allele model.
Additional file 8: Figure S5. The forest plot for VDR rs2228570 polymorphism in the subgroup analysis by ethnicity under the allele model.
Additional file 9: Figure S6. The forest plot for VDR rs2228570 polymorphism in the subgroup analysis by the source of controls under the allele model.
Additional file 10: Figure S7. The forest plot for VDR rs731236 polymorphism in the subgroup analysis by ethnicity under the allele model.
Additional file 11: Figure S8. The forest plot for VDR rs731236 polymorphism in the subgroup analysis by the source of controls under the allele model.
Additional file 12: Figure S9. The forest plot for VDR rs7975232 polymorphism in the subgroup analysis by ethnicity under the allele model.
Additional file 13: Figure S10. The forest plot for VDR rs7975232 polymorphism in the subgroup analysis by the source of controls under the allele model.

Abbreviations

BH: Benjamini & Hochberg; CNKI: China National Knowledge Infrastructure; dbSNP: single nucleotide polymorphism database; EMBASE: Excerpta Medica Database; HWE: Hardy-Weinberg equilibrium; LDR: Ligase detection reactions; NOS: Newcastle-Ottawa quality assessment scale; ORs: Odd ratios; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; SNP: Single nucleotide polymorphism; VDR: Vitamin D Receptor; WOS: Web of Science

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Authors’ contributions

JL and MY designed the study. JL, LS, and JS extracted, analyzed, and interpreted the data. JL and MY drafted the manuscript. All authors read and approved the final version of the manuscript.

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