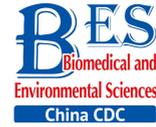


Original Article



Association between the *SUMO4* M55V Polymorphism and Susceptibility to Type 2 Diabetes Mellitus: A Meta-analysis*

ZHANG Qun¹, LIU Di², ZHAO Zhong Yao², SUN Qi², DING Li Xiang^{3,#}, and WANG You Xin^{2,#}

1. Chinese Center for Disease Control and Prevention, Beijing 102206, China; 2. Beijing Key Laboratory of Clinical Epidemiology, School of Public Health, Capital Medical University, Beijing 100069, China; 3. Department of Orthopedics Surgery, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Abstract

Objective The aim of this study is to determine whether the *SUMO4* M55V polymorphism is associated with susceptibility to type 2 diabetes mellitus (T2DM).

Methods A meta-analysis was performed to detect the potential association of the *SUMO4* M55V polymorphism and susceptibility to T2DM under dominant, recessive, co-dominant (homogeneous and heterogeneous), and additive models.

Results A total of eight articles including 10 case-control studies, with a total of 2932 cases and 2679 controls, were included in this meta-analysis. The significant association between the *SUMO4* M55V polymorphism and susceptibility to T2DM was observed in the dominant model (GG + GA versus AA: $OR = 1.21$, 95% $CI = 1.05-1.40$, $P = 0.009$), recessive model (GG versus GA + AA: $OR = 1.29$, 95% $CI = 1.07-1.356$, $P = 0.010$), homozygous model (GG versus AA: $OR = 1.41$, 95% $CI = 1.06-1.56$, $P = 0.001$), and additive model (G versus A: $OR = 1.18$, 95% $CI = 1.08-1.29$, $P = 0.001$), and marginally significant in the heterozygous model (GA versus AA: $OR = 1.16$, 95% $CI = 0.98-1.36$, $P = 0.080$). In subgroup analyses, significant associations were observed in the Chinese population under four genetic models excluding the heterozygous model, whereas no statistically significant associations were observed in the Japanese population under each of the five genetic models.

Conclusion The meta-analysis demonstrated that the G allele of the *SUMO4* M55V polymorphism could be a susceptible risk locus to T2DM, mainly in the Chinese population, while the association in other ethnic population needs to be further validated in studies with relatively large samples.

Key words: *SUMO4*; Type 2 diabetes mellitus (T2DM); Polymorphisms; Meta-analysis

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INTRODUCTION

D iabetes mellitus, a complex and chronic disease, has become a major public health problem and imposes new

challenges on health systems^[1]. The International Diabetes Federation's latest assessment shows that 387 million people (8.3% of adults) suffer from diabetes, and the number of patients is expected to rise above 592 million by 2035^[2]. Diabetes has had a

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#Correspondence should be addressed to WANG You Xin, PhD, Associate Professor, Tel: 86-10-83911779, E-mail: wangy@ccmu.edu.cn; DING Li Xiang, MD, PhD, Director and professor, Tel: 86-10-63926161, E-mail: Dinglixiang@medmail.com.cn

Biographical note of the first author: ZHANG Qun, male, born in 1973, PhD, majoring in medical informatics.

massive impact on China in recent decades. Growing evidence shows that China has a very high incidence of diabetes, and approximately 92.4 million adults currently have diabetes in China^[3]. Type 2 diabetes (T2DM), the most common form of diabetes, is characterized by insulin resistance^[4]. Several studies have indicated that susceptibility genes and environmental factors play significant roles in the development of T2DM^[5-6]. Multiple genes are thought to be involved, each producing a small effect on T2DM risk^[7].

Despite the differing pathogenesis of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), epidemiological data have indicated that these two types of diabetes display familial clustering, which suggests a common genetic basis between them^[8]. Several susceptibility genes have been reported to be associated with both T1DM and T2DM^[9]. The small ubiquitin-like modifier (SUMO) is a protein that attaches to target proteins and controls the target proteins' stability or activity^[10]. *SUMO4* is the fourth member of the SUMO family and is mainly expressed in the immune system^[11]. The *SUMO4* gene is located at a T1DM susceptibility locus (IDDM5) on chromosome 6q25, and a single nucleotide polymorphism (SNP) is associated with susceptibility to T1DM^[11-13]. *In vitro* studies have shown that *SUMO4* negatively regulates nuclear factor κ B (NF- κ B) transcriptional activity, which is a key transcriptional pathway involved in immune response and inflammation^[11]. Inflammation induces inhibition of the insulin signaling pathway, which leads to insulin resistance and contributes to the development of T2DM^[14].

Some epidemiology studies reported that the *SUMO4* M55V polymorphism is associated with susceptibility to T2DM^[15-19], while other studies did not favor the association^[20-23]. For example, Noso et al. (2009) reported that the *SUMO4* M55V polymorphism is associated with an increased risk of T2DM in a population recruited from the western region of Japan^[15], whereas other studies conducted in Wakayama and Toyoto did not confirm this association, neither in an allelic model, nor in additive, dominant, and recessive models^[20]. Therefore, the association between the *SUMO4* M55V polymorphism and T2DM remained controversial. Two separate meta-analyses were conducted to explore the association between the *SUMO4* M55V polymorphism and T2DM, and revealed an association^[24-25]. However, these studies only conducted meta-analyses based on alleles or

combined genotypes, without taking genetic models into account.

The patterns of inheritance of the *SUMO4* M55V polymorphism are not clear, and more than half of the studies did not support the association between the *SUMO4* M55V polymorphism and T2DM. Therefore, we performed this updated meta-analysis to validate the association between the *SUMO4* M55V polymorphism and T2DM under dominant, recessive, co-dominant (homozygous and heterozygous), and additive models.

METHODS

Search Strategy and Inclusion Criteria

A comprehensive literature search was conducted of the online databases MEDLINE (Medical Literature Analysis and Retrieval System Online), China National Knowledge Infrastructure (CNKI), Sinomed, and WanFang up to December 21, 2016. The following medical subject headings and keywords were used in the search strategy: 'Small ubiquitin-like modifier 4' or '*SUMO4*,' 'type 2 diabetes mellitus' or 'type 2 diabetes' or 'T2DM,' and 'rs237025' or 'Met55Val' or 'M55V,' or 'A163G.' References lists of the retrieved articles and reviews were also screened for additional articles not captured by electronic search.

Eligible studies included in the meta-analysis met all the following criteria: (1) the associations of polymorphisms in the *SUMO4* gene with T2DM; (2) case-control or cohort design; (3) provided odds ratio (OR) with 95% confidence interval (CI) or genotype frequency among case and control group; (4) study samples being unrelated individuals drawn from clearly defined populations; (5) written in English or Chinese; (6) for duplicate publications from the same population, only the paper that had the largest population, contained more useful information, or the latest one was selected. The exclusion criteria were defined as studies on animals, case reports, reviews, abstracts, editorial comments, and reports with incomplete data.

Data Extraction and Quality Appraisal

The following information was extracted: first author, year of publication, ethnicity, country of origin, sample size, age, gender, allele/genotypic frequencies and minor allele frequency in cases and controls and *P*-value for the allele frequency. The quality of studies was evaluated independently by

two investigators (ZHANG Qun and LIU Di) according to the Newcastle-Ottawa Scale (NOS). Uncertainties were resolved by discussions or by consensus with a third reviewer (ZHAO Zhong Yao). NOS evaluated studies with a star-rating system ranging from 0 (lowest) to 8 (highest) stars, which was based on three study components including selection, comparability, and outcome assessment. Studies with more than 5 points were evaluated as qualified.

Statistical Analysis

The associations of polymorphisms in the *SUMO4* gene with T2DM were estimated by calculating pooled *OR* and 95% *CI* by using RevMan 5.3. Hardy-Weinberg equilibrium (HWE) among controls was evaluated by chi-square test and $P < 0.05$ was considered as significant disequilibrium. The chi-square test and the inconsistency index (I^2) were applied to assess heterogeneity among studies. The Z-test was used to calculate the *P*-value of the overall effect for the meta-analysis. Because the true effect size might differ from study to study, random effects models were used for combined data, regardless of whether or not heterogeneity was detected in the meta-analysis. Pooled *OR* and 95% *CI* were computed by the random-effects method

of Mantel-Haenszel for combined data. Publication bias was evaluated by Begg's funnel plot and Egger's test. All the tests were two-sided, and results were considered statistically significant at $P \leq 0.05$ unless otherwise stated.

RESULTS

Characteristics of Eligible Studies

A total of 52 articles were identified after an initial search, 20 of which were duplicate articles (Figure 1). Twenty-three articles were further excluded because of duplicate sample use (5), animal or function studies (4), studies on other diseases (8), and review or comments (6) (Figure 1). From the above, we identified nine articles, which were included in the *SUMO4* M55V analysis (Table 1). One study was further excluded because of significant disequilibrium in the Hardy-Weinberg equilibrium test. Finally, eight articles including 10 case-control studies, with a total of 2932 cases and 2679 controls, were included in this meta-analysis. The study quality is summarized in Table 2. The quality of the studies included in this meta-analysis was acceptable (at least 5 points).

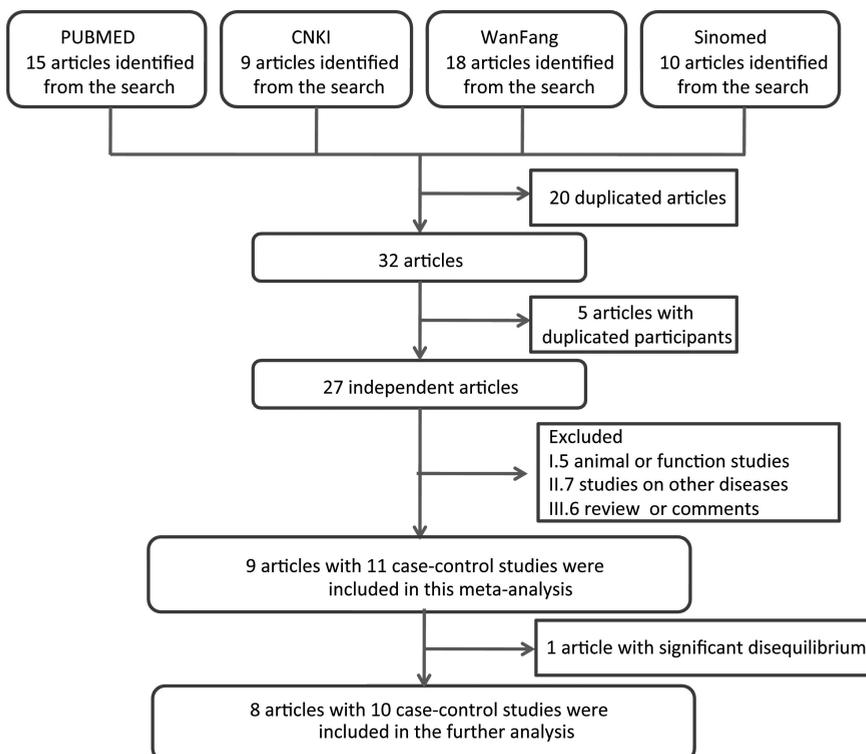


Figure 1. Flowchart of study selection.

Table 1. Characteristics of Case-control Studies Included in Meta-analysis

Study	Year	Ethnicity/Region	Population	Group	Subject Size	Diagnosis	Genotyping Method	P-value for HWE
Nosso S ^[15]	2007	Western area	Japanese	T2DM	355	ADA	Taqman SNP genotyping assay	0.690
				Control	398			0.291
Shimada T ^[20]	2009	Wakayama	Japanese	T2DM	423	WHO	Taqman SNP genotyping assay	0.716
				Control	436			0.094
Shimada T ^[20]	2009	Tokyo	Japanese	T2DM	451	WHO	Taqman SNP genotyping assay	0.408
				Control	469			0.378
Ji Z ^[17]	2010	Hunan	Chinese	T2DM	427	WHO	PCR-RFLP	0.830
				Control	281			0.079
Li B ^[21]	2011	Yunan	Chinese	T2DM	232	WHO	PCR-RFLP	0.260
				Control	102			0.126
Lin HY ^[16]	2007	Taiwan	Chinese	T2DM	574	NA	PCR-RFLP	0.193
				Control	323			0.466
Fallah S ^[22]	2010	Tehran	Irani	T2DM	50	NA	PCR-RFLP	0.493
				Control	50			0.998
Hu RT ^[23]	2009	Va	Chinese	T2DM	96	WHO	PCR-RFLP	0.487
				Control	104			0.673
Hu RT ^[23]	2009	Lalu	Chinese	T2DM	54	WHO	PCR-RFLP	0.088
				Control	234			0.817
Pu LM ^[18]	2012	Beijing	Chinese	T2DM	270	WHO	PCR-HRM	1.92×10^{-5}
				Control	282			0.086

Note. ADA: American Diabetes Association. WHO: World Health Organization. PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism restriction fragment length polymorphism. NA: not reported in the paper.

Table 2. Assessment of Case-control Studies Using Newcastle-Ottawa Scale for Evaluating Methodological Quality

Study	Case Definition	Representativeness of the Case	Selection of Controls	Definition of Controls	Comparability	Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non-Response Rate
Nosso S 2007 ^[15]	√	√	√	√	√	√	√	√
Shimada T 2009 ^[20]	√	√		√	√	√	√	√
Shimada T 2009 ^[20]	√	√		√	√	√	√	√
Lin HY 2007 ^[16]		√	√	√	√	√	√	√
Ji Z 2010 ^[17]	√	√	√		√	√	√	
Li B 2011 ^[21]	√	√		√	√	√	√	√
Hu RT 2009 ^[23]	√	√		√	√	√	√	√
Hu RT 2009 ^[23]	√	√		√	√	√	√	√
Pu LM 2012 ^[18]	√	√	√	√	√	√	√	√
Fallah S 2010 ^[12]		√	√		√	√	√	√

Meta-analysis

Figure 2 presents the forest plot of the association between the *SUMO4* M55V polymorphism (also named G163A in *SUMO4*, or rs237025) and T2DM in each studies and the meta-analysis. The significant association between the *SUMO4* M55V polymorphism and susceptibility to T2DM was observed in the dominant model (GG + GA versus AA: OR = 1.21, 95% CI = 1.05-1.40, $P = 0.009$), recessive model (GG versus GA + AA: OR = 1.29, 95% CI = 1.06-1.56, $P = 0.010$), homozygous model (GG versus AA: OR = 1.41, 95% CI = 1.15-1.71, $P = 0.001$), and additive model (G versus A: OR = 1.18, 95% CI = 1.08-1.29, $P = 0.001$), and marginally significant in the heterozygous model (GA versus AA: OR = 1.16, 95% CI = 0.98-1.36, $P = 0.080$).

No significant subgroup differences were observed (P ranged from 0.52 to 0.56 in all five genetic models). Subgroup analysis showed significant associations between the *SUMO4* M55V polymorphism and susceptibility to T2DM in the Chinese population under all but the heterozygous model (GA versus AA: OR = 1.12, 95% CI = 0.86-1.44, $P = 0.090$) and marginally significant associations in the Japanese population (P ranged from 0.13 to 0.40 in all five genetic models).

Evaluation of Publication Bias and Sensitivity

Funnel plot asymmetry was evaluated by Egger's regression test. If the line passed through the origin, it would indicate the absence of publication bias. The funnel plots and Egger's linear regression test are

shown in Figure 3. No publication biases were detected under the five genetic models (all $P > 0.05$).

A sensitivity analysis was conducted to explore the sources of heterogeneity, and the results showed that no single study affected the pooled OR and CIs in a qualitative manner.

DISCUSSION

Our study found a statistically significant association between the *SUMO4* M55V polymorphism and T2DM under dominant, recessive, co-dominant (homozygous and heterozygous), and additive models, especially in the Chinese population. In addition, publication bias tests and sensitivity analysis showed that the overall results were robust. The implication of this finding is that subjects with the G allele in the *SUMO4* M55V polymorphism are at a high risk of developing T2DM late in life.

The meta-analysis demonstrated that the *SUMO4* M55V polymorphism was associated with T2DM, consistent with several domestic and foreign reports^[15-19]. In subjects living in the western region of Japan, Noso et al. (2007)^[15] found that the frequency of the G allele was higher in T2DM patients ($P < 0.05$), and the frequency of the GG and GA genotypes in the case group was also higher than in controls, whereas these findings were not validated in subjects recruited from Wakayama and Toyoto of Japan^[20]. A study in the Taiwan, China population showed that *SUMO4* M55V polymorphism G allele carriers have a higher risk of suffering from T2DM^[16], as did two studies conducted

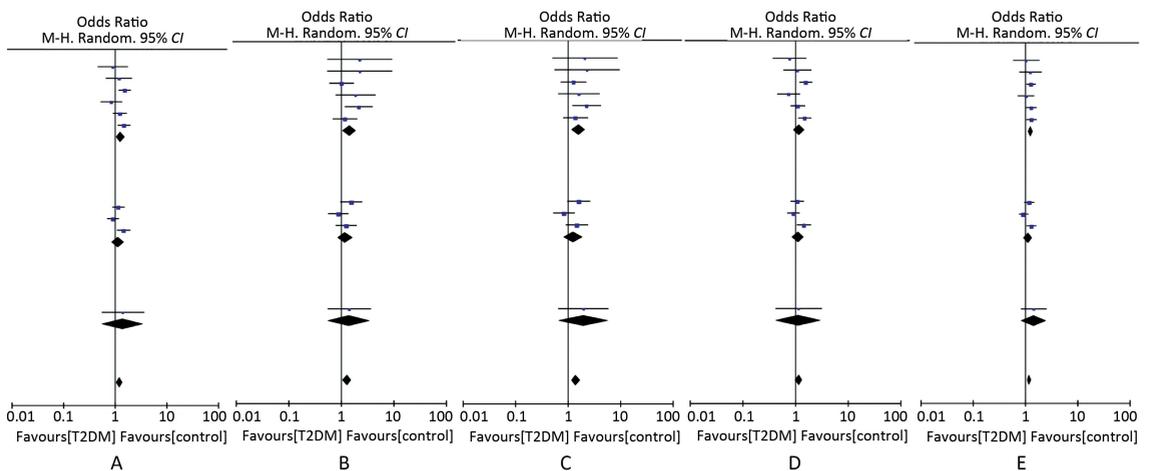


Figure 2. Forest plots of meta-analysis of the association between *SUMO4* M55V polymorphisms and T2DM in a dominant model (A), recessive model (B), homozygous model (C), heterozygous model (D), and additive model (E).

in Beijing and Hubei^[17-18]. However, studies conducted in Han Chinese and two ethnicities (Va, Lahu) recruited from the Yunan province of China did not demonstrate the same association^[21-23]. In addition, Fallah et al. (2010) found that the *SUMO4* M55V polymorphism was not associated with T2DM in the Iranian population^[22], while Sozen et al. (2014) reported that the *SUMO4* M55V polymorphism was associated with T2DM in the Turkish population^[19]. The study conducted in Turkey was excluded from this meta-analysis because of the significant Hardy-Weinberg disequilibrium, while the study conducted in Iran may have lacked statistical power (50 in each of disease and control groups). This disparity in the association between the *SUMO4* M55V polymorphism and T2DM between studies might be caused by heterogeneity in ethnicity and genetic background^[26]. In addition, the relatively small sample size in several studies also contributes to this discrepancy.

Genome-wide scans for T2DM revealed linkage of T2DM at chromosome 6q, where a susceptibility gene for T2DM (1DDM5) was mapped in African-American^[27], Chinese^[28], and Finnish populations^[29]. In addition, strong associations between the *SUMO4* M55V polymorphism and

T2DM were validated in several meta-analyses^[24,30]. The consistency in the association between the *SUMO4* M55V polymorphism and T1DM or T2DM suggested that *SUMO4* may explain the common genetic predisposition to T1DM and T2DM.

SUMO4 regulates the activation of I κ B α by sumoylation, and thus negatively regulates the activity of NF κ B^[31]. I κ B α inhibits NF- κ B by masking the nuclear localization signals (NLS) of NF- κ B proteins and keeping them sequestered in an inactive state in the cytoplasm; it also blocks the ability of NF- κ B transcription factors to bind to DNA, which is required for proper functioning of NF- κ B^[32]. NF- κ B, a transcriptional factor for inflammation, is relevant to the pathogenesis of diabetes mellitus^[33]. In addition, the interaction between NF κ B and I κ B α result in the insulin resistance *in vivo* and *in vitro* studies^[34-37]. Furthermore, the association of *SUMO4* Met55Val variation with increased insulin resistance was reported in newly diagnosed T2DM in a Chinese population^[38]. Therefore, the Met55Val variation in *SUMO4* may affect its capacity to modify I κ B α , leading to increased activity of NF κ B and increased insulin resistance and thus increase the risk of diabetes mellitus.

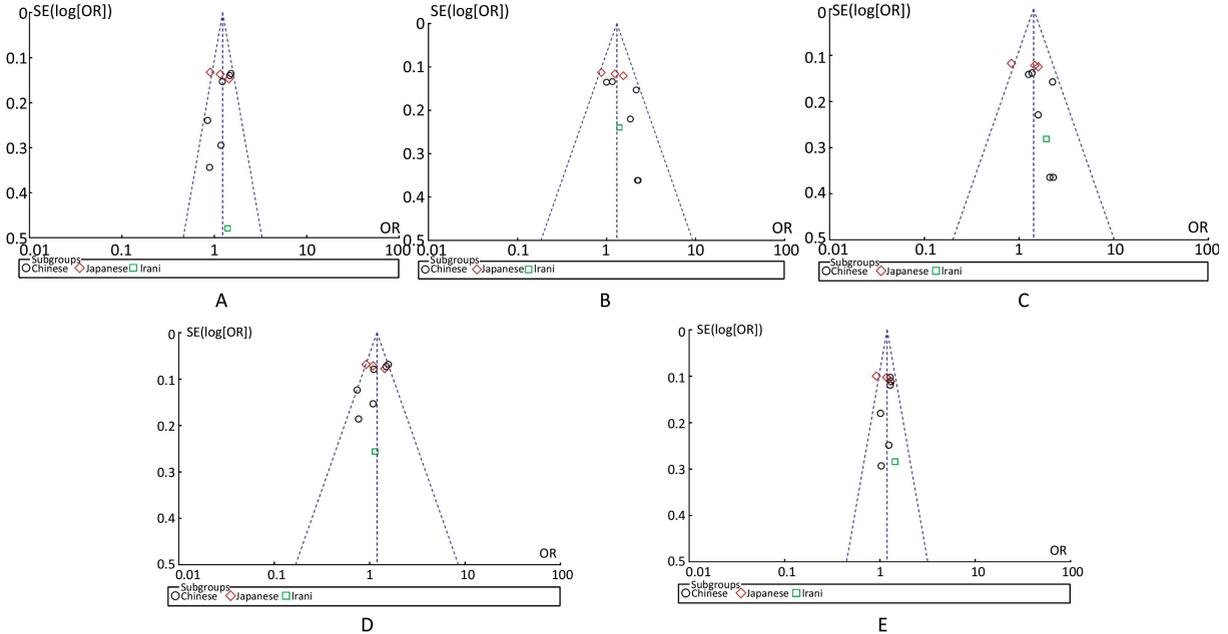


Figure 3. Publication biases indicated by the funnel plots. Figure A, dominant model, $P = 0.655$ and 0.550 in Begg's and Egger's test, respectively. Figure B, recessive model, $P = 0.245$ and 0.063 in Begg's and Egger's test, respectively. Figure C, homozygous model, $P = 0.074$ and 0.131 in Begg's and Egger's test, respectively. Figure D, heterozygous model, $P = 0.655$ and 0.237 in Begg's and Egger's test, respectively. Figure E, additive model, $P = 0.788$ and 0.866 in Begg's and Egger's test, respectively.

However, there are two limitations to our meta-analysis. First, confounding factors were not accounted for because most of the studies did not consider these. Unmeasured confounding factors might affect the observed association. Secondly, heterogeneity might lead to publication bias, because studies with negative results might not be published. Although the funnel plots and Egger's linear regression test indicated no biases, it is possible that the relatively small number of studies included in this meta-analysis led to less statistical power to detect publication biases.

To summarize, our meta-analysis demonstrated that the G allele in the *SUMO4* M55V polymorphism may be a susceptible risk locus to T2DM, especially in the Chinese population. The disparity among studies suggests that further investigations are required on the associations between the *SUMO4* M55V polymorphism and T2DM susceptibility in different ethnic groups. The *SUMO4* M55V polymorphism might be a causal factor in T2DM via its regulation of NF κ B signaling.

AUTHORS CONTRIBUTIONS

ZHANG Qun designed the study, collected the data, and wrote the manuscript; LIU Di, ZHAO Zhong Yao, and SUN Qi collected and analyzed the data; DING Lixiang designed the study. WANG You Xin designed the study, revised the manuscript.

CONFLICT OF INTEREST

All authors have no conflicts of interest.

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