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Original Article

Correlation of lipid metabolic disturbance with SOCS-3 gene variation in the Uygur nationality women in Xinjiang

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Abstract: To study the correlation of lipid metabolic disturbance with gene variation of suppressor of cytokine signaling 3 (SOCS-3) in the Uygur nationality women in Xinjiang. We Selected 1379 Uygur nationality women as research objects and proceeded genotype assay for 3 representative loci (rs12953258, rs4969168 and rs9914220) to analyze them. There were significant difference in genotypic frequency in rs12953258 between lipid metabolic disturbance group and lipid embolism group (P=0.032) and between high density lipoprotein cholesterol (HDL-C) abnormal and normal group (P=0.029). Logistic regression analysis showed that the AA genotype of rs12953258 might be a risk factors of lipid metabolic disturbance in the Uygur nationality women in Xinjiang [CC/AA: OR=3.271, 95% CI (1.092-9.797), P=0.034]. The AA genotype might be associated with HDL-C decrease and triacylglycerol increase. The AA genotype Uygur nationality women with abnormal body mass index (BMI) were more sensitive to lipid metabolic disturbance disease. SOCS-3 gene variation may be associated with lipid metabolic disturbance in the Uygur nationality women in Xinjiang, prevalence of lipid metabolic disturbance increases significantly in crowd carrying AA genotype with abnormal BMI.

Keywords: SOCS-3 gene, lipid metabolic disorder, leptin

Introduction

Lipid metabolic disturbance is one of the clinical syndrome of metabolic syndrome (MS) [1, 2] and an independent risk factor for cardiovascular diseases. It is usually affected by both genetic factors and environmental factors. Previous studies have reported that the Uygur nationality crowd are high risk group of MS (41.3%) and their dyslipidemia ratio reach to 34.8% [3, 4]. Among these lipid metabolic disturbance patients, the number of woman (50.3%) are far more than that of man (29.6%) [5]. Hetian area in Xinjiang is remote and the social environment is relative isolation. The Uygur nationality people from this area keep unity genetics background since there are no miscegenation [6], so they are ideal study population. Suppressor of cytokine signaling-3 (SOCS-3) is a negative feedback regulation factor in JAK-STAT pathway [7, 8] and involved in the generation and progress of insulin resistance [9], leptin resistance [10], immunologic diseases, inflammatory reaction diseases and tumor [11, 12]. Obese caused by leptin resistance are closely associated with lipid metabolic disturbance and so the SOCS-3 is inferred as a possible candidate gene of lipid metabolic disorder. Seldom studies are focus on the relationship between SOCS-3 gene variation and lipid metabolic disorder, especially in the Uygur nationality women with high incidence of lipid metabolic disorder. This study investigated the correlation between SOCS-3 gene variation and lipid metabolic disturbance in the Uygur nationality women.

Subjects and methods

Subjects

1379 Uygur nationality inhabitants (30-70 years old, without miscegenation history within 3 gen-

Table 1. General characteristics between dyslipidemia group and normal group

Group	Age (years)	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)	BMI (kg/m^2)
Male (*n*=521)						
normal group (*n*=157)	54.48±11.44	4.53±0.82	1.36±0.37	2.74±0.75	1.09 (0.78, 1.42)	24.87±4.70
dyslipidemia group (*n*=364)	52.35±11.32[a]	4.55±1.68	0.94±0.30[a]	2.82±1.45	1.49 (0.98, 235)[a]	27.62±4.33[a]
Female (*n*=858)						
normal group (*n*=313)	51.27±11.59	4.34±0.79	1.34±0.22	2.40±0.79	1.12 (0.88, 1.44)	26.19±4.53
dyslipidemia group (*n*=545)	49.24±10.57[a]	4.38±1.42[a]	0.98±0.37[a]	2.46±1.20	1.49 (0.99, 2.31)[a]	27.48±4.58[a]
Group		WHR (cm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	FBG (mmol/L)
Male (*n*=521)						
normal group (*n*=157)		90.09±9.03	127.82±22.87	76.66±15.04	93.72±16.42	5.32 (4.93, 6.08)
dyslipidemia group (*n*=364)		96.37±10.16[a]	130.59±24.10	79.27±14.99	96.38±16.68	5.25 (4.65, 6.21)
Female (*n*=858)						
normal group (*n*=313)		92.78±10.48	133.47±28.94	79.47±17.16	97.47±19.89	5.33 (4.82, 6.11)
dyslipidemia group (*n*=545)		95.60±9.88[a]	130.36±26.19	78.71±14.47	95.93±17.47	5.05 (4.41, 5.94)

TC: cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triacylglycerol; HDL-C: high density lipoprotein cholesterol; BMI: body mass index; WHR: Waist hip rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; FBG: fasting blood glucose; [a]P<0.05: General characteristics have significant difference compared with lipid metabolic disorder group and lipid metabolic normal group.

eration and consanguineous marriage history, without thyroid diseases, severity liver and kidney disease and tumor) from Hetian area in Xinjiang from January to March in 2010 were collected by epidemiology cross-sectional investigation. We have obtained approval from ethics committee and health bureau of local government and People's Hospital of Xinjiang Uygur Autonomous Region. All subjects gave informed consent to participate in the study.

Data collection and diagnostic criteria

Cluster random sampling method was utilized to proceed questionnaire surveys, physical examination and biochemical indicator detection. General state of health and case history included name, gender, age, smoking history, drinking history and so on. Physical examination included body height, body weight, waist hip rate (WHR), pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP) and so on. We calculated body mass index (BMI) (BMI= body height (kg)/body weight (m^2)) and regarded 18.5 kg/m^2≤BMI<24 kg/m as normal body weight, 24 kg/m^2≤BMI<28 kg/m^2 as overweight and BMI≥28 kg/m^2 as obese according to the Guide to Prevention and Control of Chinese Adult Overweight and Obese [13]. The mean arterial pressure (MAP)=1/3(SBP+2×DBP) (the MAP of normal adult are 70-105 mmHg, 1 mmHg=0.133 kPa). Diagnostic criteria for lipid metabolic disturbance were according to the Guide to Prevention of Chinese Adult Dyslipidemia and they should coincide one or more index such as cholesterol (TC)≥6.22 mmol/L, low density lipoprotein cholesterol (LDL-C)≥4.14 mmol/L, triacylglycerol (TG)≥2.26 mmol/L and high density lipoprotein cholesterol (HDL-C)<1.04 mmol/L [14]. Diagnostic criteria for hypertension were according to the Guide to Diagnostic of Chinese Hypertension (2010) (revised by the Guide to Diagnostic of Chinese Hypertension Revise Committee in 2010) and were defined as SBP≥140 mmHg and/or DBP≥90 mmHg with past history of hypertensive disease (patients who keep normal blood pressure with the help of antihypertensive drug).

Biochemical indicator detection

All research objects kept fasting and temperance for 1 day and stop diet for 12 hours to obtain ulnar vein blood in sitting position in the next morning. We centrifuged the blood with 2500 r/min (r=98/64 mm) for 30 min to separate plasma and hemocytes and then preserved them in -20°C freezer. Biochemical indicator including fasting blood-glucose (FBG), TC, HDL-C, LDL-C, TG and so on were detected by clinical laboratory of People's Hospital of Xinjiang Uygur Autonomous Region in the same batch.

DNA extraction, variation sites screening and genotype assay for SOCS-3 gene

Paxgene blood DNA kit (America AQIAGEN/BD company) were utilized to extract DNA from 200 μl hemocytes and the products were preserved at -80°C. 3 Single Nucleotide Polymo-

Table 2. Frequency distribution of SOCS-3's Genotype in dyslipidemia group and lipid metabolism of normal group [n (%)]

SNPs	Genotype	Female		Male		Total	
		dyslipidemia group	normal group	dyslipidemia group	normal group	dyslipidemia group	normal group
rs4969168	GG	229 (42.02)	124 (39.62)	48 (12.80)	24 (15.29)	387 (42.60)	175 (37.20)
	GA	244 (44.77)	154 (49.20)	158 (43.60)	82 (52.23)	402 (44.30)	237 (50.30)
	AA	72 (13.21)	35 (11.18)	158 (43.60)	51 (32.48)	119 (13.10)	59 (12.50)
	X^2	1.776		6.001		4.8	
	P	0.411		0.112		0.09	
rs9914220	TT	25 (4.60)	12 (3.83)	18 (4.97)	7 (4.46)	43 (4.80)	20 (4.20)
	CT	178 (32.78)	94 (30.03)	127 (35.08)	47 (29.94)	305 (33.70)	143 (30.20)
	CC	342 (62.62)	207 (66.14)	219 (59.94)	103 (65.60)	557 (61.50)	310 (65.50)
	X^2	1.129		1.494		2.12	
	P	0.569		0.474		0.35	
rs12953258	CC	405 (74.31)	254 (81.15)	256 (70.33)	125 (79.62)	661 (72.72)	379 (80.64)
	CA	121 (22.20)	55 (17.57)	97 (26.65)	29 (18.47)	218 (23.98)	84 (17.87)
	AA	19 (3.49)	4 (1.28)	11 (3.02)	3 (1.91)	30 (3.30)	7 (1.50)
	X^2	6.905		4.831		11.65	
	P	0.032		0.089		<0.001	

Table 3. Frequency distribution of rs12953258's Genotype in different lipid blood component of female [*n* (%)]

Group	CC	CA	AA	X^2	*P*
TC					
normal group	254 (81.15)	55 (17.57)	4 (1.28)		
abnormal group	52 (74.29)	17 (24.29)	1 (1.42)	2.616	0.27
HDL-C					
normal group	254 (81.15)	55 (17.57)	4 (1.28)		
abnormal group	313 (75.24)	85 (20.43)	18 (4.33)	7.065	0.029
LDL-C					
normal group	254 (81.15)	55 (17.57)	4 (1.28)		
abnormal group	47 (77.05)	13 (21.31)	1 (1.64)	0.549	0.76
TG					
normal group	254 (81.15)	55 (17.57)	4 (1.28)		
abnormal group	108 (72.97)	35 (23.65)	5 (3.38)	5.027	0.081

rphism (SNPs) (-920C/A (rs12953258) [15], 930A/G (rs4969168) [16] and -6732C/T (rs9914220) [17]) were selected to proceed crowd genotype assay with TaqMan-PCR technique (7900 real-time PCR system, America ABI company). Set blank and positive control for each 384-well plate and random distribution for case control samples as quality control measures for genotyping. The fetch rate of genotyping is 98.9% and the concordance rate of repeat detection is 100%.

Statistical treatment

SPSS17.0 was utilized for statistical treatment. Continuous variable coinciding with normal distribution were represented as means ± standard error and that coinciding with skewed distribution were represented as media (quartile range). Categorical variable adoption ratio was represented as percentage. T test was utilized to proceed group comparison for continuous variable coinciding with normal distribution and rank sum test was utilized to proceed that for those not coinciding with normal distribution. Analysis of variance was utilized for group comparison. X^2 test was utilized for group comparison of grouping variable. Logistic regression analysis was utilized for the influencing factors of lipid metabolic disturbance and blood fat related constitution (two-tailed test, α=0.05, P<0.05). Hardy-Weinberg equilibrium test was accomplished by SNP Alyze7.0 software (DYNACOM Co. Ltd, Mobara, Japan).

Results

Base line data

Among the 1379 subjects, 909 were suffering from lipid metabolic disturbance and the rest were in healthy condition. 364 males (26.40%) and 545 females (39.5%) were suffering from lipid metabolic disturbance and 157 males and

Table 4. The analysis of logistic regression about risk factor of dyslipidemia in female

dependent variable	risk factor	*B*	*SE*	Wales	*OR* (95% *CI*)	*P*
lipid metabolism is normal or not	rs12953258 CC					
	rs12953258 CA	0.351	0.184	3.630	1.420 (0.990, 2.036)	0.057
	rs12953258 AA	1.185	0.560	4.483	3.271 (1.092, 9.797)	0.034
	BMI	0.061	0.016	13.99	1.063 (1.030, 1.098)	<0.001
	CC+ normal BMI					
	AA+ abnormal BMI	2.201	1.060	4.314	9.032 (1.132, 72.06)	0.038
HDL-C is normal or not	rs12953258 CC					
	rs12953258 CA	0.198	0.199	0.991	1.219 (0.825, 1.801)	0.32
	rs12953258 AA	1.263	0.566	4.983	3.537 (1.167, 10.723)	0.026
	BMI	0.038	0.019	4.095	1.039 (1.001, 1.077)	0.043
TG is normal or not	rs12953258 CC					
	rs12953258 CA	0.415	0.26	2.544	1.515 (0.909, 2.524)	0.118
	rs12953258 AA	1.412	0.70	4.067	4.105 (1.041, 16.197)	0.038
	abdomen circumference	0.061	0.11	31.29	1.06 (1.041, 1.086)	<0.001
TC is normal or not	abdomen circumference	0.029	0.014	4.406	1.03 (1.002, 1.058)	0.036
LDL-C is normal or not	BMI	0.077	0.031	6.282	1.08 (1.017, 1.148)	0.012

313 females were in healthy condition among 521 male subjects (mean age 53.0±11.4 years old) and 858 female subjects (mean age 50.0±11.0 years old). Compared with male healthy group, in male lipid metabolic disturbance group, the mean age were significantly younger, the TG, BMI and abdomen circumference levels were significantly higher and the HDL-C were significantly lower (P<0.05). However, differences between groups of TC, LDL-C, MAP, SBP, DBP and FBG levels had no statistically significance (P>0.05). The above results also beseemed the comparison between female lipid metabolic disturbance group and female healthy group (**Table 1**).

Genotype frequency distribution of SOCS-3 gene variation sites

The results of rs12953258, rs4969168 and rs9914220 loci detection coincided with Hardy-Weinberg equilibrium (P>0.05). There were significant differences in rs12953258 locus genotype frequency distribution between lipid metabolic disturbance group and healthy group (P<0.001) in the crowd. AA genotype frequency in lipid metabolic disturbance group was 3.30%, which was larger than that in healthy group (1.50%). There were no significant differences in genotype frequency of rs4969168 and rs9914220 loci between the two groups (P>0.05). Among females, there were significant differences in genotype frequency distribution of rs12953258 locus between lipid metabolic disturbance group and healthy group (P=0.032). AA genotype frequency in lipid metabolic disturbance group was 3.49%, which was larger than that in healthy group (1.28%). Among males, there were no significant differences in genotype frequency distribution of 3 variation loci in SOCS-3 gene between lipid metabolic disturbance group and healthy group (P>0.05, **Table 2**).

3 genotypes frequency distribution of rs12953258 locus in female SOCS-3 gene

Among females, there were significant differences in the genotype frequency distribution of rs12953258 locus between HDL-C abnormal group and normal group (P=0.029). However, there were no significant differences in that between TC abnormal and normal group, LDL-C abnormal and normal group and TC abnormal and normal group (P>0.05, **Table 3**).

Logistic regression analysis results

Set normal or abnormal of blood TG, HDL-C and TC as dependent variables and variation loci (rs12953258, rs4969168, rs9914220), age, BMI, abdomen circumference and so on as independent variable, utilizing multiple factor Logistic regression analysis, the results showed

that AA genotype of rs12953258 may be a risk factor of lipid metabolic disturbance [CC/AA, OR=3.271, 95% CI (1.092, 9.797), P= 0.034], low HDL-C-emia [CC/AA, OR=3.537, 95% CI (1.167, 10.723), P=0.026] and high TG-emia [CC/AA, OR=4.105, 95% CI (1.041, 16.197), P=0.038] for the Uygur nationality women in Xinjiang. BMI may be a risk factor of lipid metabolic disorder, low HDL-C-emia and high LDL-C level. Abdominal circumference may be a risk factor of high TC level. The Uygur nationality women with AA genotype and abnormal BMI were more sensitive to lipid metabolic disturbance [OR=9.032, 95% CI (1.132, 72.06), P=0.038]. The association between rs4969168 and rs9914220 and blood fat and its constituents had not been found by now (**Table 4**).

Discussion

SOCS-3 gene (located in human chromosome 17q25.3), a main member of SOCS family, participate the negative feedback regulation of JAK-STAT pathway [7, 8]. SOCS-3 induce leptin resistance by interacting with leptin receptor [18] with the help of JAK-STAT pathway. Leptin resistance will lead to the decrease of lipoprotein esterase activity and disintegration level of TG and finally cause high TG level, high LDL-C level [19] and low HDL-C level [20]. So, SOCS-3 gene may be associated with lipid metabolic disorder. The results in this study show that BMI and abdomen circumference in lipid metabolic disturbance group are higher than that in healthy group, which coincide with the findings of Minwei Wang [21] and Caprio [22], suggesting that the redundant internal organs fat in abdomen type obese patients may suffer stronger lipolysis and the product TC inter blood through portal vein and cause TC increase and HDL-C decrease. In addition, the results also show that lipid metabolic disturbance of the Uygur nationality women in Xinjiang are associated with rs12953258 locus in SOCS-3 gene. AA genotype may be a susceptible genotype for lipid metabolic disorder. The rs12953258 locus in SOCS-3 gene is associated with high TG-emia and low HDL-C-emia in the Uygur nationality women. For reasons as follows: 1. Related epidemiological surveys have showed that the Uygur nationality (especially women) in Xinjiang are metabolic syndrome prevalent nation. The nationality keep particular food habits (mostly depend on meat and milk). Women in this nationality mostly live at home without work after marriage and with less amount of exercise so that they are easy to become abdomen-type obese patients [5]. Most obese patients are suffered with high leptin emia. The leptin can active JAK pathway, cause STAT protein phosphorylation and SOCS-3 expression up-regulation. SOCS-3 increase can inhibit leptin receptor signal transduction, cause leptin resistance [23] and further lead to TG level increase and HDL-C level decrease in the serum of leptin resistance patients. 2. Estrogen can inhibit the liver esterase activity, which is beneficial to apolipoprotein A1 synthesis [24] and further decrease lipoprotein [24] and LDL-C level and increase HDL-C level [25] in serum. Women in this study are prone to lipid metabolic disturbance because they are in perimenopausal period with mean age of 50.0±11.0 years old and with less estrogen in vivo. The study has not found the association between lipid metabolic disturbance and SOCS-3 gene variation. Possible reasons are as follows: 1. 3 selected variation sites can not represent other sites to make a conclusion of that they have no correlation with lipid metabolic disturbance in the Uygur nationality males. Some low frequency variation sites need further research and analyze. 2. SOCS-3 gene may not participate the generation and development progress of males' lipid metabolic disturbance or SOCS-3 gene variation affect less on the mechanism of this disease. 3. Hereditary character, social environment, life and diet are different in different races, so further research in other races are necessary. The study also find that the probability of suffering lipid metabolic disturbance in Uygur nationality females with AA genotype in rs12953258 locus e are 3.271 fold more than that with CC genotype, but that with AA genotype and abnormal BMI are 9.032 fold more than that with CC genotype and normal BMI, suggesting that lipid metabolic disturbance can be affected by both genetic factors and environmental factors, and their synergetic effects can significantly increase the disease risk.

Above all, the study results show that the lipid metabolic level is associated with SOCS-3 gene variation in the Uygur nationality women in Xinjiang. Lipid metabolic disturbance prevalence of the Uygur nationality women in Xinjiang

with AA genotype in rs12953258 locus and abnormal BMI are far higher than that in other groups. In the future, proceeding primary prevention from rs12953258 variation site of SOCS-3 gene (especially for women with AA genotype in rs12953258 variation site and abnormal BMI) will probably decrease the prevalence of lipid metabolic disturbance among the Uygur nationality women.

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Disclosure of conflict of interest

None.

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