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The functional −94 insertion/deletion ATTG polymorphism in the promoter region of *NFKB1* gene increases the risk of sporadic colorectal cancer

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ABSTRACT

Objective: To investigate the allele and genotype frequencies of *NFKB1* −94 ins/del ATTG (rs28720239) polymorphism and to evaluate the association between the polymorphism and colorectal cancer (CRC) risk in Malaysian population. *Methods*: Genomic DNA was extracted from the peripheral blood samples of 474 study subjects, which consisted of 237 histopathologically confirmed CRC patients and an equal number of cancer-free controls. The *NFKB1* −94 ins/del ATTG (rs28720239) polymorphism was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method and confirmed by DNA sequencing. The association between the polymorphic genotypes and CRC risk was evaluated by deriving odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression analysis. *Results*: The frequencies of wildtype (del/del), heterozygous (del/ins) and variant (ins/ins) genotypes in CRC patients were 31.7%, 53.6% and 14.8%, respectively, while those in cancer-free controls were 35.0%, 58.2% and 6.8%, respectively. The frequency of the variant genotype was significantly higher in cases compared to controls ($P < 0.01$). Evaluation of the risk association of the polymorphic genotypes revealed that the variant genotype could contribute to a significantly increased risk of CRC (OR = 2.42, 95% CI = 1.24–4.73, $P < 0.01$). *Conclusions*: The variant allele of *NFKB1* −94 ins/del ATTG (rs28362491) polymorphism is associated with higher risk of sporadic CRC in Malaysian population.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide [1]. Over the past few years, the incidence of CRC has been increasing, and it contributes to a significant burden of cancer-related morbidity and mortality. Among the known risk factors for CRC include lifestyle habits (such as tobacco smoking and alcohol consumption) and dietary habits (such as high consumption of red meat and low consumption of fibrous food), but these alone are not sufficient to result in colorectal carcinogenesis. CRC is a multifactorial disease caused not only by environmental factors, but also by various genetic factors as well as interactions between the two [2,3]. Mutations in high penetrance genes such as *APC* and DNA mismatch repair (MMR) genes could represent a strong genetic determinant in the pathogenesis of hereditary forms of CRC. However, these mutations account for only less than 5% of all CRC cases [4].

Over the past decades, low penetrance genetic polymorphisms have emerged as important players in the pathogenesis of various types of cancers, including CRC [5,6]. Such genetic polymorphisms play a role in predisposing an individual to CRC by influencing the risk of developing the cancer, although typically the risk modification is modest. Such genetic polymorphisms are relatively common in the general population. Hence, they contribute to a higher attributable risk of cancer compared to high penetrance genes [7]. Genetic polymorphisms of genes whose protein products are involved in colorectal carcinogenic pathways could therefore modulate CRC risk.

Nuclear factor-kappa B (NF-κB) family constitutes a class of pleiotropic transcription factors which act as central regulators to many genes known to be implicated in cancer initiation and progression [8,9]. These include genes involved in the inflammatory pathway, immune response, cell proliferation, and apoptosis, among others [10]. The p105/p50 isoforms of NF-κB is encoded by the *NFKB1* gene, which is located on chromosome 4q24. Recently, a functional polymorphism in the promoter region of *NFKB1* gene has been described, namely the −94 ins/del ATTG (rs28362491) polymorphism, which could potentially influence the transcription of the gene and therefore, the level and function of NF-κB protein

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[11]. Considering the critical role of NF-κB in numerous cancer-related pathways, we hypothesized that this polymorphism could play a role in modulating the risk of CRC. Indeed, several research groups have investigated the link between the polymorphism and CRC risk, but the results obtained thus far were inconsistent. For instance, while Song et al. [12] reported that the ins/ins genotype of the polymorphism could increase the risk of CRC in a Southern Chinese population, Lewander et al. [13] showed a lack of association between the polymorphism and CRC risk among Chinese. In addition, Lewander et al. [13] also showed that the del allele of the polymorphism could contribute to an increased CRC risk in a Swedish population, which concurred to the observation by Andersen et al. in a Danish population [14]. However, no study has been taken so far to evaluate the association between the polymorphism and CRC risk among Malaysians. Hence, a case–control study was designed to investigate the frequencies of *NFKB1* −94 ins/del ATTG (rs28362491) polymorphic genotypes in Malaysian CRC patients and cancer-free controls, as well as to evaluate the association between the above-mentioned polymorphism and CRC risk in Malaysian population.

2. Materials and methods

2.1. Recruitment of study subjects

The study was approved by the Research Review Board and Human Research Ethics Committee of Universiti Sains Malaysia (USM) (No. USMKK/PPP/JEPeM[201.4 (1.2)], dated April 21, 2008) and Medical Review and Ethics Committee (MREC) of Ministry of Health, Malaysia (No. KKM/NIHSEC/08/0804/P09-581, dated July 9, 2010). For this hospital-based case–control study, a total of 237 histopathologically confirmed CRC patients and 237 cancer-free controls were recruited from (1) Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, (2) Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, and (3) Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia. Controls were selected from healthy volunteers and individuals who visited the participating hospitals for regular health examination. They were biologically unrelated to the cases, apparently free from any form of cancer, and were not associated with medical conditions. Subjects with familial adenomatous polyposis, ulcerative colitis, Crohn's disease or any other previous malignancy were excluded from the study. Epidemiological data, which included smoking status and alcohol use, were collected from the study subjects using a pre-structured questionnaire administered post-diagnosis.

2.2. DNA isolation

Peripheral blood was collected from the study subjects into EDTA-containing vacutainers after receiving written informed consent. Genomic DNA was isolated using QIAamp DNA Blood Mini Kit (QIAGEN, Germany) according to the manufacturer's protocol and stored at −20 °C until used for genotyping.

2.3. Genotyping

The *NFKB1* −94 ins/del ATTG (rs28362491) polymorphism was genotyped employing polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The primers used for amplification of the region of interest were 5′-TGG GCA CAA GTC GTT TAT GA-3′ and 5′-CTG GAG CCG GTA GGG AAG-3′. The PCR reaction was carried out in a 20 μl reaction mixture containing 1× Phusion High-Fidelity PCR Master Mix (Thermo Scientific, Finland) and 0.25 mM of each primer. The PCR cycle consisted of an initial denaturation step at 98 °C for 30 s, followed by 35 cycles of denaturation (98 °C for 5 s), annealing (65 °C for 5 s) and extension (72 °C for 5 s), and a final extension at 72 °C for 5 min. The 281 bp (deletion allele) or 285 bp (insertion allele) products generated were then digested using PflMI (Van91I) restriction enzyme (Thermo Scientific, Finland). The wildtype (deletion) genotype did not contain PflMI (Van91I) restriction site, hence the PCR product of 281 bp remained undigested. The insertion variants were cleaved by PflMI (Van91I) restriction enzyme into two fragments of 240 bp and 45 bp. Heterozygotes showed all three bands. The expected 45 bp band could not be clearly visualized in the gel (Fig. 1). Fifty samples were chosen at random and subjected to DNA sequencing to confirm the genotype (Fig. 2), and 100% concordance rate was achieved.

2.4. Statistical analysis

Statistical analysis was carried out by using SPSS version 19. The differences in the genotype and allele frequencies of *NFKB1* −94 ins/del ATTG polymorphism between cases and controls were calculated employing χ^2 test. The associations of the polymorphic genotypes with CRC risk was determined by deriving the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) from binary logistic regression analysis. The homozygous wild type genotype was used as the reference in the analysis (OR = 1.00). An association with a P value of less than 0.05 was considered to be significant.

3. Results

3.1. Characteristics of study subjects

A total of 237 CRC patients and 237 cancer-free controls were recruited into this study. The characteristics of the study subjects are shown in Table 1. Among the cases, 129 (54.4%) were males and 108 (45.6%) were females, while among the controls, 119 (50.2%) were males and 118 (49.8%) were females. The age range of the cases was 27–94 years old, with a mean of 61.5 ± 12.8 years and a median of 62 years. On the other hand, the range of the controls was 22–84 years of age, with a mean of 47.0 ± 12.3 years and a median of 49 years. With regard to smoking status, 87 (36.7%) and 150 (63.3%) of the cases were ever smokers and never smokers, respectively, while the distribution was 73 (30.8%) and 164 (69.2%) in controls.

3.2. Distribution and CRC risk association of NFKB1 polymorphism

The genotype and allele frequencies of the *NFKB1* polymorphism are shown in Table 2. The frequencies of homozygous

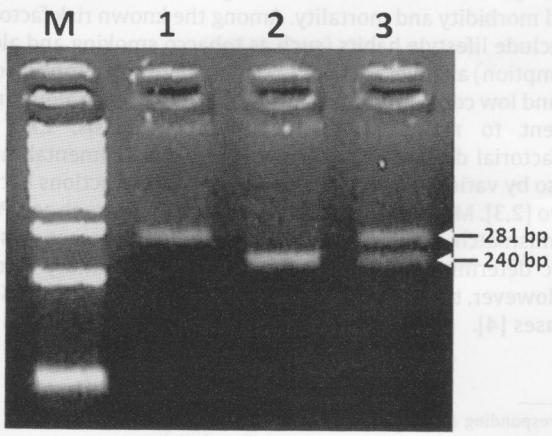

Fig. 1. PCR-RFLP analysis of *NFKB1* −94 ins/del ATTG polymorphism. M, 100 bp DNA ladder; Lane 1, homozygous deletion; Lane 2, homozygous insertion; Lane 3, heterozygous.

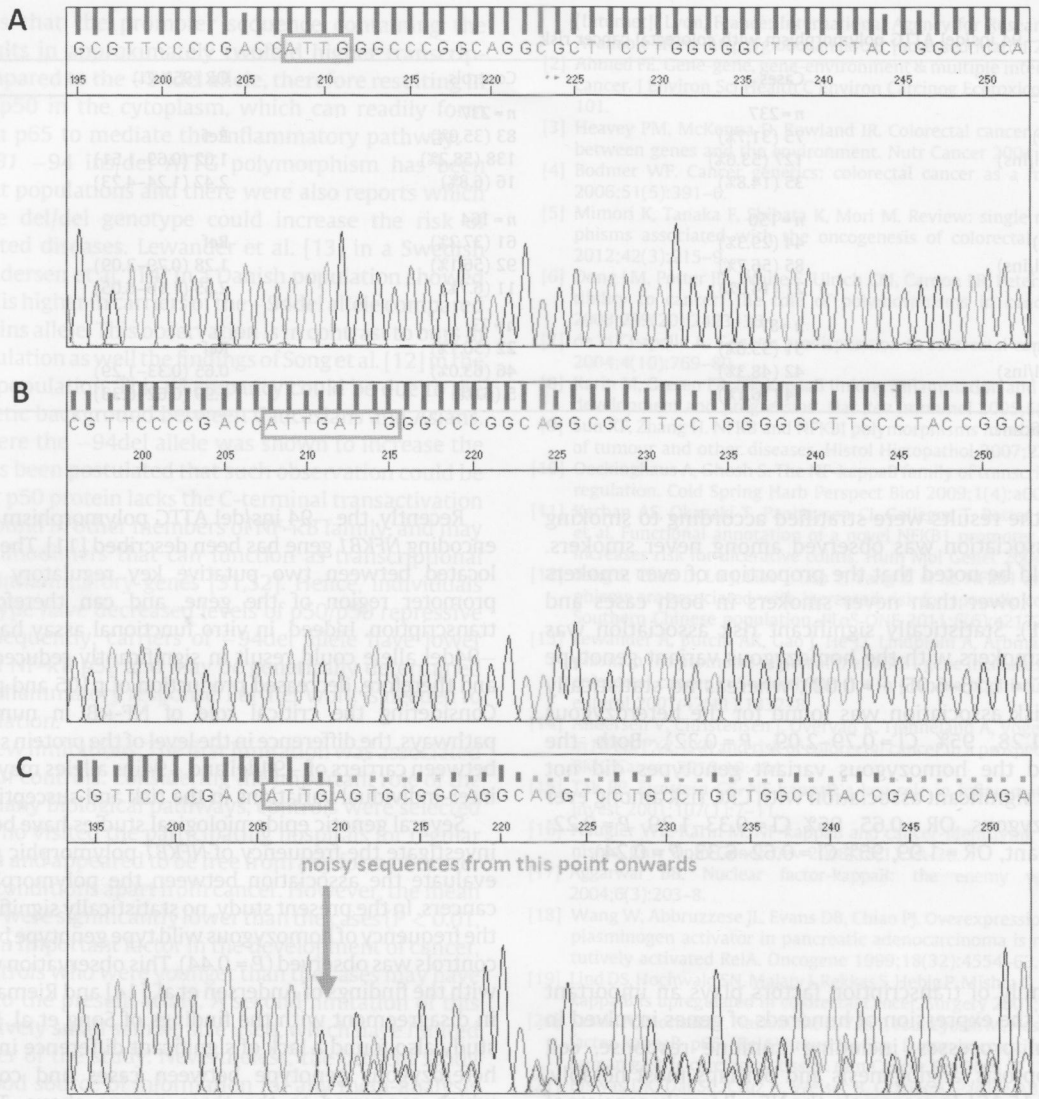

Fig. 2. Sequencing of PCR product to verify the genotype: (A) deletion allele; (B) insertion allele; (C) heterozygotes were characterized by the presence of noisy sequences immediately after the ATTG sequence.

wildtype and heterozygous genotypes did not differ significantly between cases and controls. The frequency of homozygous wildtype genotype was 31.7% in cases and 35.0% in controls ($P = 0.44$), while that of heterozygous was 53.6% in cases and 58.2% in controls ($P = 0.31$). However, significant difference in frequency between the cases and controls was observed in homozygous variant genotype (14.8% in cases and 6.8% in controls, $P < 0.01$).

Table 1
Characteristics of the study subjects.

Characteristics	Cases ($n = 237$)	Controls ($n = 237$)	P
Gender			0.36
Male	129 (54.4%)	119 (50.2%)	
Female	108 (45.6%)	118 (49.8%)	
Age			<0.01[a]
Age range	27–94	22–84	
Mean ± SD	61.5 ± 12.8	47.0 ± 12.3	
Median	62	49	
<50 years	41 (17.3%)	126 (53.2%)	
≥50 years	196 (82.7%)	111 (46.8%)	
Smoking status			0.17
Ever smoker	87 (36.7%)	73 (30.8%)	
Never smoker	150 (63.3%)	164 (69.2%)	

[a] Statistically significant.

The frequencies of insertion and deletion alleles among cases were 0.58 and 0.42, respectively, while those for controls were 0.64 and 0.36. No significant difference was observed in the insertion and deletion allele frequencies in cases and controls ($P = 0.07$).

The association between genotypes and CRC risk was estimated by using an unconditional logistic regression model, and the results obtained is shown in Table 3. No significant risk association was observed for the heterozygous (del/ins) genotype (OR = 1.02, 95% CI = 0.69–1.51, $P = 0.93$). However, the homozygous variant (ins/ins) genotype was found to significantly increase the risk of CRC in the population studied (OR = 2.42, 95% CI = 1.24–4.73,

Table 2
Distribution of *NFKB1* polymorphism.

	Cases ($n = 237$)	Controls ($n = 237$)	P value
Genotype			
Wild type (del/del)	75 (31.7%)	83 (35.0%)	0.44
Heterozygous (del/ins)	127 (53.6%)	138 (58.2%)	0.31
Variant (ins/ins)	35 (14.8%)	16 (6.8%)	<0.01[a]
Allele			
Deletion	0.58	0.64	0.07
Insertion	0.42	0.36	

[a] Statistically significant.

Table 3
Association of *NFKB1* −94 ins/del ATTG polymorphism with colorectal cancer risk.

Genotype	Cases	Controls	OR (95% CI)	*P* value
Total	*n* = 237	*n* = 237		
Wildtype (del/del)	75 (31.7%)	83 (35.0%)	Ref	–
Heterozygous (del/ins)	127 (53.6%)	138 (58.2%)	1.02 (0.69–1.51)	0.93
Variant (ins/ins)	35 (14.8%)	16 (6.8%)	2.42 (1.24–4.73)	<0.01[a]
Never smokers	*n* = 150	*n* = 164		
Wildtype (del/del)	44 (29.3%)	61 (37.2%)	Ref	–
Heterozygous (del/ins)	85 (56.7%)	92 (56.1%)	1.28 (0.79–2.09)	0.32
Variant (ins/ins)	21 (14.0%)	11 (6.7%)	2.65 (1.16–6.05)	0.02[a]
Ever smokers	*n* = 87	*n* = 73		
Wildtype (del/del)	31 (35.6%)	22 (30.1%)	Ref	–
Heterozygous (del/ins)	42 (48.3%)	46 (63.0%)	0.65 (0.33–1.29)	0.22
Variant (ins/ins)	14 (16.1%)	5 (6.9%)	1.99 (0.62–6.33)	0.24

[a] Statistically significant.

$P < 0.01$). When the results were stratified according to smoking status, similar association was observed among never smokers. However, it should be noted that the proportion of ever smokers was significantly lower than never smokers in both cases and controls ($P < 0.01$). Statistically significant risk association was found for never smokers with the homozygous variant genotype (OR = 2.65, 95% CI = 1.16–6.05, $P = 0.02$), whereas no statistically significant CRC risk association was found for the heterozygous genotype (OR = 1.28, 95% CI = 0.79–2.09, $P = 0.32$). Both the heterozygous and the homozygous variant genotypes did not show statistically significant association with CRC risk among ever smokers (heterozygous, OR = 0.65, 95% CI = 0.33–1.29, $P = 0.22$; homozygous variant, OR = 1.99, 95% CI = 0.62–6.33, $P = 0.24$).

4. Discussion

The NF-κB family of transcription factors plays an important role in regulating the expression of hundreds of genes involved in diverse biological processes, including immune response, cell proliferation, apoptosis, angiogenesis and perhaps most notably, inflammation [10,15,16]. In mammals, the NF-κB family consists of five members, namely p50 (NF-κB1), p52 (NF-κB2), p65 (RelA), RelB, and c-Rel, which are encoded by *NFKB1*, *NFKB2*, *RELA*, *RELB* and *REL* genes, respectively. Both p50 and p52 are proteolytically processed from their precursors, p105 and p100. The members of NF-κB family can form homo- and heterodimers with each other to produce distinct transcriptionally active complexes. Up to 15 different NF-κB complexes can be formed by the members of the transcription factor family, although the physiological existence of all the possible complexes has not been confirmed [10].

Among the many dimeric complexes of NF-κB, the p50/p65 heterodimer is the most abundant form and is present in almost all cell types. However, in most normal cell types, NF-κB dimers are mostly inactivated by its inhibitor IκB, except in proliferating T cells, B cells, thymocytes, monocytes and astrocytes [17]. On the contrary, in most cancer cell lines and tissues, including those of the pancreas [18], colon and rectum [19], stomach [20], breast [21], liver [22] and prostate [23], NF-κB complexes are found to be constitutively active, which implies the involvement of NF-κB in oncogenesis. In fact, the mechanistic link between NF-κB and carcinogenesis has long been suspected, given the role of the protein complex as a master regulator in inflammatory pathway [24]. Many inflammatory cytokines, such as TGF-β, TNF-α, IL-6, and IL-8, mediate their effects through the activation of NF-κB. As such, abnormal NF-κB functioning can facilitate uncontrolled proliferation, inhibition of apoptosis, metastasis and angiogenesis during malignant transformation of a cell [16].

Recently, the −94 ins/del ATTG polymorphism of the p50/p105-encoding *NFKB1* gene has been described [11]. The polymorphism is located between two putative key regulatory elements in the promoter region of the gene, and can therefore modulate its transcription. Indeed, in vitro functional assay has shown that the −94del allele could result in significantly reduced *NFKB1* message and therefore, decreased production of p105 and p50 proteins [11]. Considering the critical role of NF-κB in numerous biological pathways, the difference in the level of the protein subunits produced between carriers of −94del and −94ins alleles may contribute to the inter-individual variations in the risk and susceptibility to diseases.

Several genetic epidemiological studies have been carried out to investigate the frequency of *NFKB1* polymorphic genotypes and to evaluate the association between the polymorphism and risk of cancers. In the present study, no statistically significant difference in the frequency of homozygous wild type genotype between cases and controls was observed ($P = 0.44$). This observation was in agreement with the findings of Andersen et al. [14] and Riemann et al. [25], but in disagreement with the findings of Song et al. [12]. The present study also found a lack of significant difference in the frequency of heterozygous genotype between cases and controls ($P = 0.31$), which concurred to the three groups above. The frequency of homozygous variant genotype showed significant difference between cases and controls in the present study ($P < 0.01$), with the frequency being higher in cases than in controls. Song et al. [12] reported a similar observation as ours, but Andersen et al. [14] showed that the frequency of homozygous variant genotype was significantly higher in controls than cases. On the contrary, Riemann et al. [25] showed no significant difference in the frequency of homozygous variant genotypes between cases and controls. The inconsistency of the results obtained could probably be due to the different ethnic groups, environmental exposure and genotypic distributions of the subjects studied.

In the present study, we investigated the association between the polymorphism and CRC risk among Malaysians, and found that the variant ins/ins genotype could confer an increased risk of developing CRC to its carriers. When stratified according to smoking status, significant association was observed among never smokers who carried the *NFKB1* −94 ins/ins variant genotype, but not among ever smokers. However, it should be noted that the proportion of ever smokers was significantly lower than never smokers in both cases and controls ($P < 0.01$), which resulted in an inverse risk association (despite not statistically significant) among ever smokers who are heterozygous for the polymorphism. Nonetheless, consistent with our findings, several other groups have reported that the ins/ins genotype could increase the risk of colorectal [12], bladder [26], gastric [27], prostate [28], cervical [29], and nasopharyngeal [30] cancers. A plausible explanation for

the observation is that the promoter sequence containing the −94ins allele results in approximately twofold higher transcriptional activity compared to the −94del allele, therefore resulting in a higher level of p50 in the cytoplasm, which can readily form heterodimers with p65 to mediate the inflammatory pathway.

However, *NFKB1* −94 ins/del ATTG polymorphism has been studied in different populations and there were also reports which indicated that the del/del genotype could increase the risk of inflammatory-related diseases. Lewander et al. [13] in a Swedish population and Andersen et al. [14] in a Danish population showed that the risk of CRC is higher in carriers of the −94del allele compared to those of the −94ins allele. This observation is in contrast to ours in the Malaysian population as well the findings of Song et al. [12] in the Southern Chinese population. This discrepancy could be due to the differences in genetic background between Caucasians and Asians. In populations where the −94del allele was shown to increase the risk of cancer, it has been postulated that such observation could be due to the fact that p50 protein lacks the C-terminal transactivation domain typically found in other members of NF-κB family, and may form inhibitory homodimers that can function as transcriptional repressors for proinflammatory genes [31,32]. Hence, individuals with del/del genotype have decreased levels of p50/p50 repressive homodimers. Consequently, carriers of −94del allele have lower levels of functional NF-κB p50 and may be genetically determined towards a higher inflammatory response. Further work is needed to confirm this postulation.

This study has few limitations. The first limitation was associated with the selection of controls. Considering the important role of the NF-κB protein in many biological pathways, controls were selected from individuals who visited the participating hospitals for regular health examination and appeared to be free from any form of cancer and other medical conditions apart from cancer. However, the mean ages of the controls were significantly lower than the cases ($P < 0.01$, Table 1). As age is an important factor in the development of cancer, the selection of controls who were younger than the cases may have introduced bias into the present study. A second limitation of this study was the relatively small sample size used, which have limited the statistical power of the study. Nevertheless, the present study could serve as a good source of information for any meta-analysis that is to be carried out in the future.

In conclusion, to the best of our knowledge, this is the first study to evaluate the association between *NFKB1* −94 ins/del ATTG polymorphism and CRC risk in Malaysian population. Our results indicated that the homozygous variant (ins/ins) genotype of the polymorphism could increase the risk of CRC in Malaysian population by more than twofold and could be considered as a potential CRC predisposition factor.

Conflict of interest statement

The authors declare no conflict of interest.

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