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To cite this article: Fangwei Li MD, Yanting Zhu MD, Xinming Xie MD, Rui Ke MD, Shaojun Li MD, Lu Liu MD, Jun Lu MD & Manxiang Li MD (2017): Interleukin-12B gene polymorphisms and bronchial asthma risk: A meta-analysis, Journal of Asthma, DOI: [10.1080/02770903.2016.1277536](https://doi.org/10.1080/02770903.2016.1277536)

To link to this article: <http://dx.doi.org/10.1080/02770903.2016.1277536>



Accepted author version posted online: 13 Mar 2017.
Published online: 13 Mar 2017.



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Interleukin-12B gene polymorphisms and bronchial asthma risk: A meta-analysis

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ABSTRACT

Objective: This meta-analysis aims to investigate whether interleukin-12B (IL-12B) –1188A/C or the promoter polymorphisms may be a risk factor for asthma. **Data Sources:** Web of Science, PubMed, China National Knowledge Infrastructure (CNKI) and Wanfang databases were searched (updated August 20, 2015). **Study selections:** Articles evaluating the association between IL-12B genetic polymorphisms and asthma risk were selected. **Results:** 13 eligible studies with a total of 5092 subjects were finally included in this meta-analysis. For IL-12B –1188A/C, analysis by ethnicity indicated that there was a markedly reduced risk for asthma in East Asian (CC + AC vs. AA: OR = 0.64, 95% CI = 0.50–0.81, $P < 0.001$). For IL-12B promoter, analysis by ethnicity indicated there was a markedly increased risk in East Asian (MM vs. WM + WW: OR = 1.57, 95% CI = 1.18–2.10, $P = 0.002$). Analysis by allergic state revealed the similar results in atopic subgroup. **Conclusions:** IL-12B –1188 C allele may be a protective factor against asthma in East Asian. In addition, promoter MM genotype may be a risk factor for asthma in East Asian and allergic people.

ARTICLE HISTORY

Received 16 May 2016
Revised 13 December 2016
Accepted 26 December 2016

KEYWORDS

Asthma; genetic; IL-12B; meta-analysis; polymorphisms

Introduction

Bronchial asthma is a chronic inflammatory airway disease characterized by airway inflammation, airway hyperresponsiveness, and reversible airflow obstruction [1]. The development of asthma appears to be determined by genetic and environmental factors [2]. Numerous studies about the correlation between polymorphisms of cytokine genes and asthma susceptibility have been published [3–5]. Interleukin-12 (IL-12) is an important immunoregulatory cytokine modulating the balance between Th1/Th2 helper lymphocytes and providing a functional link between innate and acquired immune responses [6]. IL-12 is produced by dendritic cells, Langerhans cells, mononuclear phagocytic cells, and mast cells [7]. Accumulated evidences have shown that IL-12 is associated with the development of asthma [8,9].

Interleukin-12B (IL-12B) gene is located in chromosome 5q31.1–33.1, which encodes IL-12 subunit p40, and is linked to asthma susceptibility and asthma-related phenotypes [10–12]. Several polymorphisms in IL-12B gene have been identified. A single-nucleotide polymorphism (SNP) at position –1188 (also called rs3212227) in 3'UTR region presents adenosine (A) or cytosine (C), and a number of studies on the association of IL-12B –1188A/C polymorphisms with asthma have been

conducted [13–17]. In addition, several other studies have indicated that SNP in the promoter region of IL-12B are also associated with asthma susceptibility [11,18–20]. However, a single study performed in an individual medical center with small sample size may not have sufficient power to draw a reliable conclusion; and the results from different studies are contradictory and inconclusive. Therefore, it is important to clarify the relationship between IL-12B gene polymorphisms and asthma susceptibility based on all published studies. The aim of the present study is to address this issue using meta-analysis.

Materials and methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [21].

Identification of eligible studies

To identify all eligible studies that investigated the association between IL-12B –1188A/C or the promoter polymorphisms and asthma risk, a comprehensive electronic search of Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Database was performed until August 20, 2015. We

Table 1. Main characteristics of all eligible studies.

First author	Year	Country	Ethnicity	Allergic states	Case			Control			P for HWE	Quality score
					AA	AC	CC	AA	AC	CC		
Morales1 [13]	2013	Spain	Caucasian	Atopic	87	59	9	98	35	6	0.221	8
Morales2 [13]	2013	Spain	Caucasian	NA	22	17	1	98	35	6	0.221	8
Chen [14]	2011	China	East Asian	NA	86	78	33	133	181	55	0.605	9
Movahedi [15]	2008	Iran	Caucasian	NA	16	41	0	72	60	8	0.323	8
Trajkov [16]	2008	Macedonia	Caucasian	NA	48	24	2	160	113	18	0.741	9
Hirota1 [17]	2005	Japan	East Asian	Atopic	84	144	68	101	273	175	0.762	9
Promoter W/M					WW	WM	MM	WW	WM	MM		
Xu [11]	2013	China	East Asian	Atopic	60	31	9	77	26	2	0.909	9
Tug [20]	2009	Turkey	Caucasian	NA	9	21	23	0	22	38	0.082	7
Hirota2 [17]	2005	Japan	East Asian	Atopic	72	132	81	162	273	112	0.878	8
Hirota3 [17]	2005	Japan	East Asian	Atopic	176	88	10	340	194	19	0.171	8
Khoo1 [19] ^a	2004	Australia	Caucasian	NA	14	31	18	12	22	15	0.490	7
Khoo2 [19] ^a	2004	Australia	Caucasian	NA	25	58	34	12	22	15	0.490	7
Morahan [18] ^a	2002	Australia	Caucasian	NA	32	53	33	69	148	76	0.853	9

HWE, Hardy–Weinberg equilibrium; NA, not available.

^aThe ethnicity distribution involved has been confirmed via requesting information from the original authors.

applied various combinations of the following medical subject headings and key words: (interleukin-12 or IL-12 or IL-12B or cytokine) and (polymorphisms or variation or SNP) and asthma.

Inclusion and exclusion criteria

The studies identified from the above-mentioned databases were screened by two independent authors (Fangwei Li and Xinming Xie) according to the following predesigned inclusion criteria: (1) case–control design; (2) evaluating the correlation of IL-12B –1188A/C or the promoter polymorphisms with asthma risk; (3) providing sufficient data to calculate the odds ratio (OR) and its corresponding 95% confidence interval (CI); (4) not republished data.

Qualitative assessment

The qualities of the included studies were accessed by two investigators (Yanting Zhu and Lu Liu), respectively, according to the Newcastle–Ottawa Scale (NOS), which scored studies by the selection of study groups, the comparability of the groups, and the exposure of study [22]. We considered a study awarded 0–3, 4–6, or 7–9 as a low-, moderate-, or high-quality study, respectively. Discrepancies were resolved by consensus and discussion.

Data extraction

Data of eligible studies were extracted by two reviewers (Shaojun Li and Rui Ke) independently and in duplicate according to the predesigned data collection form. The following information was extracted: first author, publication year, country of origin, ethnicity, allergic state, number of both asthma cases and control subjects, and phenotypic distribution in both groups. Discrepancies occurring during the process of study

inclusion and data extraction were resolved by discussion with a third reviewer (Yanting Zhu), and consensus on each item was achieved eventually.

Data analysis

The statistical analysis was conducted using Stata software (Version 12.0; Stata Corporation, USA). Hardy–Weinberg equilibrium (HWE) in controls was tested by the chi-squared test, and it was considered statistically significant when *P*-value was less than 0.05. Heterogeneity among studies was examined with the χ^2 -based *Q* testing and *I*² statistics [23]. The pooled ORs of asthma were performed for the allele model (for –1188 A/C: C allele vs. A allele; for the promoter: mutant [M] allele vs. wild [W] allele), the dominant model (for –1188 A/C: CC + AC vs. AA; for the promoter: MM + WM vs. WW) and the recessive model (for –1188 A/C: CC vs. AC + AA; for the promoter: MM vs. WM + WW), respectively. The statistical significance of the pooled OR was assessed with the *Z* test and Bonferroni correction [24] was used to control for the multiple testing in view of fifteen comparisons under investigation (significance was set at 0.05/15 = 0.003). Publication bias was examined with Begg's test [25] and Egger's test [26] and the *P*-value <0.05 indicated significant publication bias.

Results

Characteristics of eligible studies

A total of 1816 papers were obtained with the initial search of databases. After screening, 13 case–control studies in 10 eligible articles with a total of 5092 participants (1809 cases and 3283 controls) fulfilled the inclusion criteria, from which genotype data of –1188A/C and the promoter W/M were obtained (Table 1). The flowchart

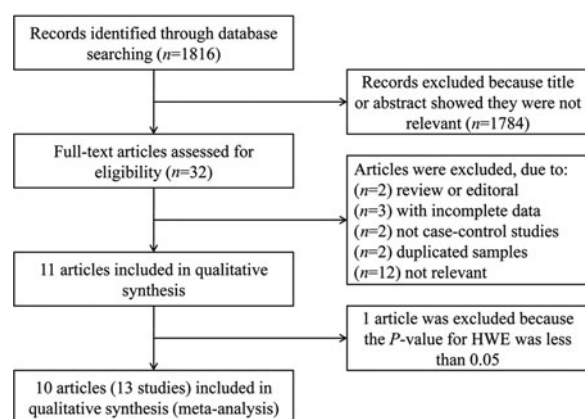


Figure 1. Flowchart shows study selection procedure.

of selection of studies and reasons for exclusion are presented in Figure 1.

Meta-analysis of IL-12B gene polymorphisms and bronchial asthma

A summary of association between IL-12B –1188A/C or the promoter W/M polymorphisms and asthma risk is shown in Table 2. Significance was set at 0.003 using Bonferroni correction for the multiple testing.

In the overall analysis for IL-12B –1188A/C polymorphisms, there was no significant association between –1188A/C polymorphisms and asthma risk. Subgroup analysis by ethnicity indicated that there was a significantly reduced risk for asthma in East Asian (CC + AC vs. AA: OR = 0.64, 95% CI = 0.50–0.81, $P < 0.001$), but not in Caucasian. The details are presented in Figure 2.

For IL-12B promoter polymorphisms in the overall analysis, we found no significant association between promoter W/M polymorphisms and asthma risk under any of the models. In the subgroup analysis by ethnicity, results indicated a markedly increased risk for asthma in East Asian (MM vs. WM + WW: OR = 1.57, 95% CI = 1.18–2.10, $p = 0.002$), but not in Caucasian. When the data

were stratified by allergic state, a significantly increased risk was found for asthma in atopic subgroup (MM vs. WM + WW: OR = 1.57, 95% CI = 1.18–2.10, $p = 0.002$). The results are shown in Figure 3.

Sensitivity analysis

Sensitivity analysis was also performed to explore the potential influence of each individual study on the overall results by deleting one single study each time from the pooled analysis for –1188A/C or the promoter, respectively. No substantial change was demonstrated in the overall studies, indicating that no individual study could affect the pooled OR significantly (Figure 4).

Heterogeneity and publication bias

For IL-12B –1188A/C in recessive model (CC vs. AC + AA), there was low heterogeneity (indicated by I^2 -statistics) among studies. However, obvious heterogeneity was observed for –1188A/C in allele (C allele vs. A allele) and dominant models (CC + AC vs. AA). For IL-12B promoter, significant heterogeneity was observed under all of the models. After stratifying by ethnicity and allergic state, respectively, heterogeneity was decreased in recessive model (MM vs. WM + WW). The details are presented in Table 2. For publication bias, results were observed with all P -value > 0.05 of Begg's test and Egger's test (Table 3).

Discussion

A number of studies have been conducted to investigate the association between IL-12B gene polymorphisms and asthma risk [13–15,17–19]. Morales et al. indicated that –1188A/C polymorphisms in IL-12B gene contribute to asthma [13,14]. Moreover, Tug et al. reported a significant association between IL-12B promoter W/M polymorphisms and asthma [11,20]. However, Khoo et al.

Table 2. The results of meta-analysis.

–1188A/C	C allele vs. A allele			CC + AC vs. AA			CC vs. AC + AA		
	OR (95% CI)	$P_{(Z)}$	I^2 (%)	OR (95% CI)	$P_{(Z)}$	I^2 (%)	OR (95% CI)	$P_{(Z)}$	I^2 (%)
Overall	1.03 (0.75, 1.42)	0.839	79.6	1.13 (0.68, 1.87)	0.641	85.2	0.80 (0.53, 1.20)	0.272	32.0
Caucasian	1.25 (0.82, 1.92)	0.297	69.1	1.57 (0.84, 2.93)	0.159	77.8	0.71 (0.30, 1.66)	0.429	11.6
East Asian	0.77 (0.60, 0.99)	0.040	59.0	0.64 (0.50, 0.81)	<0.001	0.0	0.83 (0.47, 1.48)	0.536	75.4
Atopic	1.03 (0.44, 2.41)	0.937	92.9	1.02 (0.32, 3.26)	0.977	93.7	0.78 (0.40, 1.53)	0.475	45.0
NA	0.95 (0.65, 1.41)	0.815	67.7	1.05 (0.50, 2.23)	0.898	84.9	0.68 (0.24, 1.93)	0.469	45.0
Promoter W/M	M allele vs. W allele			MM + WM vs. WW			MM vs. WM + WW		
Overall	1.04 (0.78, 1.37)	0.801	75.4	1.10 (0.79, 1.52)	0.580	56.5	1.10 (0.76, 1.58)	0.626	54.9
Caucasian	0.83 (0.56, 1.21)	0.326	63.2	0.88 (0.48, 1.62)	0.677	48.2	0.87 (0.63, 1.21)	0.410	26.3
East Asian	1.33 (0.88, 2.01)	0.170	81.9	1.25 (0.81, 1.93)	0.306	72.4	1.57 (1.18, 2.10)	0.002	31.4
Atopic	1.33 (0.88, 2.01)	0.170	81.9	1.25 (0.81, 1.93)	0.306	72.4	1.57 (1.18, 2.10)	0.002	31.4
NA	0.83 (0.56, 1.21)	0.326	63.2	0.88 (0.48, 1.62)	0.677	48.2	0.87 (0.63, 1.21)	0.410	26.3

$P_{(Z)}$, P -value for pooled OR with the Z test; NA, allergic states not available.

Significant results after Bonferroni correction for multiple testing ($P < 0.003$) were marked in bold characters.

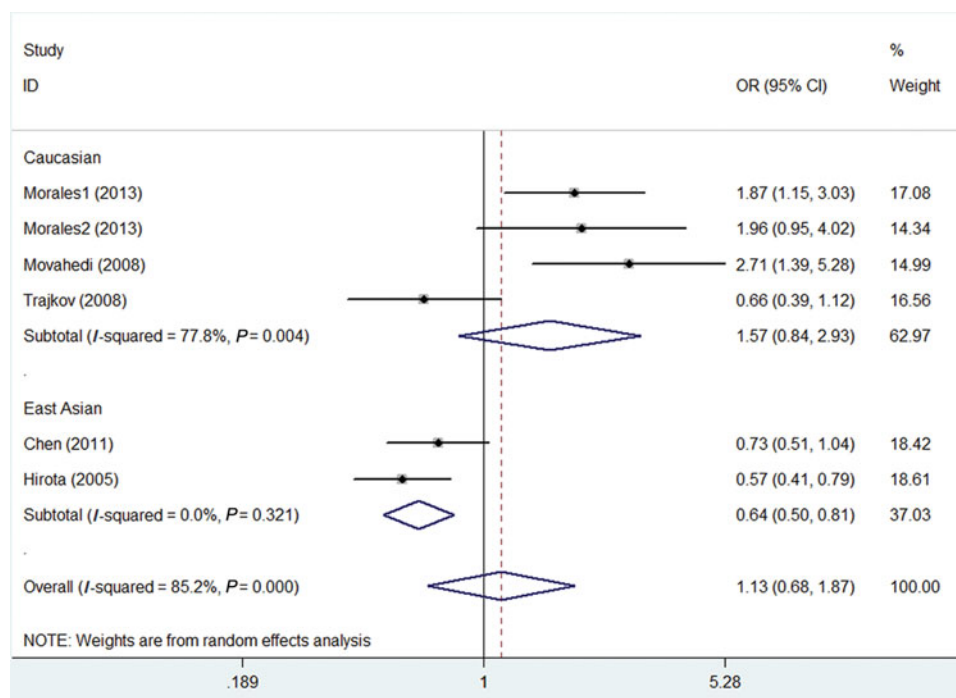


Figure 2. Forest plot for the association between IL-12B –1188 A/C polymorphisms and asthma risk in subgroup analysis by ethnicity (CC + AC vs. AA). NA, allergic states not available.

pointed out that genetic variation in the IL-12B gene does not significantly contribute to asthma susceptibility or severity [16,19]. Therefore, it is critical to systematically evaluate all studies from different groups and to quantify the overall association between IL-12B –1188A/C or the promoter W/M polymorphisms and asthma.

To our knowledge, this is the first meta-analysis about IL-12B gene polymorphisms and asthma susceptibility. In the present meta-analysis, we have combined 13 eligible studies with 1809 cases and 3283 controls to yield summary statistics, indicating that –1188 C allele might be a protective factor against asthma in East Asian. Meanwhile, promoter MM genotype have been shown to be a risk factor for the development of asthma in East Asian and allergic people.

IL-12B gene encodes the p40 subunit of IL-12, a cytokine that is a major regulator of Th1 and Th2 responses [27]. IL-12B –1188A/C or the promoter W/M gene polymorphisms have been shown to modulate the

secretion and activity of IL-12 [11,28]. Depletion of IL-12 increases susceptibility to development of airway hyperresponsiveness [29]. Naseer et al. have found that the expression of IL-12 is reduced in bronchial biopsy samples from asthmatic individuals [30]. Morahan et al. consider IL-12 to be a key part in the induction of antiviral host defense [18]. In addition, IL-12 negatively regulates inflammation responses in asthma by binding to its receptor on a variety of inflammatory cells and airway structural cells and then causing activation of signal transducer and activator of transcription (STAT) 4 signaling pathway leading to some protective cytokines production and ultimately inflammation repression [31,32]. To some extent, these findings suggest that –1188A/C or the promoter W/M polymorphisms in IL-12B gene may be associated with asthma susceptibility.

Several limitations should be considered when interpreting the results. First, the relationship between IL-12B polymorphisms and asthma risk in African or American

Table 3. Results of publication bias test.

Polymorphisms	Compared genotype	Begg's test		Egger's test	
		z-value	P-value	t-value	P-value
–1188A/C	C allele vs. A allele	0.75	0.452	2.14	0.099
	CC + AC vs. AA	1.50	0.133	2.62	0.059
	CC vs. AC + AA	0.38	0.707	–0.32	0.764
Promoter W/M	M allele vs. W allele	0.00	1.000	–0.48	0.652
	MM + WM vs. WW	0.30	0.764	–0.42	0.694
	MM vs. WM + WW	0.00	1.000	–0.68	0.525

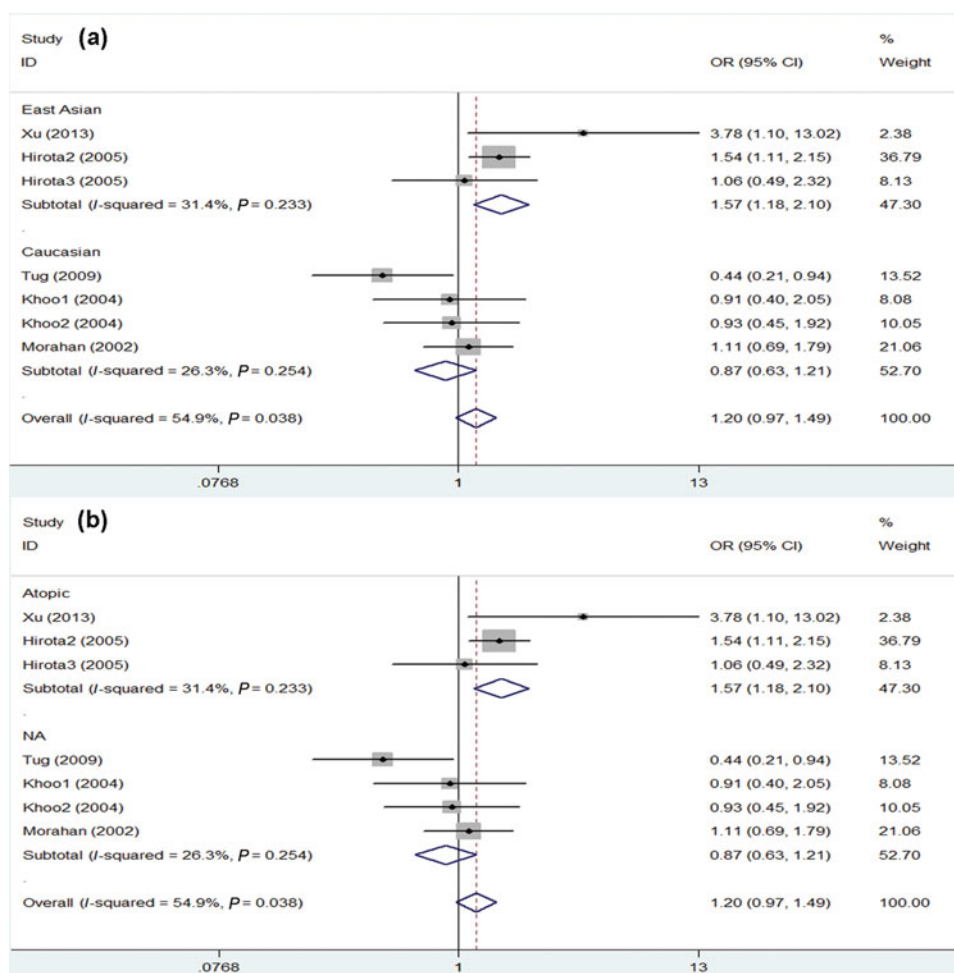


Figure 3. Forest plot for the association between IL-12B promoter polymorphisms and asthma risk: (a) in subgroup analysis by ethnicity (MM vs. WM + WW); (b) in subgroup analysis by allergic state (MM vs. WM + WW). NA, allergic states not available.

was not analyzed in the present study due to insufficiency of relevant studies in literatures. Second, heterogeneity still existed in some subgroup analysis. Third, only published studies with sufficient data were included but publication bias may have occurred even though the results of Begg's test or Egger's test did not detect it. Finally, asthma is a complex and multifactorial disease; multiple genetic alterations are associated with the development of asthma.

Although it would be interesting to know the interaction among different genes on the development of asthma by a double analysis through the effects of various combination of SNPs in different positions, we were unable to perform such analysis due to the absence of such published studies.

In conclusion, the current meta-analysis indicates that IL-12B –1188C allele is a protective factor against asthma

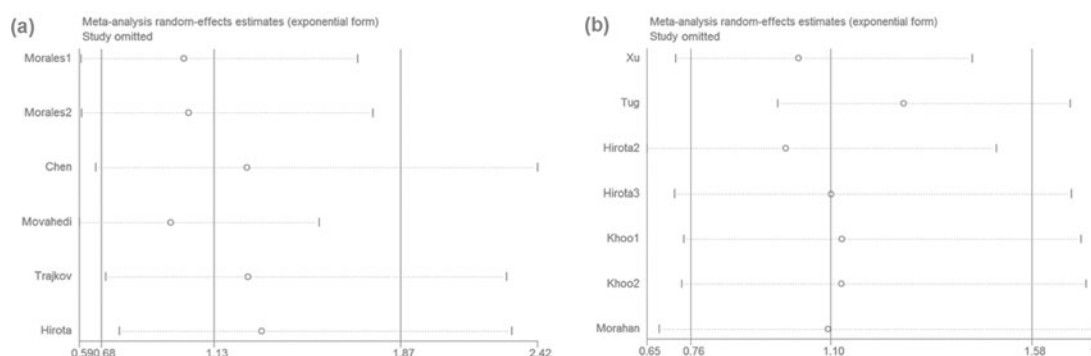


Figure 4. Sensitivity analysis for the association between: (a) IL-12B –1188 A/C polymorphisms and asthma risk (CC + AC vs. AA); (b) IL-12B promoter polymorphisms and asthma risk (MM vs. WM + WW).

in East Asian. In addition, the promoter MM genotype of IL-12B is a risk factor for asthma in East Asian and allergic people.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 81330002).

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