Association between *SLC2A9* Genetic Variants and Risk of Hyperuricemia in a Uygur Population*

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Summary: This study aimed to test the effects of five single nucleotide polymorphisms within *SLC2A9* on uric acid level in a special ethnic population, the Uygurs in Xinjiang, China. According to our inclusion and exclusion criteria, Uygur adults from Xinjiang constituted the study population. There were 1053 Uygur adults with hyperuricemia and 1373 normal Uygur adults who served as controls. Five single nucleotide polymorphisms within *SLC2A9* (rs938557, rs7679916, rs7349721, rs13101785, and rs13137343) were selected with the HapMap dataset and TaqMan assays. We found that, in normouricemia group, rs938557 was significantly correlated with uric acid (β=11.39±3.74, *P*=0.0024) adjusting for age, gender and BMI; rs7679916 and rs13137343 were marginally associated with uric acid concentration (β=5.77±3.09, *P*=0.0626; β=-5.99±3.08, *P*=0.0520). In the hyperuricemia group, no SNP was found to possibly influence uric acid concentration. None of these SNPs showed significant association with hyperuricemia after controlling for age, gender and BMI. There were significant or marginal correlations between certain single nucleotide polymorphisms in the *SLC2A9* region and uric acid concentration in Uygur normouricemia samples. In turn, some of these single nucleotide polymorphisms in *SLC2A9* may increase the risk of hyperuricemia.

Key words: *SLC2A9*; genotyping; hyperuricemia; Uygur ethnic

Humans show higher uric levels than other mammalian species because of the inactivation of hepatic uricase. Elevated serum uric acid (SUA) levels have been shown to be correlated with disorders such as gout, renal disease, metabolic syndrome, diabetes, hypertension, and adverse cardiovascular outcomes[1, 2]. The incidence of primary hyperuricemia in men has been reported to be 21.6% (95% CI, 18.9%–24.6%) in China[3]. In recent decades, the prevalence and incidence of hyperuricemia-induced gout has doubled among Americans[4]. As approximately 70% of serum uric acid is excreted by the kidney[5], the kidney plays a key role in SUA homeostasis. However, the exact mechanism of urate transport in the kidney is unknown. Recent genome-wide association studies (GWAS) have revealed the complex interplay between membrane transporters involved in urate homeostasis in the kidney[6], and several single nucleotide polymorphisms (SNPs) in the genes encoding these membrane transporters have been strongly correlated with SUA levels[7, 8]. The *SLC2A9* (solute carrier protein 2 family, number 9) region on chromosome 4 encodes the glucose transporter and generates altered splice variants that are highly expressed in the proximal nephron, which is a key site for urate processing in the kidney, and strongly associated with SUA and

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hyperuricemia[9, 10]. Almost all of those GWAS studies, however, were conducted exclusively in populations of European descent. This paper reports the first analysis of the effects of five SNPs within the *SLC2A9* gene on hyperuricemia and the serum urate concentration in a special ethnic population: the Uygurs. The Uygur ethnic group originated in Europe but now resides in Asia and therefore may represent a transitional population of Eurasia. Thus, our results may help to identify the basic molecular pathogenesis of hyperuricemia in different ethnic populations. Studies of hyperuricemia in non-European descendants will help to reveal the relevance of other ethnic groups, as the effects of *SLC2A9* genetic variants on uric acid concentration and hyperuricemia may vary across ethnic groups. This variance is presumably due to substantial differences in lifestyle. The aim of this study was to examine the association between polymorphisms in *SLC2A9* and the susceptibility to hyperuricemia in Uygur population.

1 MATERIALS AND METHODS

1.1 Participants

In 2012, a total of 2426 participants were recruited from the population-based cross-sectional survey (Health Investigation). This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University, and it was conducted according to the standards of the Declaration of Helsinki. All of the participants fully understood the purpose of this study, and every participant signed written informed consent before the study. For inclusion in our study, the Uygurs in the hyperuricemia group were between 20 to 70 years of age with SUA levels greater than 7.0 mg/dL for men and 6.0 mg/dL for women at 2 weeks before the start of the study. Our study included approximately equal number of normal participants from the same area. The following exclusion criteria were applied: (1) acute onset of gouty arthritis or renal stones; (2) significant liver or renal dysfunction, hematological diseases, oncological diseases, or other life-threatening diseases; (3) any condition that requires a prescription for diuretics or analgesic agents; and (4) treatment with an anti-hyperuricemia agent within 4 weeks before the start of the study.

1.2 The Criteria for Diagnosis

The diagnostic criteria for hyperuricemia were confirmed by routine laboratory testing. Hyperuricemia was diagnosed when the SUA levels were higher than 420 μmol/L in men and 360 μmol/L in women[6, 11].

1.3 Blood Tests and Data Collection

Physical examinations were administered to the participants, and the examinations included measurements of height (measured in centimeters with an error less than 0.5 cm). Other data included body weight (measured in kilograms with an error of less than 0.1 kg) and waist circumference (WC, calibrated weekly within 1 mm using a flexible ruler). The WC was measured between the lowest rib and the iliac crest of the participants, at the midway point of a gentle expiration. Blood pressure was measured three times with an automatic clinical blood pressure monitor in a sitting position following a standard protocol. All of the participants rested for at least 10 min before the physical examinations.

Peripheral venous blood samples were collected after an overnight fasting, and participants consuming any alcohol or high-fat foods the night before were excluded from the study. SUA, triglycerides, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), blood urea nitrogen (BUN) and serum creatinine (SCR) were measured with chemiluminescence methods on an autoanalyzer (Modular 7060, Hitachi, Ltd., Japan). All of the laboratory tests were performed in the same certificated clinical laboratory. Quality control measures were made for the estimation of all the variables.

1.4 *SLC2A9* SNP Selection and Genotyping

The International Haplotype Mapping (HapMap) (http://www.hapmap.org) SNP database was chosen to select SNPs in the *SLC2A9* region. According to the Hardy-Weinberg P-value and the minor allele frequency (MAF) of HapMap SNPs, five candidate SNPs in *SLC2A9* non-coding region (including rs938557, rs7679916, rs7349721, rs13101785, and rs13137343) which had passed the test for Hardy-Weinberg equilibrium (P>0.05) with MAF >0.05 were selected for further genotyping. These five SNPs have been selected for the evaluation of polymorphisms in *SLC2A9* with gout in a Chinese male population[10], while no study revealed the association between these SNPs and serum uric acid level. Samples were genotyped with TaqMan assays (Prism 3100; Applied Biosystems, USA). The genotype distribution of the SNPs was calculated from Hardy-Weinberg equilibrium (P>10^{-4}).

1.5 Statistical Analysis

The data were summarized as N (percentage) for category variables, and means±standard deviations for continuous variables. Differences in measurements between groups were compared with Student's t-test and Pearson's Chi-square test. The SNPs were tested for correlation with uric acid concentration and hyperuricemia by means of linear regression analysis with the Cochran-Armitage trend test, respectively. These analyses were conducted with the Windows software package (SPSS, USA) and the Plink Software Package to evaluate SNP-SNP interaction effects. Results were considered statistically significant when the P value was <0.05.

On the basis of an estimated effect size of genetic loci for uric acid (2–10 μmol/L per allele), our samples had over 80% power to detect an SNP effect with a MAF of 0.2 to 0.5 at the level of significance of 0.05.

2 RESULTS

2.1 The Clinical Characteristics of the Population

The data indicated that the quantitative variables in the hyperuricemia group were higher than those in the control group, with the exception of the HDL-C levels. Except for body mass index (BMI), WC, BUN, and SCR, the values for other quantitative variables were significantly different between the hyperuricemia group and the control group (all $P<0.05$). In addition, a higher prevalence of central obesity, hypertension, and hypertriglyceridemia was observed in the group with hyperuricemia than in the control group ($P<0.05$) (table 1).

2.2 Correlation of Uric Acid Levels and Hyperuricemia with Five Loci of *SLC2A9*

We tested the association of genotype with uric acid levels and hyperuricemia by multiple linear regression analysis and the Cochran-Armitage trend test adjusting for age, gender and BMI, respectively. There was no significant association between these five SNPs and uric acid when adjusted for age, gender and BMI in the total population (table 2). When we further evaluated the association of these SNPs with uric acid in the control group (table 3), we found that rs938557 was significantly correlated with uric acid (β=11.39±3.74, P=0.0024) adjusting for age, gender and BMI. Rs7679916 and rs13137343 were associated with uric acid marginally (β=5.77±3.09, P=0.0626; β=–5.99±3.08, P=0.0520). However, as to the association between these SNPs and hyperuricemia, none of these SNPs showed significant relation with hyperuricemia after controlling for age, gender and BMI (table 4).

2.3 The Uric Acid Concentration in Individuals with Different Genotypes of Five Loci for the Hyperuricemia Group and the Control Group

The uric acid concentrations were further compared between three genotypes for these SNPs in hyperuricemia group and control group, respectively.

Table 1 Comparison of the quantitative variables between the control group and the hyperuricemia group

Variable(s)	Control group	Hyperuricemia group	*P*-value
Number of subjects	1373	1053	
Age (years)	44.58±12.42	46.86±12.45	<0.0001
Male/female	804/633	569/420	0.440
BMI (kg/m^2)	26.47±4.95	26.66±4.82	0.405
WC (cm)	94.00±14.58	95.14±14.43	0.097
SBP (mmHg)	121.80±18.22	124.60±19.07	0.002
DBP (mmHg)	78.30±11.68	80.10±14.09	0.004
FBG (mmol/L)	5.11±1.42	5.26±1.74	0.017
BUN (mmol/L)	5.52±3.32	5.73±3.58	0.054
SCR (mmol/L)	77.37±36.91	76.38±28.47	0.234
TG (mmol/L)	2.20±1.96	2.46±1.85	0.001
TC (mmol/L)	3.97±1.72	4.22±1.57	0.018
HDL-C (mmol/L)	1.23±0.65	1.12 ± 0.13	0.037
LDL-C (mmol/L)	2.84±1.26	2.88±0.30	0.028
SUA (μmol/L)	259.8±78.5	465.7±72.8	<0.0001

Data are represented as the means±SD or *n* (%) unless otherwise indicated. Mean differences were considered significant at $P<0.05$. Mean±SD, mean±standard deviation; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; BUN, blood urea nitrogen; SCR, serum creatinine; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, serum low-density lipoprotein; SUA, serum uric acid

Table 2 Association of the five candidate alleles of *SLC2A9* with uric acid concentration in the total population

SNP ID	Position	Coded/other allele	MAF	Uric acid (μmol/L)			Uric acid (μmol/L)	
				CC	GC	GG	Beta (SE)	*P* value
rs938557	9827556	T/C	0.22	361 (249, 442)	344 (247, 436)	370 (264, 434)	1.84 (4.75)	0.6980
rs7679916	10042160	T/C	0.47	349 (241, 439)	352 (245, 440)	368 (265, 440)	4.49 (3.86)	0.2444
rs7349721	10042562	A/T	0.32	328 (230, 434)	359 (252, 444)	358 (255, 438)	–0.81 (4.21)	0.8468
rs13101785	10042915	T/A	0.50	364 (265, 441)	351 (243, 440)	351 (244, 436)	–5.84 (3.76)	0.1449
rs13137343	10043028	A/C	0.47	369 (266, 441)	352 (245, 439)	349 (242, 440)	–4.65 (3.84)	0.2264

*Data are shown as median (interquartile range). G: Coded allele, C: other allele. Evaluation of the association between SNPs and uric acid concentration with linear regression analysis. *P* values were adjusted for age, gender and BMI. Associations were considered significant at $P<0.05$. MAF: minor allele frequency

Table 3 Association of the five candidate alleles of *SLC2A9* with uric acid concentration in the control group

SNP ID	Position	Coded/other allele	Uric acid (μmol/L)			Uric acid (μmol/L)	
			CC	GC	GG	Beta (SE)	*P* value
rs938557	9827556	T/C	261 (199, 317)	266 (200, 318)	297 (230, 353)	11.39 (3.74)	0.0024
rs7679916	10042160	T/C	254 (194, 312)	260 (199, 318)	272 (207, 324)	5.77 (3.09)	0.0626
rs7349721	10042562	A/T	243 (188, 309)	263 (200, 320)	248 (201, 320)	–1.61 (3.35)	0.6313
rs13101785	10042915	T/A	272 (207, 328)	260 (198, 318)	260 (199, 313)	–4.76 (3.01)	0.1143
rs13137343	10043028	A/C	274 (210, 328)	261 (200, 319)	254 (194, 312)	–5.99 (3.08)	0.0520

*Data are shown as median (interquartile range). G: Coded allele, C: other allele. The associations between SNPs and uric acid concentration were evaluated with linear regression analysis in the control group adjusting for age, gender and BMI. Associations were considered significant at $P<0.05$.

Table 4 Association of the five candidate alleles of *SLC2A9* with hyperuricemia

SNP ID	Position	Coded/ other allele	MAF	Hyperuricemia (cases *vs.* controls)		Additive model		Recessive model		Dominant model	
				Case	Control	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
rs938557	9827556	T/C	0.22	0.229	0.208	0.940 (0.799, 1.105)	0.4526	0.882 (0.563, 1.384)	0.5856	0.937 (0.771, 1.137)	0.5085
rs7679916	10042160	T/C	0.47	0.536	0.519	1.035 (0.907, 1.182)	0.6053	1.086 (0.881, 1.339)	0.4404	1.006 (0.803, 1.260)	0.9572
rs7349721	10042562	A/T	0.32	0.318	0.328	0.982 (0.850, 1.135)	0.8069	0.968 (0.800, 1.172)	0.7405	1.002 (0.730, 1.376)	0.9890
rs13101785	10042915	T/A	0.50	0.485	0.506	0.930 (0.818, 1.058)	0.2709	0.922 (0.745, 1.140)	0.4526	0.889 (0.718, 1.101)	0.2809
rs13137343	10043028	A/C	0.47	0.537	0.521	0.977 (0.857, 1.114)	0.7293	1.019 (0.814, 1.276)	0.8687	0.928 (0.753, 1.143)	0.4818

Association of the SNPs with hyperuricemia was evaluated by the Cochran-Armitage trend test. *P* values were adjusted for age, gender and BMI. Associations were considered significant at $P<0.05$. MAF: minor allele frequency

As shown in fig. 1, in control group, individuals with T allele showed higher uric acid levels than individuals with C allele for rs938557 ($P=0.0172$). And there was marginal difference between individuals in the control group with different genotypes for rs7349721 ($P=0.0623$) and rs13137343 ($P=0.0744$). However, in hyperuricemia group, no SNP showed any significant difference in individuals with different genotypes.

3 DISCUSSION

Five different SNPs within *SLC2A9* were tested for its association with uric acid levels and hyperuricemia in the Uygur population were genotyped. No significant association was found between certain SNPs in *SLC2A9* and uric acid concentration in the total Uygur ethnic group. Our results further characterized the genetic variants of *SLC2A9* that might influence uric acid metabolism in the normouricaemia group, and found that some of these SNPs might be associated with increasing uric acid levels. However, there was no significant association between these SNPs and hyperuricemia in the Uygur ethnic population. Consequently, how *SLC2A9* affects uric acid metabolism in other ethnic groups who live in the same area with the Uygur should be studied in the future.

Historically, uric acid was considered as a waste product, but in recent studies, uric acid has been postulated to be an important molecule with multiple functions. In particular, uric acid has been linked with human diseases including nephrolithiasis, gout, metabolic syndrome, diabetes, hypertension, and adverse cardiovascular outcomes[12].

It is known that approximately 70% of total uric acid is excreted via the kidney[13]; therefore, the kidney plays a key role in uric acid homeostasis. Furthermore, hyperuricemia in gout is mostly due to reduced urate excretion, as the kidney has an enormous capacity for urate reabsorption. Further study in the mechanisms of renal handling of urate has been hampered by the differences between the human kidney and animal models. However, recent findings from human genetics and GWAS studies have indicated new details about the molecular mechanisms of urate transport[13]. Most of these studies were focused on the renal urate transport system, which has been generally considered the most influential regulator of serum urate homeostasis.

It has been demonstrated that genetic variants of *SLC2A9* are strongly correlated with reduced urinary urate clearance, which fits with the notion that common variations of *SLC2A9* lead to increased serum urate levels[14]. In a recent study, the authors demonstrated that *SLC2A9* is responsible for approximately 4% of the variance in serum urate levels[15, 16], and many GWAS analyses have shown that certain polymorphisms in *SLC2A9* are significantly correlated with elevated uric acid levels and hyperuricemia[17].

In this study, we selected Uygur subjects in China as our study subjects for three main reasons. First, the Uygurs are a separate ethnic group from other populations in China and live in a confined area, and they rarely intermarry with other nationalities, so they have a different genetic background compared with the main Han ethnic group in China. Previous

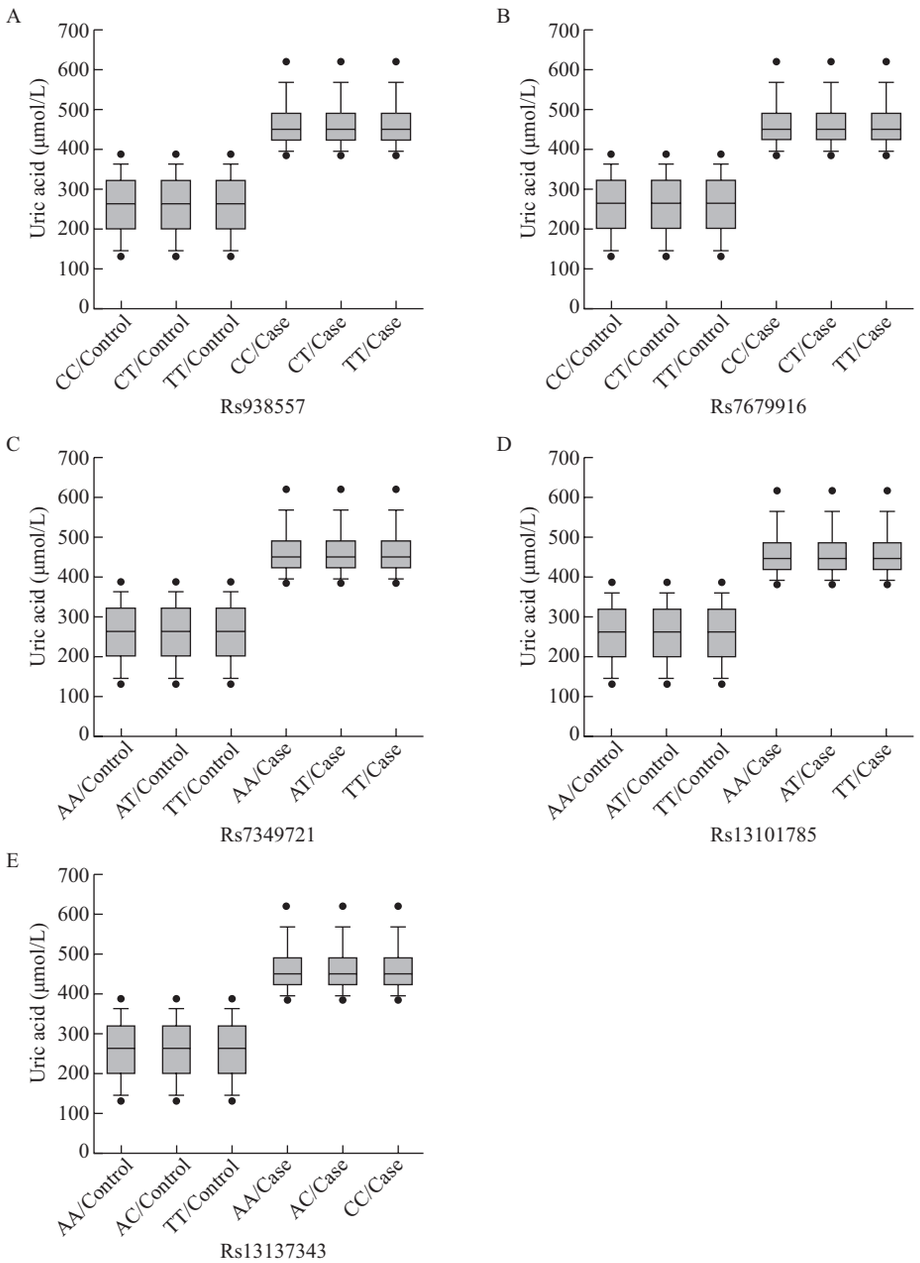

Fig. 1 Comparison of uric acid concentration between hyperuricemia and control groups according to five SLC2A9 genotypes
A: The uric acid levels were significantly different (P=0.0172) across genotypes of rs938557 in the control group. B: The uric acid levels were not significantly different across genotypes of rs7679916 in both the hyperuricemia and control groups (P=0.1626, P=0.1212). C: The uric acid levels were significantly different (P=0.0623) across genotypes of rs7347921 in the control group. D: There were no significant differences in genotypes of rs13101785 between the hyperuricemia group and control group (P=0.3575; P=0.2283). E: The uric acid levels were marginally different (P=0.0744) across genotypes of rs13137343 in the control group.

studies have sought to identify the ancestral origin of human populations by DNA sequencing technology, using mummies, although the Uygurs have only lived in Xinjiang for eight hundred to one thousand years. Before the Uygurs immigrated to Xinjiang, there were local populations distinct from the Uygurs. The remains of these predecessors of the Uygurs who lived three thousand years ago, were unearthed three thousand years ago from a dry desert in the Tarim Basin of Xinjiang, China, and these remains showed that the Uygur ethnic group that lives in Xinjiang originated from Europe[18, 19]. Second, most Uygurs practice the Islam religion, and they live in a special environment with different lifestyles and dietary habits. Third, we previously found that Uygurs show low uric acid concentrations and a low prevalence of hyperuricemia[20–22]. This study was the first to analyze the effects of five SNPs within the *SLC2A9* gene on hyperuricemia and the serum urate concentration in the Uygur population. Thus, our results contribute

to a greater understanding of the basic molecular pathogenesis of hyperuricemia in different nations.

Although the differences in the allele and genotype distributions of five loci in the *SLC2A9* gene were not significant between the hyperuricemia group and the control group, we found a marginal significance for the correlation between rs13101785, rs13137343 and uric acid. The uric acid levels among different genotypes for five loci in *SLC2A9* were compared between the hyperuricemia group and the control group. The hyperuricemia group, especially those individuals with the T allele, showed higher uric acid levels than those with the C allele of rs7679916. Individuals with the T allele also showed higher uric acid levels than those with the A allele of rs7347921 and rs13101785. Individuals with the C allele showed higher uric acid levels than individuals with the A allele of rs13137343.

Our study explored SNPs in *SLC2A9* in Uygurs, which enabled us to address why certain populations show different uric acid concentrations and a different prevalence of hyperuricemia. Some limitations of this study should be acknowledged. First, the number of enrolled study subjects in both groups may not have been sufficient for detailed analysis, and some potentially associated variants may have remained undetected. Second, genetic variants of the genes encoding urate transporters are limited within exon-intron boundaries. Further functional study might help to clarify the function of *SLC2A9*. Third, based on the cross-sectional design, we were unable to evaluate the effect of the selected SNPs on uric acid level, further propective studies are urged to clarify the the heritability explained by *SLC2A9* gene. Moreover, as with many other complex disorders, hyperuricemia is thought to be the result of a complicated network of numerous susceptibility loci, many of which exert additive or synergistic effects[23]. It is of practical importance to explore the physiology of the uric acid metabolism in the kidney and the role of uric acid transporters in uric acid homeostasis. Thus, our study sheds light on novel physiological actions of the uric acid transporter, its importance in drug effects and the genetic effect on uric acid levels in different ethnic groups.

Our results show that three loci (rs938557, rs7679916 and rs13137343) of SLC2A9 may contribute to an increased uric acid in the normouricaemia group. In particular, this study indicated an association between specific SNPs in the *SLC2A9* region and uric acid levels/hyperuricemia susceptibility in Uygur individuals. This finding, however, needs to be confirmed with a larger population size of this ethnic group.

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Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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