Review

FoxP3 rs3761548 polymorphism predicts autoimmune disease susceptibility: A meta-analysis

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Abstract

Background and aims: Autoimmune diseases (ADs) are associated with loss of self-tolerance leading to immune-mediated destruction of host tissues and organs. FoxP3 polymorphism (–3279 A/C, rs3761548) was shown to associate with AD susceptibility, but the results were inconsistent. This study performed a meta-analysis to investigate the FoxP3 –3279 A/C polymorphism for AD susceptibility.

Methods: A total of eight published case-control studies, including 1844 cases and 1857 controls were retrieved from the PubMed database for the meta-analysis. Heterogeneity was assessed with a standard Q-statistic test and I² test. Crude pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to estimate the FoxP3 polymorphism and AD risk according to the random-effective model and fixed-effect model.

Results: A significant relationship between FoxP3 –3279 A/C gene polymorphism and ADs was found under the allelic (OR: 1.477, 95% CI: 1.326–1.645, P = 0.000), homozygous (OR: 2.094, 95% CI: 1.390–3.153, P = 0.000), recessive (OR: 1.804, 95% CI: 1.083–3.008, P = 0.024), dominant (OR: 1.323, 95% CI: 1.154–1.516, P = 0.000), and additive (OR: 1.516, 95% CI: 1.360–1.689, P = 0.000) genetic models. However, there was no significant association between FoxP3 –3279 A/C polymorphism and ADs under the heterozygous genetic model (OR: 1.202, 95% CI: 0.899–1.606, P = 0.215).

Conclusion: FoxP3 –3279 A/C polymorphism may influence AD risk, especially, the A allele variant carriers of FoxP3 –3279 A/C polymorphism definitively associated with AD susceptibility.

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http://dx.doi.org/10.1016/j.humimm.2013.08.270
1. Introduction

Autoimmune diseases (ADs) are a heterogeneous group of complex diseases and caused by loss of self-tolerance, leading to immune-mediated destruction of host tissues and organs [1]. Worldwide, there is approximately five percent of the population suffering ADs, which include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, Graves’ disease, Hashimoto’s disease, Crohn’s disease, primary biliary cirrhosis, myasthenia gravis, alopecia areata, psoriasis, and vitiligo [2,3]. To date, the exact etiology of ADs is still not fully understood, although these diseases have been known to be induced by genetic and environmental factors [4]. Individuals with different ADs exhibit different epidemiological features and clinical manifestations, but all ADs share similar etiological mechanisms [5], i.e., the host immunoresponses to self-antigens cause damage to the tissues and organs. To date, much research focuses strongly on individual clinical diseases even though these autoimmune phenotypes could represent pleiotropic outcomes of specific, common disease genes that underlie similar immune-genetic mechanisms [6,7]. For example, distinct ADs occur within an individual and within a family, suggesting that ADs share a similar genetic susceptibility [8]. A previous meta-analysis also showed that clinically distinct ADs had a number of disease susceptibility loci identified by whole genome profiling [9]. Thus, it is reasonable to suspect that ADs share the major genetic susceptibility factors.

Indeed, in recent years, a number of possible genetic mutations have been investigated for AD susceptibility using meta-analyses. The data showed that polymorphisms of IL-10, TNF-α, TRAF1–C5 and STAT4 rs7574865 suggested increased risk of AD [10–12], whereas polymorphisms of other genes, such as TNF −308 A/G and −238 A/G, were not associated with AD risk [13]. However, investigation of gene and environment interaction could help us to identify risk factors and susceptible genes for AD development and progression and then to develop novel treatment strategies for the effective control of ADs. To this end, immunoregulatory T (Treg) cells play an important role in regulating immune responses, alteration of which may contribute to AD development and progression. CD4+/CD25+ Treg cells have been demonstrated to be involved in the maintenance of tolerance to self-antigens and the induction of non-responsiveness to allo-antigens [14–17]. Furthermore, the forkhead box P3 (FoxP3) gene is primarily expressed in Treg cells under normal physiological conditions. The FoxP3 gene is located on chromosome Xp11.23 [18,19] and FoxP3 protein regulates T-cell activation and functions as a transcriptional repressor to downregulate cytokine production in T-cells [14,20–23]. Thus, FoxP3 gene polymorphisms can lead to the lack of functional CD4+/CD25+ Treg cells in the human body and, therefore, induce autoimmune reactions and diseases, such as type 1 diabetes and inflammatory primary biliary cirrhosis [24–26]. A functional single nucleotide polymorphism (SNP) of the FoxP3 gene (−3279 A/C, rs3761548) has been implicated in development of allergic rhinitis [27,28]. Thereafter, a number of studies associated FoxP3 polymorphism (−3279 A/C, rs3761548) with AD risk, but many of the studies reported inconsistent data, possibly because of the low statistical power of the individual studies [14,26,29–32]. Therefore, in this study, we performed a meta-analysis of the published data to investigate the association of FoxP3 −3279 A/C polymorphism with AD susceptibility.

2. Materials and methods

2.1. Literature search strategy

For this meta-analysis, we searched different public databases, including EMBASE, PubMed, and Chinese National Knowledge Infrastructure (CNKI) databases without language restrictions. The last searches were performed on December 20, 2012 and, during the searches, we utilized a combination of medical subjective headings (Mesh) and key words (i.e., “forkhead box P3”, “FoxP3”, “−3279 A/C”, “rs3761548”, “autoimmune diseases” and “polymorphism”). The scope of the literature search was subsequently enlarged to include the reference lists of the retrieved publications.

2.2. Inclusion and exclusion criteria

After retrieval of published studies from the databases, we created both inclusion and exclusion criteria. The inclusion criteria were: (i) studies that included autoimmune diseases that were diagnosed according to their classification criteria [33–40]; (ii) studies that evaluated the association of −3279 A/C polymorphism with ADs; (iii) case-controlled or cohort studies; and (iv) original publications containing independent data that provided enough data to calculate odds ratios (ORs). The exclusion criteria included: (i) studies that contained overlapping data with other studies; (ii) studies in which the genotype or allele frequency could not be calculated; and (iii) studies that were case-only, review papers, or not population-based.

2.3. Data extraction

Relevant data (including the first author, year of publication, country, ethnicity, disease phenotype, genotyping method, source of control, total number of cases and controls, genotype frequency in the case and controls, and Hardy–Weinberg equilibrium status) were extracted from each publication independently by two investigators. Disagreements regarding retrieved data were discussed and a consensus was reached for each case.

2.4. Statistical analysis

Six genetic models were selected to be analyzed for association between FoxP3 −3279 A/C polymorphism and ADs: allele, additive, recessive, dominant, heterozygote or homoyzgous model. The Hardy–Weinberg equilibrium in the control group was examined by a Chi-square test and P < 0.05 was considered as statistically significant disequilibrium. The summarized odds ratio (OR) with 95% confidence intervals (CIs) that was determined by the Z test was used to estimate the FoxP3 polymorphism and AD risk. A P-value less than 0.05 was considered statistically significant. Heterogeneity was assessed using a standard Q-statistic test and I² test was used to quantify inconsistency. If the P-value of the Q-test was less than 0.1, or an I² value ≥50%, ORs were pooled according to the random-effect model (DerSimonian and Laird). Otherwise, the fixed-effective model (Mantel–Haenszel) was used [41,42]. Publication bias was assessed by Egger’s test and Begg’s funnel plots [43]. All statistical analyses were performed by using STATA version 12.0 (StataCorp, College Station, TX).

3. Results

3.1. Literature review and description of included studies

In this study, we retrieved a total of 352 publications after a search of PubMed, EMBASE, and CNKI databases. The precise screening process is shown in Fig. 1. After reviewing full text publications, we excluded 346 studies and obtained six publications with eight qualified case-control studies for this meta-analysis, which included 1844 cases and 1857 controls. Among these eight studies, six were conducted in Asian populations [14,29–32] and two in Caucasian populations [26]. Controls of three studies were
population-based [29,30] and the other five studies [14,26,31,32] were hospital-based population. The ADs studied in the articles included Graves’ disease (GD) [29], Hashimoto’s disease (HD) [29], Crohn’s disease (CD) [26], primary biliary cirrhosis (PBC) [26], myasthenia gravis (MG) [30], alopecia areata (AA) [31], psoriasis [32], and vitiligo [32]. The distributions of FoxP3 –3279 A/C genotypes and genotyping derived from the studies are shown in Table 1. The genetic distributions of the control groups in all types and genotyping derived from the studies are shown in Table 1.

3.2. Test of heterogeneity

As shown in Table 2, significant heterogeneity was found using the recessive ($P_{\text{heterogeneity}} = 0.001$), heterozygous ($P_{\text{heterogeneity}} = 0.005$), homozygous ($P_{\text{heterogeneity}} = 0.040$). In contrast, there was no significant heterogeneity under the additive ($P_{\text{heterogeneity}} = 0.366$), dominant ($P_{\text{heterogeneity}} = 0.672$), allele ($P_{\text{heterogeneity}} = 0.271$), or the fixed-effective models. After that, subgroup analyses were performed for ethnicity, source of controls, genotyping method, and Hardy—Weinberg equilibrium of controls. The diminished heterogeneities were found in some of these subgroups using the recessive, heterozygous, and homozygous models.

3.3. Meta-analysis results

Significant association of FoxP3 –3279 A/C polymorphism with AD risk was found after the data were analyzed by using the allelic (OR: 1.477, 95% CI: 1.326–1.645, $P = 0.000$), homozygous (OR: 2.094, 95% CI: 1.390–3.153, $P = 0.000$), recessive (OR: 1.804, 95% CI: 1.083–3.008, $P = 0.024$), dominant (OR: 1.323, 95% CI: 1.154–1.516, $P = 0.000$), or additive (OR: 1.516, 95% CI: 1.360–3.169, $P = 0.000$) genetic models. In contrast, there was no statistically significant association between FoxP3 –3279 A/C polymorphism and ADs using the heterozygous genetic model (OR: 1.202, 95% CI: 0.899–1.606, $P = 0.215$) (Table 2).

Furthermore, subgroup analyses were then performed to investigate the effect of source of control, ethnicity, HWE violation and genotyping method on such an association; the data are shown in Table 2. Among Asian populations, increased risk of AD was found with the allelic (OR: 1.481, 95% CI: 1.318–1.664), additive (OR: 1.527; 95% CI: 1.358–1.717), dominant (OR: 1.287, 95% CI: 1.115–1.486) or homozygous (OR: 1.966; 95% CI: 1.135–3.406) genetic models. Among Caucasians, increased risk of AD was also found with the allelic (OR: 1.451; 95% CI: 1.089–1.932), additive (OR: 1.451; 95% CI: 1.089–1.932), dominant (OR: 1.680; 95% CI: 1.092–2.583) or homozygous (OR: 2.095; 95% CI: 1.148–3.821) genetic models. Moreover, increased risk for of AD hospital-based studies was observed using these five genetic models (allelic, OR: 1.512, 95% CI: 1.349–1.694; additive, OR: 1.557, 95% CI: 1.360–1.689; recessive, OR: 2.449, 95% CI: 1.506–3.982; dominant, OR: 1.310, 95% CI: 1.133–1.515; homozygous, OR: 2.667, 95% CI: 1.929–3.687), but not in population-based studies.

Significant increased risk of AD was observed in studies without Hardy—Weinberg equilibrium violation with four genetic models (additive, OR: 1.522, 95% CI: 1.361–1.702; recessive, OR: 2.189, 95% CI: 1.296–3.645; dominant, OR: 1.297, 95% CI: 1.127–1.493; or homozygous, OR: 2.441, 95% CI: 1.638–3.639), while elevated risk was found in the studies with Hardy—Weinberg equilibrium violation with three genetic models (dominant, OR: 1.757, 95% CI: 1.022–3.020; heterozygous, OR: 2.237, 95% CI: 1.135–4.408; or allelic, OR: 1.481, 95% CI: 1.326–1.645). In addition, significant associations were reached in the subgroup of non-restrict fragment length polymorphism (RFLP) to detect gene SNPs using the five genetic models (allelic, OR: 1.423, 95% CI: 1.250–1.620; additive, OR: 1.477, 95% CI: 1.296–1.684; recessive, OR: 2.046, 95% CI: 1.335–3.135; dominant, OR: 1.342, 95% CI: 1.143–1.577; or homozygous, OR: 2.382, 95% CI: 1.697–3.343), whereas significant associations were found in the subgroup of RFLP to detect gene SNPs using two genetic models (allelic, OR: 1.604, 95% CI: 1.321–1.948; or additive, OR: 1.604, 95% CI: 1.321–1.948).

3.4. Sensitivity analysis

Sensitivity analysis was performed to explore the individual study’s influence on the pooled results [44]. After each study was sequentially omitted from the pooled analysis, the results of this meta-analysis showed that there was no substantial change of data on all six models. This finding indicated that the results of the present analysis are very stable.

3.5. Publication bias

To estimate any possible publication bias, Begg’s funnel plots were performed; the shape of funnel plots was symmetrical in the allelic, additive, dominant, and heterozygous genetic models (Fig. 2). Afterwards, Egger’s linear regression test was used to quantitatively assess the publication bias. The data showed no evi-
In this meta-analysis, we demonstrated that FoxP3 –3279 A/C polymorphism might contribute to AD susceptibility, including Graves' disease, Hashimoto's disease, Crohn's disease, primary biliary cirrhosis, myasthenia gravis, alopecia areata, psoriasis, and vitiligo. Using the allelic (OR, 1.477), homozygous (OR, 2.094), recessive (OR, 1.804), dominant (OR, 1.523), and additive (OR, 1.516) genetic models, a trend was found between FoxP3 –3279 A/C polymorphism and increased risk of ADs, whereas there was less significant association found using the heterozygous genetic model (OR, 1.202). Thus, this meta-analysis confirmed that FoxP3 –3279 A/C polymorphism contributes to AD risk.

In these eight eligible studies, A allele variant carriers were shown to increase the risk of alopecia areata [31], psoriasis [14], vitiligo [32], consistent with our meta-analysis. Park et al. [26] and Inoue et al. [29] also showed that there has been significant association of A allele variant carriers with CD and GD risk using the dominant model. These results together demonstrated that the A allele variant carriers of FoxP3 –3279 A/C polymorphism definitively contribute to AD susceptibility.

Furthermore, in the subgroup analysis using ethnicity as a determinant, significantly increased AD risk was observed in both Asian and Caucasian populations using additive, dominant, homozygous and allelic genetic models. The results suggest that FoxP3 –3279 A/C polymorphism may have a similar effect in different ethnicities with different environments, life styles, and genetic diversities. In the subgroup analysis stratified by source of controls, we found that an increased risk for AD was evident in the hospital-based studies all of the genetic models with the exception of the recessive model.

4. Discussion

Table 1
Characteristics of eligible studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Ethnicity</th>
<th>Disease phenotype</th>
<th>Source of control</th>
<th>Genotyping method</th>
<th>Case/ control (N)</th>
<th>Case Genotypes</th>
<th>Allele frequency</th>
<th>Control Genotypes</th>
<th>Allele frequency</th>
<th>HWE (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Inoue</td>
<td>2010</td>
<td>Japan</td>
<td>CD</td>
<td>PB</td>
<td>PCR-RFLP</td>
<td>109/71</td>
<td>7</td>
<td>27</td>
<td>64</td>
<td>155</td>
<td>5</td>
</tr>
<tr>
<td>N. Inoue</td>
<td>2010</td>
<td>Japan</td>
<td>HD</td>
<td>PB</td>
<td>PCR-RFLP</td>
<td>78/71</td>
<td>3</td>
<td>12</td>
<td>57</td>
<td>18</td>
<td>126</td>
</tr>
<tr>
<td>Lin Gao</td>
<td>2010</td>
<td>Han</td>
<td>Psoriasis</td>
<td>HB</td>
<td>PCR-SSP</td>
<td>524/549</td>
<td>35</td>
<td>163</td>
<td>326</td>
<td>233</td>
<td>815</td>
</tr>
<tr>
<td>Ogypark</td>
<td>2005</td>
<td>Caucasian</td>
<td>CD</td>
<td>HB</td>
<td>PCR-DS</td>
<td>93/107</td>
<td>20</td>
<td>49</td>
<td>24</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>Ogypark</td>
<td>2005</td>
<td>Caucasian</td>
<td>PB</td>
<td>HB</td>
<td>PCR-DS</td>
<td>82/107</td>
<td>16</td>
<td>42</td>
<td>24</td>
<td>74</td>
<td>90</td>
</tr>
<tr>
<td>Zhang J</td>
<td>2012</td>
<td>Han</td>
<td>AA</td>
<td>PB</td>
<td>PCR-RFLP</td>
<td>118/124</td>
<td>1</td>
<td>33</td>
<td>84</td>
<td>35</td>
<td>201</td>
</tr>
<tr>
<td>Yang S</td>
<td>2010</td>
<td>Han</td>
<td>MG</td>
<td>PB</td>
<td>PCR-RFLP</td>
<td>240/248</td>
<td>121</td>
<td>86</td>
<td>119</td>
<td>328</td>
<td>324</td>
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<tr>
<td>Li HS</td>
<td>2008</td>
<td>Han</td>
<td>Vitiligo</td>
<td>HB</td>
<td>PCR-SSP</td>
<td>600/600</td>
<td>72</td>
<td>146</td>
<td>382</td>
<td>290</td>
<td>910</td>
</tr>
</tbody>
</table>

Note: CD, Croasses' disease; HD, Hashimotes's disease; CD, Crohn's disease; PB, primary biliary cirrhosis; MG, myasthenia gravis; AA, alopecia areata; PB, population-based; HB, hospital-based; HWE, Hardy-Weinberg equilibrium; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSP, polymerase chain reaction with sequence-specific primers; PCR-DS, polymerase chain reaction-direct sequence.

Table 2
Data of the pooled studies in this meta-analysis.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Source of control</th>
<th>Ethnicity</th>
<th>HWE violation</th>
<th>Genotyping method</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PB</td>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td>OR (95% CI)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.664</td>
<td>0.549</td>
<td>0.423</td>
<td>1.83</td>
<td>0.029</td>
<td>1.08</td>
<td>0.271</td>
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<td></td>
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<td>5</td>
<td>2.449</td>
<td>0.007</td>
<td>0.700</td>
<td>1.065</td>
<td>0.008</td>
<td>1.224</td>
<td>0.559</td>
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<tr>
<td></td>
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<td>2</td>
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<td>0.822</td>
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<td>1.595</td>
<td>0.739</td>
<td>1.451</td>
<td>0.238</td>
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<td>6</td>
<td>1.805</td>
<td>0.001</td>
<td>0.802</td>
<td>1.127</td>
<td>0.003</td>
<td>1.527</td>
<td>0.331</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>2.189</td>
<td>0.555</td>
<td>0.814</td>
<td>1.081</td>
<td>0.014</td>
<td>1.527</td>
<td>0.271</td>
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<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.785</td>
<td>0.002</td>
<td>0.311</td>
<td>2.237</td>
<td>0.293</td>
<td>1.412</td>
<td>0.104</td>
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<td></td>
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<td>4</td>
<td>1.108</td>
<td>0.001</td>
<td>0.269</td>
<td>1.266</td>
<td>0.002</td>
<td>1.222</td>
<td>0.225</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>2.046</td>
<td>0.124</td>
<td>3.135</td>
<td>1.190</td>
<td>0.225</td>
<td>1.282</td>
<td>0.451</td>
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<tr>
<td></td>
<td></td>
<td>8</td>
<td>1.804</td>
<td>0.001</td>
<td>1.083</td>
<td>1.202</td>
<td>0.005</td>
<td>1.516</td>
<td>0.366</td>
</tr>
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</table>

Q-test was used to generate the P values. N, the number of studies included in subgroup. HWE, Hardy-Weinberg equilibrium; RFLP, restriction fragment length polymorphisms; PB, population-based; HB, hospital-based.
heterozygous genetic model. However, there was no statistically significant association found in the population-based studies. This inconsistent result suggests that a selection bias was a major problem that may have contributed to association of this gene SNP with AD risk. The hospital-based controls may not be truly representative of the general population and, thus, may produce unreliable results. Therefore, strict matching criteria to select proper control participants are important for reducing selection bias in future studies. Furthermore, the subgroup analysis using the genotyping method showed that a significant increased risk of AD was observed in the studies using the non-RFLP method in all of the genetic models with the exception of the heterozygous genetic model. The significant increased risk was only found in the studies using RFLP method in the additive and allelic genetic models. The RFLP method has been widely used to detect SNPs because of its relative simplicity, but the method has limitations. First, RFLP is not a direct method and its discriminatory power depends on the restriction enzymes to cleave the particular restriction sites. Moreover, the high reaction temperature used for RFLP may decrease the sensitivity of assay [45]. In this meta-analysis, we also found other genotyping methods (such as PCR-SSP and PCR-direct sequence) for detection of SNPs. PCR-SSP and PCR-direct sequence may have high sensitivity and accuracy in SNP genotyping [46,47]; thus, they are much more reliable and accurate for SNP detection than that of RFLP and may be the future choice for identification of SNPs in molecular epidemiology studies.

Furthermore, the subgroup analysis according to the Hardy–Weinberg equilibrium violation showed that only one study violated the Hardy–Weinberg equilibrium [29]. After excluding this study, a significant association with AD risk was found in all of the genetic models except for the allelic genetic model. Deviation from the Hardy–Weinberg equilibrium may contribute to some methodological weaknesses, such as genotyping errors, biased selection of subjects, and population stratification; thus, more well-designed studies are needed to confirm this association [48].

In addition, evidently significant heterogeneity among these eight studies occurs using the recessive, heterozygote (D), homozygous (E), and recessive(F) models. To reduce the heterogeneity, we utilized the random-effect models to analyze the data. As shown in Table 2, heterogeneities were reduced or removed in the subgroup, indicating that the heterogeneities may be due to multiple factors, such as ethnicity, selection of controls, gender, genotyping method, and prevalence of lifestyle factors.

Mechanistically, FoxP3 gene plays an important role in T-cell regulation and immune homoeostasis. For example, the CD4+/CD25/FoxP3+ Treg cells play an important role in immune response and the maintenance of peripheral tolerance against foreign antigens [49–52]. However, the deficiency or dysfunction of CD4+
CD25+ Treg cells causes a breach in self-tolerance and produces autoimmune diseases in animals and in humans (such as severe allergic and inflammatory bowel disease) [20,53–55]. Clinically, an autoimmune diseases in animals and in humans (such as severe allograft rejection) [1,2]. Thus, alteration of FoxP3 expression and functions could contribute to AD development. As for the FoxP3 – 3279 A/C polymorphism, it is localized in the Foxp3 promoter region as a functional polymorphism, which may directly or indirectly alter the level of FoxP3 protein expression in cells [14,26,59]. This meta-analysis indeed confirms that FoxP3 – 3279 A/C polymorphism is associated with the susceptibility of different ADs.

However, this study does have some limitations. First, the current analysis had a relatively small number of studies (n = 8), cases and controls, which may limit the statistical power of our analyses. Second, the controls of our included study were not uniformly defined; they were selected either from hospitals or from the population. Third, both the funnel plot and Egger’s test indicated that two of the six studies did have a publication bias. Fourth, to date, there were no GWAS data supporting FoxP3 – 3279 A/C polymorphism for association with the susceptibility of these six different ADs. Thus, a large-scale population-based study is needed to confirm our current data.

In conclusion, this meta-analysis showed that FoxP3 – 3279 A/C polymorphism had an influence on the risk of ADs. However, the exact mechanism by which the FoxP3 gene polymorphism influences the pathogenesis of ADs remains to be determined. Moreover, future studies are needed to investigate whether the SNP rs3761548 affects expression levels of FoxP3 protein and determine the role of FoxP3 protein in regulation of Treg cell activity.

Acknowledgments

This work was supported in part by a Grant from the Nature Science Foundation of China (8120851 to L.D.).

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