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RAPID COMMUNICATION

Mutant *rs189037* in *ataxia-telangiectasia mutated* gene had a negative association with metabolic syndrome but not cognitive decline in centenarians

Approximately 20%—25% of adults encounter metabolic syndrome (MetS) worldwide, and MetS is a risk factor for cognitive decline (CD) development. Patients with MetS have an 11.48-fold increased incidence of CD compared with those without MetS.[1] *Ataxia-telangiectasia mutated* (*ATM*) gene encodes *ATM* kinase, which belongs to the phosphatidylinositol 3-hydroxy kinase family. Reduced *ATM* gene expression creates an inhibitory hippocampal function, excitatory/inhibitory imbalance, and finally CD.[2] Based on the China Hainan Centenarian Cohort Study (CHCCS) performed in 18 cities and counties of Hainan, we showed that the frequency of *CC* genotype in single nucleotide polymorphism (SNP) *rs189037* was significantly higher and that of *TT* genotype was significantly lower in centenarians with MetS than in those without MetS. Compared with *CC* and *CT* genotypes, *TT* genotype was negatively and significantly associated with MetS but not CD. This study demonstrated that mutant SNP *rs189037* in *ATM* gene had a significantly negative association with MetS but not CD in Chinese centenarians.

A cohort study of centenarians (CHCCS), in China, was conducted from June 2014 to December 2016 in 18 cities and counties of Hainan Province, China. A total of 399 centenarians were included in this study with a median age of 102 (range: 100—116 years). No centenarian in this study had a clearly established neurodegenerative disease. This study was approved by the ethics committee of Hainan Hospital, Chinese People's Liberation Army General Hospital (301HNLL-2016-01). Written informed consent was obtained from all participants before the initiation of this study.

Based on a standardized protocol, interview questionnaires, physical examinations, and blood analyses were conducted by our well-trained research team. According to the worldwide consensus on the definition of MetS established by the International Diabetes Federation, the centenarians were considered to have MetS if they had abdominal obesity and at least two of the following factors were satisfied: high blood pressure (systolic blood pressure/SBP $\geq$ 130 mmHg, diastolic blood pressure/DBP $\geq$ 85 mmHg or previously diagnosed hypertension), high blood glucose (fasting blood glucose/FBG $\geq$ 5.6 mmol/L or previously diagnosed diabetes mellitus), and abnormal blood lipids (triglyceride $\geq$ 1.7 mmol/L, high-density lipoprotein cholesterol/HDL-C $<$ 1.0 mmol/L in males and $<$1.3 mmol/L in females or previously diagnosed dyslipidemia). Furthermore, the index of cognitive function was a mini-mental state examination scale. The cutoff points for identifying CD were different for people who had different levels of education. Illiteracy with 17 points, elementary school level with 20 points, and junior high school level with 24 points were identified as CD.

Genomic DNA was isolated from peripheral blood samples using a QIAamp DNA Mini kit and eluted using 60 μL of buffer AE (Qiagen, Hilden, Germany). The concentration and purity of DNA were assessed using the Gen5 CHS 2.01 Software on the Eon microplate spectrophotometer (BioTeK, Winooski, Vermont, USA). SNP *rs189037* in *ATM* gene was genotyped in all participants using polymerase chain reaction (PCR)-restriction fragment length polymorphism and confirmed in 180 participants (>15%) by sequencing using a 3730XL automatic DNA sequencer (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA). The forward and reverse primers were 5′-GCTGCTTGGCGTT GCTTC-3′ and 5′-CATGAGATTGGCGGTCTGG3′ (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA), respectively. PCR was performed in 12.5 μL total volume containing 1 μL of genomic DNA. The ATM promoter region contains two Sac

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II restriction enzyme sites, and one of them is present in SNP *rs189037* (C/T) only when $T \rightarrow C$ substitution at nucleotide 116 occurs. All genotypes were determined as follows: three fragments of 46 bp, 116 bp, and 125 bp, respectively, for *CC* genotype; two fragments of 125 bp and 162 bp, respectively, for *TT* genotype; and four fragments of 46 bp, 116 bp, 125 bp, and 162 bp, respectively, for *CT* genotype.

Basic characteristics and genotype distribution of SNP *rs189037* in centenarians were shown in Table S1. Compared with centenarians without MetS, those with MetS had fewer males, higher WC, SBP, FBG, and TG levels, and lower HDL-C levels (all $P < 0.05$). Moreover, the frequency of CC genotype was significantly higher and that of TT genotype was significantly lower in centenarians with MetS than in those without MetS ($P < 0.05$). The distribution of genotype frequency in centenarians with and without MetS was consistent with Hardy Weinberg equilibrium ($P > 0.05$).

Table 1 shows the associations of MetS and CD with genotype groups of SNP *rs189037* in multivariate logistic regression analyses. Compared with *CC* [OR (95% CI): 0.264 (0.088—0.798)] and CT [OR (95% CI): 0.240 (0.080—0.723)] genotypes, *TT* genotype was negatively and significantly associated with MetS (all $P < 0.05$). Compared with *CC* [OR (95% CI): 0.631 (0.220—1.810)] and CT [OR (95% CI): 0.451 (0.167—1.219)] genotype, *TT* genotype was not significantly associated with CD (all $P > 0.05$). Compared with *CC* genotype, *CT* genotype was not significantly associated with MetS [OR (95% CI): 1.125 (0.637—1.984)] and CD [OR (95% CI): 1.327 (0.655—2.686)] (all $P > 0.05$).

Table S2 also shows the associations of MetS and CD with genotype groups of SNP *rs189037* in multivariate logistic regression analyses. Compared with $CT + CC$ genotype, *TT* genotype was negatively and significantly associated with MetS [OR (95% CI): 0.263 (0.091—0.756); $P < 0.05$] but not CD [OR (95% CI): 0.576 (0.226—1.470); $P > 0.05$]. Compared with *CC* genotype, $TT + CT$ genotype was not significantly associated with MetS [OR (95% CI): 0.860 (0.498—1.484)] and CD [OR (95% CI): 1.153 (0.591—2.246)] (all $P > 0.05$). Compared with $TT + CC$ genotype, *CT* genotype was not significantly associated with MetS [OR (95% CI): 1.491 (0.868—2.562)] and CD [OR (95% CI): 1.524 (0.805—2.883)] (all $P > 0.05$).

Human lifespan is the combined result of the multiple processes done by numerous genetic factors. While aging is also a complex process including the influence of not only multiple genetic but also non genetic factors. Genes are major contributors to aging, and SNPs may be associated with aging. *ATM* gene prevents cellular senescence, death, or cycle arrest and protects individuals from ROS-induced DNA damage. Because MetS may result from the lack of serine/threonine kinase *ATM*, it is highly necessary to investigate the association between SNP *rs189037* and MetS in centenarians.[2] Schneider et al found that the lack of an *ATM* allele worsens the development of IR and MetS in *ApoE* gene-deficient mice. Furthermore, mitoq, as a mitochondria-targeted antioxidant, reduces mitochondrial oxidative damage and inhibits the development of MetS in fat-fed and *ATM*-deficient mice. Simultaneous inhibition of oxidative stress pathways reduces ROS levels and improves MetS in obese mice.[3] A deficiency of *ATM* due to ROS can cause DNA damage by leading to DNA double-strand breaks and resulting in telomere dysfunction. Thus, *ATM* mutations may predispose individuals to metabolic dysfunction and play an important role in MetS. This study found that mutant SNP *rs189037* was negatively and significantly associated with MetS in Chinese centenarians.

ATM kinase plays an important role in the process of neuronal cell loss in neurodegenerative diseases. ATM deficiency causes mouse neurons to re-enter the cell cycle and die, suggesting that mutant SNP *rs189037* increases the risk of developing neurodegenerative diseases.[4] However, the results of this study showed no significant association between mutant SNP *rs189037* and CD. Similar results were similarly found by Ding et al, that mutant *rs189037* SNP was not directly associated with CD in the Chinese population.[5]

This study demonstrated that mutant SNP *rs189037* in *ATM* gene had a significantly negative association with MetS but not CD in Chinese centenarians, which needs to be confirmed by basic experiments and clinical studies.

Ethics declaration

The current study received the approval from Ethics Committee of Hainan Hospital of Chinese People's Liberation Army General Hospital (Sanya, Hainan; approval number: 301HNLL-2016-01). Before the current study, written informed consent was required from all participants.

Table 1 Multivariate logistic regression of MetS and CD with genotype groups of *rs189037* in centenarians.

Characteristics	TT/CT		CT/CC		TT/CC	
	Exp(B) (95% CI)	*P*	Exp(B) (95% CI)	*P*	Exp(B) (95% CI)	*P*
Age	0.922 (0.823—1.033)	0.159	1.069 (0.987—1.157)	0.100	1.041 (0.920—1.176)	0.525
Males	1.334 (0.515—3.456)	0.552	1.213 (0.594—2.477)	0.596	1.707 (0.680—4.285)	0.255
Nationality	0.493 (0.194—1.254)	0.138	0.934 (0.597—1.463)	0.767	0.471 (0.180—1.232)	0.125
MetS	0.240 (0.080—0.723)	0.011	1.125 (0.637—1.984)	0.685	0.264 (0.088—0.798)	0.018
Education level	0.779 (0.518—1.172)	0.231	1.375 (0.955—1.980)	0.086	1.154 (0.728—1.828)	0.543
CD	0.451 (0.167—1.219)	0.117	1.327 (0.655—2.686)	0.432	0.631 (0.220—1.810)	0.392
Smoking	1.672 (0.560—4.991)	0.357	0.579 (0.264—1.273)	0.174	0.824 (0.303—2.244)	0.705
Drinking	0.531 (0.219—1.289)	0.162	1.370 (0.759—2.474)	0.296	0.679 (0.267—1.725)	0.416

Note: MetS, metabolic syndrome; CD, cognitive decline; CI, confidence interval.

Data availability

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interests

The authors declare that they have no competing interests.

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Author contributions

All authors contributed to the design of the study and participated in data collection and analysis and manuscript draft. All authors read and approved the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2023.06.023.

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