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Impact of V-ets Erythroblastosis Virus E26 Oncogene Homolog 1 Gene Polymorphisms Upon Susceptibility to Autoimmune Diseases

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A Meta-Analysis

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Abstract: V-ets erythroblastosis virus E26 oncogene homolog 1 (ETS1) is recognized as a gene of risk to autoimmune diseases (ADs). Two single nucleotide polymorphisms (SNPs) in ETS1 (rs1128334 G>A and rs10893872 T>C) were considered associated with AD risk. However, the results remain conflicting.

We performed a meta-analysis to evaluate more precise estimations of any relationship. We searched PubMed, OvidSP, and Chinese National Knowledge Infrastructure databases (papers published prior to September 12, 2014) and extracted data from eligible studies. Meta-analysis was performed using the STATA 12.0 software. Random effect model or fixed effect model were chosen according to the study heterogeneities.

A total of 11 studies including 7359 cases (9660 controls) for rs1128334 and 8 studies including 5419 cases (7122 controls) for rs10893872 were involved in this meta-analysis. Overall, our results showed that there were significant associations for rs1128334 with AD risk in 5 genetic models, both in pooled analysis and in systemic lupus erythematosus (SLE) subgroup, and in 3 genetic models of the uveitis subgroup. Although for rs10893872, the results showed that there were significant associations in allele model both in pooled analysis and in SLE subgroup.

As a conclusion, this meta-analysis demonstrated that these 2 SNPs (rs1128334 and rs10893872) in ETS1 were associated with ADs risk.

INTRODUCTION

Autoimmune diseases (ADs) are initiated by abnormal immune response to self-antigen and can result in immune-mediated tissue destruction and chronic disabilities.1,2 There are >100 ADs and syndromes, which cause a heavy economic burden in the world, about >$100 billion annually.3 More evidence has emerged and showed that genetic background played an important role in the pathogenesis of ADs.4,5

The sustained pathology of ADs could be widely regulated by a variety of molecules; V-ets erythroblastosis virus E26 oncogene homolog 1 (ETS1) was included as 1 possibility. ETS1 was the first member of ETS oncogene family, and could regulate tumor development and progression.6 Evidence shows that ETS1 could engage into immunology by downregulating the differentiation of not only B cell but also T helper 17 (Th17) cell.7,8 Recent articles show that ETS1 was associated with some types of ADs.9–11 ETS1 can be recognized as a risk gene of ADs. Single nucleotide polymorphisms (SNPs) or mutations in the genetic sequence may alter the expression of the gene.12–16

METHODS

Publication Search

A systematic search was performed in PubMed, OvidSP, and Chinese National Knowledge Infrastructure databases covering all the papers published before September 12, 2014. The search strategy was as follows: (autoimmune OR autoimmune disease OR autoimmunity) AND (polymorphism OR polymorphisms OR variation OR variations OR mutation OR mutations OR variant OR variants) AND (ETS1 OR ETS-1 OR rs1128334 OR rs10893872). The references in these studies were also read to find additional publications on this topic. Articles included met the following criteria: case–control...
study; evaluation of ETS1 polymorphisms (rs1128334 or rs10893872) and risk of ADs; available and usable data of genotype frequency.

Data Extraction
Two authors (Y.Z. and M.L.) independently extracted the data from eligible studies. Data extracted by Y.Z. and M.L. were checked by the third author J.L. The remaining disagreements were discussed and judged by these 3 authors. The following information was extracted: the first author, publication year, diseases, country, genotyping methods, number of cases and controls, the gender distribution of cases and controls, number of genotypes and alleles, Hardy–Weinberg equilibrium (HWE) in control subjects, and the frequency of major allele in controls. Study qualities were judged according to the criteria modified from previous publications23–26 (supplementary Table S1, http://links.lww.com/MD/A289).

Statistical Analysis
Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as a measure of the association between these 2 SNPs (rs1128334 and rs10893872) and AD risk. Allele model and other different type of genetic models (heterozygote, homozygote, dominant, and recessive) were used. In addition to comparing among all subjects, the stratified comparisons were also used according to different ethnicities and different diseases. The between-study heterogeneity was measured by Cochran (Q) and Higgins (I²) tests. If the heterogeneity was considered significant (P < 0.05), the random effects model was used to estimate the pooled OR. Otherwise, the fixed effects model was conducted. Also, logistic meta-regression analysis was carried out, if there was obvious significant heterogeneity, to explore potential sources of heterogeneity. The examined characteristics include publication years, countries, genotyping methods, number of alleles and genotypes, number of female and male patients, and the frequency of major allele in SNP in controls. The HWE was examined using χ² test with significance set at P < 0.05. Sensitivity analysis was performed to evaluate the effect of each study on the combined ORs by deleting each study in each turn. Potential publication bias was evaluate the effect of each study on the combined ORs by Funnel plots and Egger test. An asymmetric plot and the P value <0.05 was recognized as significance. All statistical analyses were performed by STATA 12.0 software (STATA Corp, College Station, TX). As a meta-analysis study, ethical approval of this study is not required. This study was reported following the PRISMA guidelines.

RESULTS
Study Characteristics
A total of 432 articles matched the search strategy and an additional article¹ was found by scanning the references of original papers. After step-by-step screening of the titles, abstracts and full-texts of the articles, as shown in Fig. 1, there were 7 articles appropriate for this meta-analysis, which contained 11 studies for rs1128334, with 7359 cases (9660 controls), and 8 studies for rs10893872, with 5419 cases (7122 controls).

Within all 7 articles, 2 kinds of genotyping methods were used. Only the Asian race was included. The patients in these studies with Behcet Disease (BD), Vogt–Koyanagi–Harada syndrome (VKH), Fuchs uveitis syndrome (FUS), and pediatric uveitis (PU) were all suffering uveitis, which is a common syndrome of ADs. So, these studies were included into uveitis subgroup. There was 1 study not in HWE in control group,¹⁰ and there was not enough data in another article.¹⁰ The detail characteristics are shown in Table 1.

Association Between ETS1 rs1128334 G>A Polymorphism and ADs Risk
First, the association between rs1128334 G>A polymorphism and the risk of AD was analyzed. Significantly increased risks of A allele, GA genotype, AA genotype and GA+AA genotype with ADs were observed in each genetic model in the pooled analyses, respectively (allele model, A vs G, OR 1.28, 95% CI 1.16–1.42, P = 0.000; heterozygote model, GA vs GG, OR 1.19, 95% CI 1.07–1.38, P = 0.030; homozygote model, AA vs GG, OR 1.72, 95% CI 1.24–2.40, P = 0.001; dominant model, GA+AA vs GG, OR 1.28, 95% CI 1.07–1.53, P = 0.006; recessive model, OR 1.57, 95% CI 1.19–2.06, P = 0.001) (Table 2 and Fig. 2A–E).

Next, we analyzed the studies by subgroup analysis according to diseases. In systemic lupus erythematosus (SLE) subgroup, there were increased disease risks in A allele, GA genotype, AA genotype and GA+AA genotype with ADs were observed in each genetic model, respectively (allele model, A vs G, OR 1.44, 95% CI 1.24–1.68, P = 0.000; heterozygote model, GA vs GG, OR 1.61, 95% CI 1.29–2.01, P = 0.000; homozygote model,
| First Author | Year | Diseases | Country | Case Sample Size | Female/Male | Genotyping Methods | Genotype Allele | Control Genotype Allele | HWE of Control \((P\text{ value})\) | Frequency of G Allele in Controls | Quality |
|--------------|------|----------|---------|-----------------|-------------|-------------------|----------------|------------------------|-----------------|--------------------------|--------|
| Yang10       | 2010 | SLE      | China (Hong Kong) | 1073 | 1742 | 966/107 | TaqMan | 1274 872 | 2261 1223 | 0.65 | 6 |
| Yang10       | 2010 | SLE      | China (Shanghai) | 920  | 1053 | 818/102 | TaqMan | 1127 713 | 1379 727 | 0.65 | 6 |
| Yang10       | 2010 | SLE      | Thailand | 314 | 519 | 293/21 | TaqMan | 407 221 | 711 327 | 0.69 | 6 |
| Yang10       | 2010 | SLE      | China (Hefei) | 951 | 860 | 898/53 | TaqMan | 1145 757 | 1210 510 | 0.70 | 6 |
| Zhou17       | 2012 | FUS      | China | 219 | 612 | 102/117 | 262/350 | TaqMan | 104 85 30 | 293 145 264 | 276 72 804 420 | Y (0.992) | 0.66 | 9 |
| Guo18        | 2013 | SLE      | China | 230 | 462 | 34/29 | TaqMan | 78 107 45 | 263 197 227 | 201 34 655 269 | Y (0.245) | 0.71 | 8 |
| Dang19       | 2014 | SLE      | China绝对值 | 370 | 576 | 507/69 | TaqMan | 122 179 69 | 423 317 285 | 252 39 822 330 | N (0.000) | 0.71 | 8 |
| Shan19       | 2014 | AS       | China | 1340 | 1500 | TaqMan | 552 625 163 1729 951 | 718 | 637 145 2073 927 | Y (0.830) | 0.69 | 8 |
| Wei19        | 2014 | PU       | China | 520 | 1204 | 278/242 | 659/545 | PCR-RFLP | 205 253 64 659 381 | 515 544 145 1574 834 | Y (0.942) | 0.65 | 9 |
| Zhou22       | 2014 | BD       | China | 809 | 1132 | 131/678 | 513/619 | PCR-RFLP | 315 366 128 996 622 | 485 510 137 1480 784 | Y (0.869) | 0.65 | 10 |
| Zhou22       | 2014 | VKH      | China | 613 | 1132 | 287/326 | 513/619 | PCR-RFLP | 252 264 97 768 458 | 485 510 137 1480 784 | Y (0.869) | 0.65 | 10 |

| rs10893872   |      |          |         |                |           |                   |                |                        |                |                         |        |
|--------------|------|----------|---------|-----------------|-------------|-------------------|----------------|------------------------|-----------------|--------------------------|--------|
| Yang10       | 2010 | SLE      | China (Hong Kong) | 1073 | 1742 | 966/107 | TaqMan | 1130 1016 | 1992 1492 | 0.57 | 6 |
| Yang10       | 2010 | SLE      | China (Shanghai) | 920 | 1053 | 818/102 | TaqMan | 1000 840 | 1219 887 | 0.58 | 6 |
| Yang10       | 2010 | SLE      | Thailand | 314 | 519 | 293/21 | TaqMan | 320 308 | 598 440 | 0.58 | 6 |
| Yang10       | 2010 | SLE      | China (Hefei) | 951 | 860 | 898/53 | TaqMan | 1065 837 | 1064 656 | 0.62 | 6 |
| Zhou17       | 2012 | FUS      | China | 219 | 612 | 102/117 | 262/350 | PCR-RFLP | 34 103 82 171 267 | 121 316 175 | 558 666 | Y (0.313) | 0.46 | 9 |
| Wei19        | 2014 | PU       | China | 520 | 1204 | 278/242 | 659/545 | PCR-RFLP | 93 218 209 404 636 | 225 620 359 1070 1338 | Y (0.137) | 0.44 | 9 |
| Zhou22       | 2014 | BD       | China | 809 | 1132 | 131/678 | 513/619 | PCR-RFLP | 141 393 275 675 943 | 214 583 335 1011 1253 | Y (0.158) | 0.45 | 10 |
| Zhou22       | 2014 | VKH      | China | 613 | 1132 | 287/326 | 513/619 | PCR-RFLP | 127 329 157 583 643 | 214 583 335 1011 1253 | Y (0.158) | 0.45 | 10 |

AS = ankylosing spondylitis; BD = Behcet disease; FUS = Fuchs uveitis syndrome; HWE = Hardy–Weinberg equilibrium; PCR-RFLP = Polymerase chain reaction - restriction fragment length polymorphism; PU = pediatric uveitis; SLE = systemic lupus erythematosus, VKH = Vogt–Koyanagi–Harada syndrome.
AA vs GG, OR 4.01, 95% CI 2.86–5.62, \( P = 0.000 \); dominant model, GA+AA vs GG, OR 1.95, 95% CI 1.58–2.40, \( P = 0.000 \); recessive model, OR 3.12, 95% CI 2.28–4.27, \( P = 0.000 \) (Table 2 and supplementary Figure S1A–E, http://links.lww.com/MD/A289). In the uveitis subgroup, there were increased risks in A allele and AA genotype in allele model (A vs G, OR 1.11, 95% CI 1.03–1.20, \( P = 0.000 \), homozygote model (AA vs GG, OR 1.29, 95% CI 1.09–1.52, \( P = 0.000 \)).

**TABLE 2.** Stratified Analysis of Association Between ADs Risk and rs1128334

| Gene Model | Stratify | Study, n | Effects size | Heterogeneity |
|------------|----------|----------|--------------|---------------|
|            |          |          | OR (95% CI)  | \( I^2, \% \) | \( P \)       |
| Allele model (A vs G) | Total | 11 | 1.28 (1.16–1.42) | 79.5 | 0.000 | Random |
|            | Diseases SLE | 6 | 1.44 (1.24–1.68) | 81.5 | 0.000 | Random |
|            | Diseases Uveitis | 4 | 1.11 (1.03–1.20) | 0.0 | 0.444 | Fixed |
|            | Total | 7 | 1.18 (1.02–1.38) | 65.8 | 0.008 | Random |
| Heterozygote model (GA vs GG) | Total | 7 | 1.61 (1.29–2.01) | 0.0 | 0.765 | Fixed |
|            | Diseases SLE | 2 | 1.05 (0.94–1.17) | 34.7 | 0.204 | Fixed |
|            | Diseases Uveitis | 4 | 1.05 (0.94–1.17) | 0.411 | 0.000 | Random |
|            | Total | 7 | 1.72 (1.24–2.40) | 84.1 | 0.000 | Random |
| Homozygote model (AA vs GG) | Total | 7 | 4.01 (2.86–5.62) | 0.0 | 0.839 | Fixed |
|            | Diseases SLE | 2 | 1.29 (1.09–1.52) | 0.0 | 0.564 | Fixed |
|            | Diseases Uveitis | 4 | 1.29 (1.09–1.52) | 0.030 | 0.000 | Random |
|            | Total | 7 | 1.28 (1.07–1.53) | 77.8 | 0.000 | Random |
| Dominant model (GA+AA vs GG) | Total | 7 | 4.01 (2.86–5.62) | 0.0 | 0.797 | Fixed |
|            | Diseases SLE | 2 | 1.95 (1.58–2.40) | 0.0 | 0.283 | Fixed |
|            | Diseases Uveitis | 4 | 1.10 (0.99–1.22) | 21.2 | 0.564 | Fixed |
|            | Total | 7 | 1.57 (1.19–2.06) | 79.6 | 0.000 | Random |
| Recessive model (AA vs GG+GA) | Total | 7 | 3.12 (2.28–4.27) | 0.0 | 0.925 | Fixed |
|            | Diseases SLE | 2 | 1.25 (1.08–1.46) | 0.0 | 0.495 | Fixed |
|            | Diseases Uveitis | 4 | 1.25 (1.08–1.46) | 0.004 | 0.000 | Random |

AD = autoimmune disease; CI = confidence interval; OR = odds ratio.

**FIGURE 2.** Forest plots of overall analysis of ADs risk associated with ETS1. (A–E) Forest plots of overall analysis of ADs risk associated with rs1128334. (A) Allele model, A vs G, random model; (B) heterozygote model, GA vs GG, random model; (C) homozygote model, AA vs GG, random model; (D) dominant model, GA+AA vs GG, random model; (E) recessive model, AA vs GG+GA, random model. (F) Forest plots of overall analysis of ADs risk associated with rs10893872. Allele model, C vs T, random model. AD = autoimmune disease; CI = confidence interval; ETS1 = V-ets erythroblastosis virus E26 oncogene homolog 1; OR = odds ratio.

http://links.lww.com/MD/A289
P = 0.003), and recessive model (AA vs GG + GA, OR 1.25, 95% CI 1.08–1.46, P = 0.004), respectively (Table 2 and supplementary Figure S1F–H, http://links.lww.com/MD/A289).

### Association Between ETS1 rs10893872 T>C Polymorphism and AD Risk

For the association between rs10893872 T>C polymorphism and AD risk, there was significantly increased risk of C allele in overall comparison in allele model (C vs T, OR 1.17, 95% CI 1.08–1.28, P = 0.000) (Table 3 and Fig. 2F). Based on the data limitation, the stratified analysis could only be conducted in the allele model, and the increased risk was found in SLE subgroup (allele model, C vs T, OR 1.22, 95% CI 1.14–1.30, P = 0.000) (Table 3 and supplementary Figure S1I, http://links.lww.com/MD/A289).

### Evaluation of Heterogeneity

The heterogeneities among studies were obvious in the overall comparisons (rs1128334, $I^2 = 79.5\%$, $Q^2 = 0.022$, $P = 0.000$; rs10893872, $I^2 = 65.1\%$, $Q^2 = 0.010$, $P = 0.005$). The meta-regression analysis was conducted to further explore sources of heterogeneity. Several factors were tested as potential sources of heterogeneity, including publication years, countries, genotyping methods, number of genotypes and alleles, number of female and male patients, and the frequencies of major allele for each SNP in controls. For rs1128334, the genotyping methods (adjusted $R^2 = 40.83\%$) and the frequency of G allele in control (adjusted $R^2 = 73.00\%$) could partially explain the heterogeneity, whereas for rs10893872, the heterogeneity could not be explained by any of the potential sources above.

### Sensitivity and Publication Bias Analysis

We performed the sensitivity analysis to test the influence of a single study on the overall meta-analysis by deleting each study once a time. As a result, the pooled estimate did not show significant difference (data not shown), which indicated that the results were statistically reliable. No evidence of publication bias was found in current meta-analysis, identified by the Begg test ($P = 0.640$ for rs1128334, $P = 0.711$ for rs10893872) and Egger test ($P = 0.546$ for rs1128334, $P = 0.569$ for rs10893872) (Fig. 3).

## DISCUSSION

ETS1 is a member of the ETS transcription factor families. It is expressed by a variety of cell types and regulates several functions in some cell signaling pathways. The differentiation of both B cell and T_{H}17 cell could be inhibited by ETS1. Animal experiments showed that lupus-like disease could easily be developed in ETS1-deficient mice. Then, ETS1 was found to be associated with SLE based on human data. As the clinical and immunological overlap of SLE and other ADs, other researchers found the association of ETS1 and ankylosing spondylitis (AS).

Some articles reported the relationship between 2 variants (rs1128334 and rs10893872) in ETS1 and susceptibility to ADs, such as SLE, BD, and VKH. However, the results remain conflicting. Maybe due to different disease types included in ADs, some studies showed that these 2 SNP in ETS1 were associated with susceptibility to ADs, whereas other studies did not. Therefore, we conducted this meta-analysis, including pooled analysis and subgroup analysis based on different disease types, in order to better understand whether these 2 SNPs contribute to the susceptibility to ADs.

For rs1128334, A allele, GA genotype, AA genotype, and GA + AA genotype were all found correlated with increased risk of ADs in each genetic model, both in pooled analyses and in SLE subgroup. Moreover, the increased disease risk of A allele and AA genotype were also found in the allele model, homozygote model and recessive model in Uveitis subgroup. For rs10893872, C allele was found to be associated with increased disease risk in allele model, both in pooled analyses and in SLE subgroup. However, there was not any significant association in other genetic models.

There are some limitations in our studies. First, although there were 7 articles included, the studies for some stratified analyses were limited. For example, there were only 2 studies for SLE subgroup in analyses for rs1128334, except in the allele model, whereas there was not enough data to do the stratified analysis for rs10893872 in 4 genetic models, except in the allele model. Also, there was only the data about Asian populations. Further studies based on other ethnic populations will be needed. Second, there were obvious heterogeneities between different groups for some genetic models. Although the meta-regression and sensitivity analyses were conducted, and we found that in rs1128334 the variation of G allele frequency in controls and different genotyping methods could partly explain

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**TABLE 3. Stratified Analysis of Association Between ADs Risk and rs10893872**

| Gene Model                  | Study, n | OR (95% CI) | $P$   | $I^2$ (%) | $P$   | Effect Model |
|-----------------------------|----------|-------------|-------|-----------|-------|--------------|
| Allele model (C vs T)       | 8        | 1.17 (1.08–1.28) | <0.001 | 65.1      | 0.005 | Random       |
| SLE                         | 4        | 1.22 (1.14–1.30) | <0.001 | 0.0       | 0.635 | Fixed        |
| Uveitis                     | 4        | 1.12 (0.95–1.33) | 0.179 | 79.4      | 0.002 | Random       |
| Heterozygote model (TC vs TT)| 4        | 0.97 (0.84–1.12) | 0.664 | 0.0       | 0.651 | Fixed        |
| Homozygote model (CC vs TT) | 4        | 1.21 (0.89–1.64) | 0.227 | 72.8      | 0.012 | Random       |
| Dominant model (TC + CC vs TT)| 4        | 1.05 (0.91–1.20) | 0.513 | 6.0       | 0.363 | Fixed        |
| Recessive model (CC vs TT + TC)| 4       | 1.23 (0.92–1.66) | 0.164 | 84.6      | 0.000 | Random       |

AD = autoimmune disease; CI = confidence interval; OR = odds ratio; SLE = systemic lupus erythematosus.
some heterogeneity, the results still needed to be treated with caution. Third, only 2 SNPs in ETS1 were included in this study. Some other SNPs in ETS1 also could contribute to susceptibility to ADs. Not only should the effect of these SNPs, but the interaction or network among these related genes also be studied in the future. Furthermore, studies investigating the gene-environment interactions will also help to make clear of the role of these SNPs in the pathology of ADs. Finally, since ADs consist of diverse diseases, the relationship of these SNPs with other type of ADs, such as rheumatoid arthritis, inflammatory bowel disease and seronegative spondyloarthropathies, should be investigated in the future.

As a conclusion, our study demonstrated that these 2 SNPs (rs1128334 and rs10893872) in ETS1 confer risk of ADs. Considering the limitation of our study, large sample studies including different ethnic populations and other type of ADs will be needed to confirm the results of this analysis.

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