

REVIEW

RANTES Gene Polymorphisms Are Not Associated with Rheumatoid Arthritis and Atopic Dermatitis: A Meta-Analysis

Dan Wen, Xin Du, Yan Qiao, Jian-Zeng Dong, and Chang-Sheng Ma

Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

Background: A few recent studies have suggested that regulated on activation, normal T cell expressed and secreted (RANTES) polymorphisms (-403 G/A, -28C/G) are associated with rheumatoid arthritis (RA) and atopic dermatitis (AD). However, there still existed studies that did not confirm this correlation. **Objective:** The objective of this study was to evaluate the relationships of RANTES and RA and AD using a meta-analysis. **Methods:** Pubmed, Embase, and Cochrane library databases were systemically searched. Data were extracted by two independent reviewers, and pooled odds ratio (OR) with 95% confidence interval (CI) were calculated. **Results:** Eight studies were enrolled, including a total of 548 RA cases and 493 controls of -403G/A, 305 RA cases and 303 controls of -28C/G, and 705 AD cases and 578 controls of -403G/A in this meta-analysis. In RA, the overall OR and 95% CI of -403A were 1.41, 1.10–1.82 ($p = 0.391$) and 2.18, 1.30–3.66 ($p = 0.335$) in dominant and recessive models, respectively. The overall OR and 95% CI of -28G in RA were 1.35, 0.91–2.01 ($p = 0.707$) and 3.32, 1.29–8.52 ($p = 0.559$) in dominant and recessive models, respectively. Moreover, the overall OR and 95% CI of -403A in AD were 1.38, 1.08–1.76 ($p = 0.421$) and 1.06 and 0.65–1.72 ($p = 0.361$) in dominant and recessive models, respectively. **Conclusions:** This meta-analysis showed that RANTES -403G/A and -28C/G were not associated with RA and AD.

Keywords: atopic dermatitis, meta-analysis, polymorphism, RANTES, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by increased autoantibody expression, destruction of articular cartilage, and immune cells infiltration in and around the joints [1–4]. Atopic dermatitis (AD) is a chronic inflammatory skin disease which is usually associated with allergic respiratory disorders. While the pathogenesis of RA and AD is currently unclear, a growing body of evidence suggests that inflammatory and immune responses are closely related to RA and AD progression [5–7]. Several cytokines and chemokines are involved in the pathogenesis of these two disorders. Regulated on activation, normal T cell expressed and secreted (RANTES), a member of the CC chemokine family also known as CCL5, has the chemotactic properties on inflammatory cells and other cell types by activating chemokine receptors. It is usually expressed by various cell types, including activated T

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Address correspondence to Dr. Chang-Sheng Ma, MD, PhD, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China. E-mail: chshma@vip.sina.com

lymphocytes, monocytes, fibroblasts, and airway epithelial, endothelial, renal epithelial, and mesangial cells. RANTES, as a mediator of inflammatory response, could direct the movement of circulating lymphocytes, monocytes, basophils and eosinophils to the places of inflammation, and mediate multiple biological effects [8–11].

It has reported that NF- κ B pathway was associated with the promoter region of the RANTES gene [12]. Two RANTES gene promoter polymorphisms of -403 G/A and -28C/G were indicated to affect the promoter activity and increase the expression of RANTES. RANTES gene polymorphisms have become increasingly recognized as important mediators of several autoimmune disorders, including RA and AD [13–17]. Although various studies have demonstrated the correlations between RANTES (-403G/G and -28C/C) polymorphisms and RA and AD currently, the findings still remain controversial about. Therefore, we performed this meta-analysis to observe these correlations.

METHODS

Search Strategy

Two independent reviewers searched Pubmed, Embase, and Cochrane library databases systemically and extensively to obtain the case-control genetic association of RANTES polymorphisms with RA and AD studies without any language restrictions. The Medical Subject Heading (MeSH) and keyword terms “RANTES,” “CCL5,” “rheumatoid arthritis,” “atopic dermatitis,” and “polymorphism” were used as search criteria.

Study Selection and Data Abstraction

The inclusion criteria for the gene association studies in this meta-analysis were as follows: (1) case-control studies and cohort studies; (2) original data on genotype and allele distributions and frequencies were available for case and control subjects; (3) genotype distributions of the controls were in the Hardy-Weinberg equilibrium. Data abstraction was performed by two independent reviewers. Meta-analysis was performed for a certain polymorphism of RANTES only when data could be available from three or more unduplicated studies.

Statistical Analysis

Chi-square test was used to determine whether the genotype distributions of the controls were in the Hardy-Weinberg equilibrium. Heterogeneity between studies was tested with both Cochran's test and I^2 statistics; $p < 0.1$ or $I^2 > 50\%$ indicated significant heterogeneity in this study [18]. Publication bias was assessed by funnel plot and the Egger's regression test [19]. Data of this meta-analysis were analyzed by Stata software (version 12.0; Stata Corporation, College Station, TX, USA), and p value of <0.05 was considered statistically significant.

RESULTS

Studies Included in the Meta-Analysis

A total of eight relevant case-control and cohort studies with RANTES (-403G/A and -28C/G) and RA and AD were identified by searching Pubmed, Embase, and Cochrane library databases systemically and extensively. All these eight articles with usable data met the inclusion criteria and were enrolled in this meta-analysis, including five articles on -403G/A with RA, three on -28C/G with RA, three on -403G/A with AD, and two on -28C/G with AD [16, 17, 20–25]. The number of studies about -28C/G with AD enrolled was too small to be included in this meta-analysis. Finally, the included

TABLE 1. Characteristics of included studies in the meta-analysis.

Gene polymorphism (genotypes)	Disease	First author (Ref)	Year	Sample size (case/control)	Case genotypes	Control genotypes
-403G/A (GG/GA/AA)	RA	Yao et al. [22]	2009	107/139	46/52/9	72/57/10
	RA	Elsaadany et al. [17]	2011	47/15	19/16/12	11/2/1
	RA	Wang et al. [20]	2005	151/149	65/63/23	75/66/8
	RA	Goldbergova et al. [16]	2012	144/125	89/50/5	82/39/4
	RA	Makki et al. [21]	2000	99/65	68/26/5	50/15/0
	AD	Kozma et al. [24]	2002	128/303	86/38/4	211/84/8
	AD	Tanaka et al. [25]	2006	389/177	161/184/44	88/67/22
	AD	Nickel et al. [23]	2000	188/98	110/72/6	70/28/0
	RA	Yao et al. [22]	2009	107/139	77/17/13	104/31/4
-28C/G (CC/CG/GG)	RA	Elsaadany et al. [17]	2011	47/15	36/7/4	12/2/1
	RA	Wang et al. [20]	2005	151/149	119/30/2	128/20/1

studies provided 548 RA cases and 493 controls of -403G/A; 305 RA cases and 303 controls of -28C/G; and 705 AD cases and 578 controls of -403G/A for this analysis. The characteristics of included studies in this meta-analysis are given in Table 1.

The Association of RANTES (-403G/A and -28C/G) and RA Susceptibility

We compared the minor allele with the major allele in dominant and recessive models. In RA, the overall odds ratio (OR) and 95% confidence interval (CI) of -403A were 1.41, 1.10–1.82 ($p = 0.391$) and 2.18, 1.30–3.66 ($p = 0.335$) in dominant and recessive models, respectively (Figure 1). The overall OR and 95% CI of -28G were 1.35, 0.91–2.01 ($p = 0.707$) and 3.32, 1.29–8.52 ($p = 0.559$) in dominant and recessive models, respectively (Figure 2; Table 2). Funnel plot and the Egger's regression test showed publication bias among studies of -403G/A in RA ($p = 0.026$ and 0.590 in dominant and recessive models, respectively). Funnel plot and the Egger's regression test showed no publication bias among studies of -28C/G in RA ($p = 0.936$ and 0.194 in dominant and recessive models, respectively).

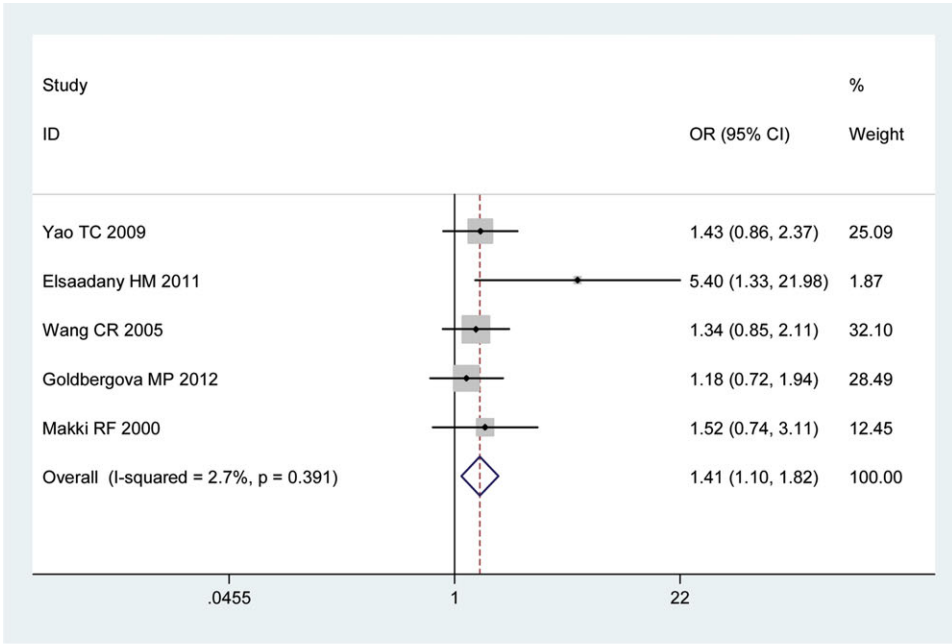
The Association of RANTES -403G/A and AD Susceptibility

The overall OR and 95% CI of -403A in AD were 1.38, 1.08–1.76 ($p = 0.421$) and 1.06, 0.65–1.72 ($p = 0.361$) in dominant and recessive models, respectively (Figure 3; Table 2). Funnel plot and the Egger's regression test showed no publication bias among studies ($p = 0.771$ and 0.183 in dominant and recessive models, respectively).

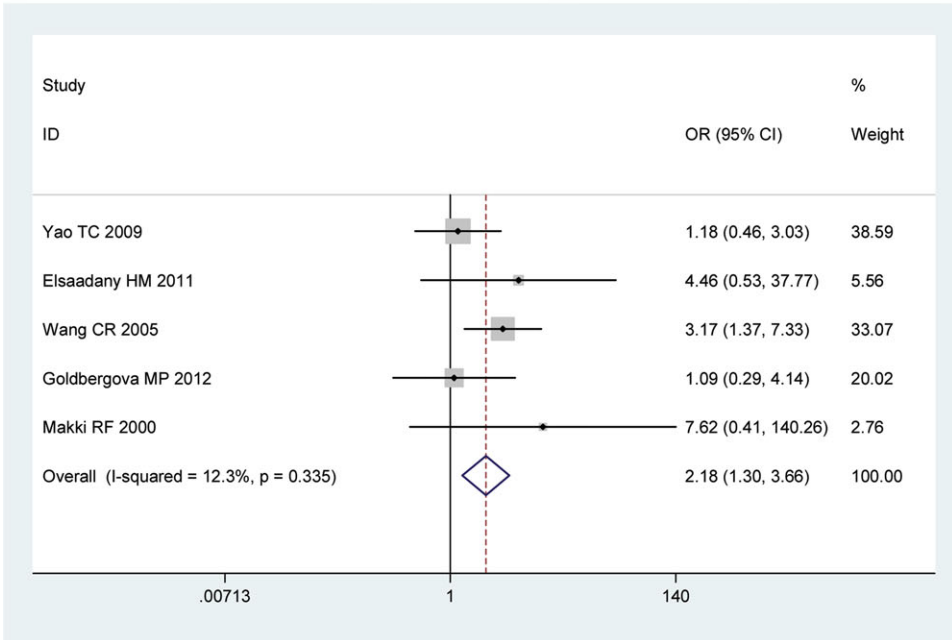
TABLE 2. Association between RANTES gene polymorphisms and RA and AD in different genetic models.

Disease	Gene polymorphism	Number of studies	Genetic model	OR	95% CI	<i>p</i> value
RA	-403G/A	5	Dominant	1.41	1.10–1.82	0.391
			Recessive	2.18	1.30–3.66	0.335
	-28C/G	3	Dominant	1.35	0.91–2.01	0.707
			Recessive	3.22	1.29–8.52	0.559
AD	-403G/A	3	Dominant	1.38	1.08–1.76	0.421
			Recessive	1.06	0.65–1.72	0.361

OR: odds ratio; CI: confidence interval.



A



B

FIGURE 1. Association between RANTES-403G/A polymorphism and RA in different genetic models. (A) Association between RANTES-403G/A polymorphism and RA in dominant model. (B) Association between RANTES-403G/A polymorphism and RA in recessive model.

DISCUSSION

Data of this meta-analysis indicated that RANTES gene polymorphisms (-403G/A and -28C/G) were not associated with RA and AD.

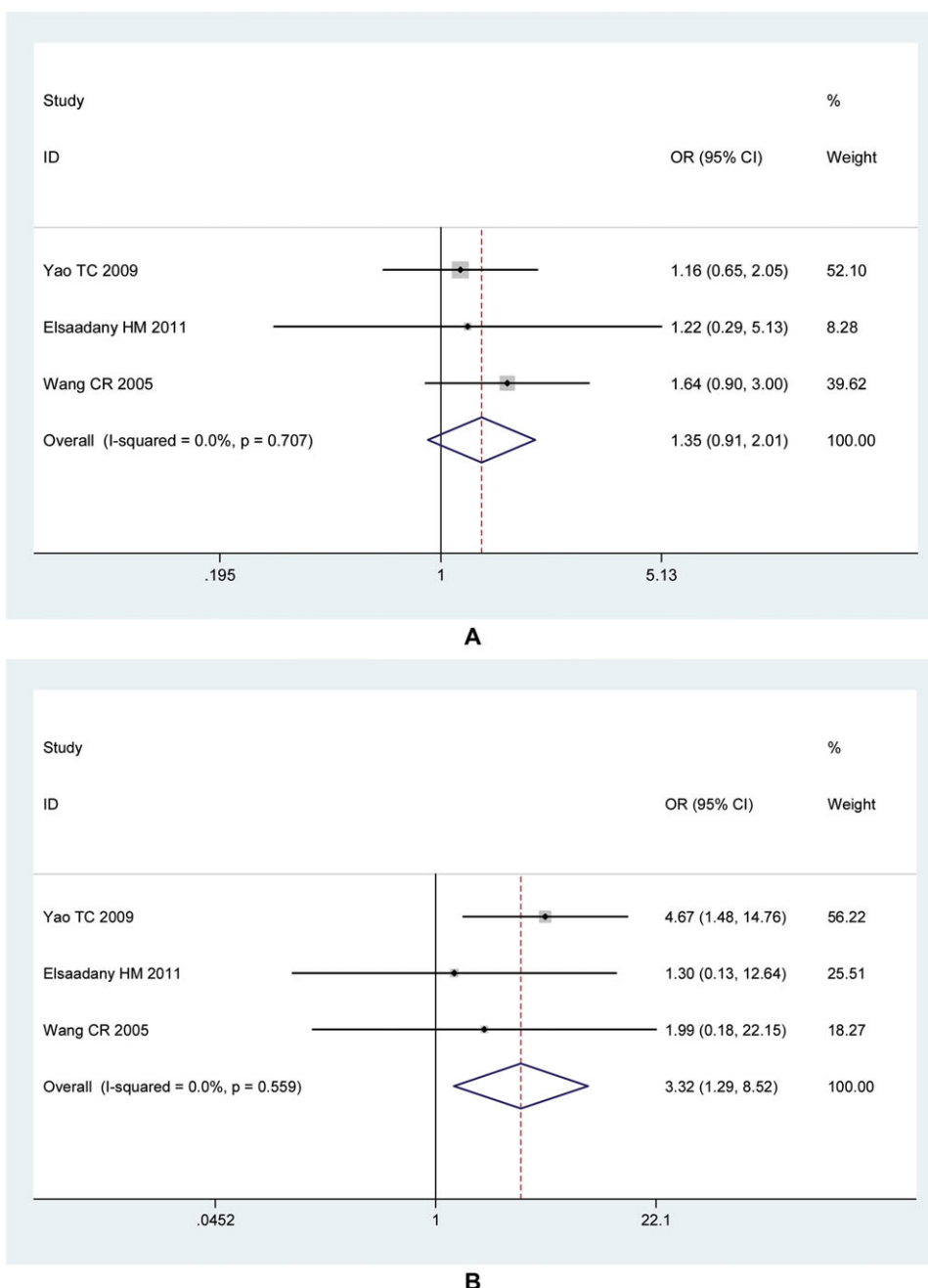


FIGURE 2. Association between RANTES-28C/G polymorphism and RA in different genetic models. (A) Association between RANTES -28C/G polymorphism and RA in dominant model. (B) Association between RANTES -28C/G polymorphism and RA in recessive model.

RANTES is a potent chemoattractant, which plays an important role in immune and inflammatory regulation processes. The RANTES gene is located on chromosome 17q11.2-q12, which comprises three exons and two introns. The RANTES gene polymorphisms have been observed to influence the activity of transcription and protein

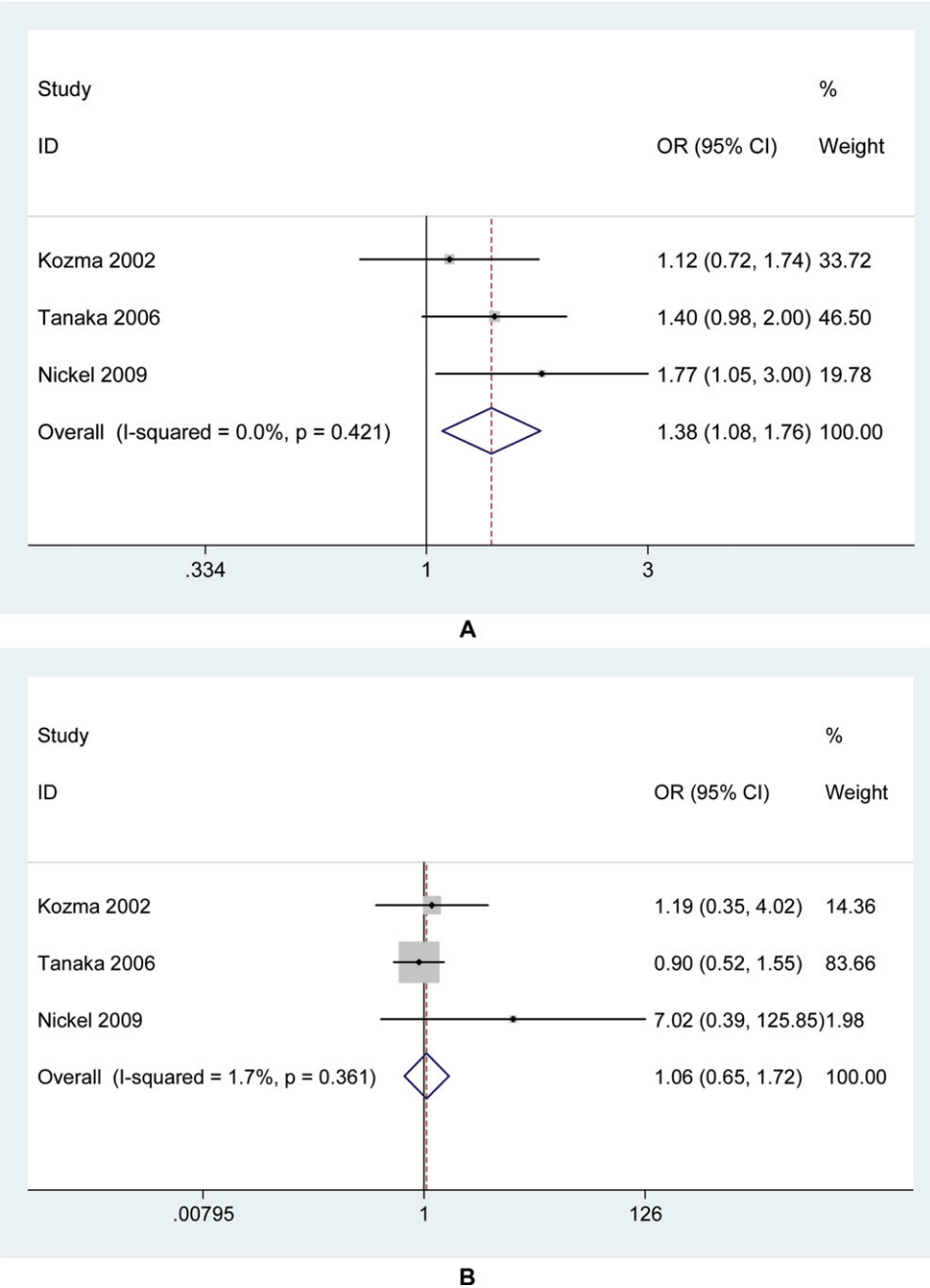


FIGURE 3. Association between RANTES-403G/A polymorphism and AD in different genetic models. (A) Association between RANTES-403G/A polymorphism and AD in dominant model. (B) Association between RANTES-403G/A polymorphism and AD in recessive model.

expression in humans, and are associated with the susceptibility, progression, and severity of various diseases [17, 26].

Increased RANTES levels have been observed in serum, synovial fluid, and synovial tissue in RA, indicating the role of RANTES in the pathogenesis of this disorder [27–29].

The RANTES protein is highly expressed in AD skin. The -403G/A polymorphism is correlated to enhanced RANTES production in patients with AD [13, 14].

At present, previous investigation findings about the association between the RANTES gene polymorphisms and the risk of RA still remain inconsistent. Yao et al. [22] found that the RANTES -28C/G polymorphism was a risk factor for juvenile RA in Chinese population. However, no significant differences in frequencies or genotype distributions were showed between the -403G/A polymorphism and this disorder susceptibility. Similar findings showed that the RANTES -403G/A polymorphism did not contribute to RA susceptibility and/or severity in Caucasians [16].

In contrast to these results, Wang et al. [20] observed significantly higher frequencies of A allele and A/A genotype at the promoter -403 position, suggesting the association of -403G/A polymorphism with adult RA onset in Chinese population. Furthermore, Elsaadany et al. [17] recognized that individuals with -403A allele were at significant positive risk for RA, while those with -403G allele were at negative risk for RA. RANTES -403G/A polymorphism was related to the development and activity of RA in Egyptians. However, no such differences were found about -28C/G polymorphism. In addition, Makki et al. [21] also reported the relationship of RANTES -403G/A polymorphism and RA susceptibility with marginal statistical significance in Spanish population. The inconsistent findings of the association between the two positions and RA might be due to the stronger effect of -403G/A on the regulation of RANTES transcription comparing with the -28C/G. Moreover, the -403A allele might be a reflection of linkage disequilibrium with the -28G allele [17].

As far as the correlations between RANTES -403G/A and AD susceptibility was concerned, discrepancy was also found in recent investigations. Nickel et al. [23] first reported that -403A allele was associated with AD in German children, indicating the contribution of this mutation to the development of AD. Also, Tanaka et al. [25] observed relationship between -403A variant and AD susceptibility with high IgE productivity in Japanese population. However, Kozma et al. [24] found no such association of -403A allele with AD in Hungarian children.

In the present study, in dominant and recessive models, the data showed no association between RANTES -403A allele and the susceptibility of RA and AD. Moreover, RANTES -28G allele was also not correlated with RA susceptibility. These findings demonstrated that gene polymorphisms at -403 and -28 positions may not contribute to the pathogenesis of RA and AD.

The susceptibility of RA and AD might be due to the interaction of various gene, environment, and endocrine factors. The differences among the previous studies in the association of RANTES gene promoter polymorphisms with RA and AD might be due to relatively small sample size, ethnic differences genetic linkage and phenotypic heterogeneity. Therefore, further observations using multiple ethnic populations are needed in order to determine the correlations between RANTES promoter polymorphisms and RA or AD susceptibility more precisely.

CONCLUSIONS

In conclusion, we concluded that RANTES gene polymorphisms (-403G/A and -28C/G) were not associated with RA and AD susceptibility.

Declaration of Interest

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

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