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RESEARCH LETTER

Association of genetic variations of *PRDM16* with metabolic syndrome in a general Xinjiang Uygur population

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Introduction

The function of brown fat in metabolic syndrome (MetS) has been followed with great interest in recent years. Positive regulatory domain containing 16 (PRDM16) has been shown to control a bidirectional cell fate switch between skeletal myoblasts and brown adipocytes [1]. We hypothesized that genetic variants within the *PRDM16* gene may be associated with MetS. At present, only one study so far has reported a genetic association between *PPRDM16* and MetS [2]. So, the aim of this study was to search for common and novel sequence variations in *PRDM16* and to determine whether variants in this gene influence susceptibility to MetS.

Materials and methods

Subjects

For this study, we randomly recruited a total of 1,399 Uygur subjects, with no miscegenation within the past three generations. Based on their present history and on a clinical examination, subjects with secondary hypertension, type 1 diabetes, stroke, excessive drinking, and cancer were excluded from the study. An epidemiological cross-sectional investigation by multistage cluster sampling was performed on the selected subjects.

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MetS was defined using the criteria of the International Diabetes Federation (IDF); the criteria for non-MetS was non-visceral obesity (WC <90 cm for males; <80 cm for female) and ≤2 for the other dysfunction components of MetS. Fasting lipid profiles included total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride concentrations. Genomic DNA was extracted from the blood sample of each subject using the PAXgene Blood DNA kit (PreAnalytiX, a QIAGEN/BD company). The study was performed after obtaining informed consent from all subjects and was approved by the local ethics committee.

Genotyping

The Universal PCR Master Mix from Applied Biosystems was used in a 5 μl total reaction volume with 10 ng (1 μl) DNA per reaction. Allelic discrimination was measured automatically on the ABI PRISM HT7900 (Applied Biosystems) using the Sequence Detection Systems 2.1 software (autocaller confidence level 95%). For genotyping quality control, the case (MetS) and control (non-MetS) subjects were distributed randomly across the plates, and the sequenced samples were also genotyped to detect any genotyping errors. The call rate for genotyping was 96.4% and the concordance of duplicates was 100%.

Statistical analysis

Values are expressed as means ± SD. The distributions of patient characteristics, genotypes and allele frequencies of the SNPs between the non-MetS and MetS groups were analyzed using the Student's *t* test or by χ^2 analysis. Pearson's χ^2 test was used to evaluate the risk between different genotypes. The odds ratio (OR) and 95% confidence interval (CI) were calculated by logistic regression after

Table 1 Comparison of genotype frequencies in distributions for four polymorphisms of *PRDM16* in non-MetS and MetS subjects

Genotypes	non-MetS	MetS	Additive model				Allele model			FDR q-value	Statistical power
	n (%)	*n* (%)	Odds ratio (95%CI)	χ^2	*P*-value	FDR q-value	Odds ratio (95%CI)	χ^2	*P*-value		
rs2493292											
CC	614 (82.5)	530 (82.8)									
CT	126 (16.9)	104 (16.3)	1.027	0.862	0.650	0.398	0.988	0.02	0.889	0.985	0.050
TT	4 (0.5)	6 (0.9)	(0.786–1.342)				(0.743–1.314)				
rs2236518											
AA	264 (35.53)	281 (42.84)									
AG	377 (50.74)	296 (45.12)	0.805	8.792	0.020	0.023	0.715	8.79	0.005	0.021	0.865
GG	102 (13.73)	79 (12.04)	(0.687–0.944)				(0.575–0.889)				
rs2282198											
CC	252 (33.78)	205 (33.88)									
CT	351 (47.05)	293 (48.30)	0.957	0.531	0.77	0.421	0.993	0.53	0.968	0.985	0.050
TT	143 (19.17)	107 (17.69)	(0.859–1.066)				(0.788–1.251)				
rs870171											
GG	359 (48.3)	305 (50.3)									
GT	333 (44.8)	238 (39.3)	1.024	7.580	0.022	0.023	0.893	7.58	0.481	0.924	0.170
TT	51 (6.9)	63(10.4)	(0.863–1.224)				(0.718–1.112)				

In the additive model, odds ratios (ORs) were expressed per difference in number of minor alleles. In the dominant model, ORs were shown as heterozygotes and minor allele homozygotes compared with major allele homozygotes. OR for each SNP was adjusted simultaneously for gender and age. Statistical powers were calculated with the given ORs of dominant model, frequency, and subject numbers at a significance level of 0.05

adjustment for age and gender. Retrospective statistical powers were calculated using PS software version 2.1.31 (available at http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize).

Results

The clinical characteristics of the non-MetS and MetS subjects. There were significant differences between the Non-MetS and MetS groups for all characteristics ($P < 0.05$), excluding age (data not shown).

We assessed the association of each SNPs and MetS phenotype using the additive and allele models (Table 1). Using the additive model, we found no evidence of an association of either rs2493292 (Pro633Leu, $\chi^2 = 0.862$, $P = 0.65$) or rs2282198 (315898T>C, $\chi^2 = 0.531$, $P = 0.77$) with MetS. However, rs2236518 (367039T>G) had significantly different genotype frequencies between MetS and non-MetS (additive model, $\chi^2 = 7.822$, $P = 0.02$; allele model, $\chi^2 = 8.79$, $P = 0.005$) even after adjustment for age and gender in the logistic regression analysis [OR = 0.805 (95%CI 0.687–0.944) and OR = 0.715 (95%CI 0.575–0.889)]. Rs870171 (356981G>T) also had significantly different of genotype frequencies between the two groups but only in the additive model ($\chi^2 = 7.58$, $P = 0.022$); the significance was lost after adjustment for age and gender [additive model, OR = 1.024 (95%CI 0.863–1.224)].

Discussion

After the discovery of *PRDM16* [3], the protein has become a potential target for the development of obesity-related therapeutics, including the possibility that its genetic variation may contribute to disease. So far, there has been only one report about the relationship between genetic variations in the *PRDM16* gene and human MetS [2] which found that five genes, including *PRDM16*, were associated with MetS. Further comprehensive studies into the association of genetic variations of *PRDM16* with MetS from a more genetic point of view are needed. In present study, the commonly occurring SNP rs2236518 showed a significant negative association with MetS in a multivariable logistic regression analysis. However, we could not identify the SNP, rs17390167, reported in a previous study [2] because we only sequenced the 17 exons and the exon–intron junctions of *PRDM116* and the location of rs17390167 is outside the region that was sequenced. Rs2236518 falls outside the putative transcribed region and the current gene annotation suggests it would not be present in the mRNA sequence where it could potentially influence gene expression [4, 5]; So rs2236518 may be in

linkage disequilibrium with another functional variation within or around the *PRDM16* gene and other functional polymorphisms that play more important roles in MetS. Further investigation is needed to determine whether the rs2236518 polymorphism could influence the PRDM16 function. Obesity has been described as the central causative component in the development of MetS. The interplay between environmental and genetic factors is a major determinant of final phenotypes. Recently, it has been accepted that metabolic diseases share not only similar risk factors but also possibly similar genetic determinants [6]. So the association of rs2236518 with MetS may be an example of this. However, it still need to be verified whether the variants of *PRDM16* regulate adipose tissue mass and then subsequently contribute to the development of MetS. Thus, PRDM16 may be a new therapeutic target for metabolic disorders [3].

In conclusion, this is the first report of genetic variations in the *PRDM16* gene associated with the MetS phenotype in Uygur Chinese. Further functional analyses of the sequence variations of *PRDM16* are necessary to clarify the possible functional changes that might be caused by this genetic finding.

References

1. K.S. Seale, W. Yang, S. Chin, L.M. Rohas, M. Uldry, G. Tavernier, D. Langin, B.M. Spiegelman, Transcriptional control of brown fat determination by PRDM16. Cell Metab. **6**, 38–54 (2007)
2. Y.M. Park, M.A. Province, X. Gao, M. Feitosa, J. Wu, D. Ma, D. Rao, A.T. Kraja, Longitudinal trends in the association of metabolic syndrome with 550 k single-nucleotide polymorphisms in the Framingham Heart Study. BMC Proc. **15**(3 Suppl 7), S116 (2009)
3. S. Kajimura, P. Seale, T. Tomaru, H. Erdjument-Bromage, M.P. Cooper, J.L. Ruas, S. Chin, P. Tempst, M.A. Lazar, B.M. Spiegelman, Regulation of the brown and white fat gene programs through a PRDM16/CtBP transcriptional complex. Genes Dev. **22**(10), 1269–1275 (2008)
4. G.J. Wang, P. Yang, H.G. Xie, Gene variants in noncoding regions and their possible consequences. Pharmacogenomics **7**, 203–209 (2006)
5. D. Conklin, I. Jonassen, R. Aasland, W.R. Taylor, Association of nucleotide patterns with gene function classes: application to human 3 untranslated sequences. Bioinformatics **18**, 182–189 (2002)
6. A. Hamann, A.M. Sharma, Genetics of obesity and obesity-related hypertension. Semin Nephrol. **22**, 100–104 (2002)