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Genetic variants of the 11 beta-hydroxysteroid dehydrogenase type 1 gene influence metabolic syndrome

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Original Article

Genetic variants of the 11 beta-hydroxysteroid dehydrogenase type 1 gene influence metabolic syndrome

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Abstract

Background: Metabolic syndrome (metS) is the prominent public issue around the globe which contributes to several diseases, including type 2 diabetes, obesity, and insulin resistance (IR). At a recent time, IR due to cortisol excess has been implicated as part of metS etiology. The 11 beta- hydroxysteroid dehydrogenase type 1 (HSD11B1) gene that encodes 11 beta- hydroxysteroid dehydrogenase (11β-HSD1) enzyme has a pivotal role in maintaining serum cortisol level against IR. The aim of this study was to detect the frequency of HSD11B1 gene polymorphisms and their association with metS among the South Indian cohort. **Methods:** Our study included 613 South Indians enrolled from the Kasturba Medical College hospital, Mangalore. Their biochemical and anthropometric data were recorded. The genotyping of NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A polymorphisms were carried out using amplification refractory mutation system- polymerase chain reaction (ARMS-PCR). **Results:** NC_000001.10:g.209880259T>G polymorphism of the HSD11B1 gene was associated with metS. We observed significantly higher postprandial blood sugar (p=0.029) and lower high density lipoprotein (HDL) cholesterol (p=0.009) levels in control subjects with TG genotype compared to those with TT genotype of the NC_000001.10:g.209880259T>G. The control subjects with AA genotype of the NC_000001.10:g.209875254G>A had significantly lower diastolic blood pressure (DBP) compared to those with wild GG genotype (p=0.001). The control subjects with the combination of TG genotype of the NC_000001.10:g.209880259T>G and GG genotype of the NC_000001.10:g.209875254G>A had significantly higher blood pressure (p<0.001), blood sugar (p<0.05) and triglyceride levels (p=0.007), whereas those with the combination of TG genotype of the NC_000001.10:g.209880259T>G and GA genotype of the NC_000001.10:g.209875254G>A had significantly higher total cholesterol (p=0.008) and low density lipoprotein (LDL) cholesterol levels (p=0.023). **Conclusions:** In conclusion, NC_000001.10:g.209880259T>G polymorphism of the HSD11B1 gene is associated with metS risk, including high blood sugar, blood pressure, and lipid levels. NC_000001.10:g.209875254G>A polymorphism is not associated with metS risk in South Indian cohort. The A allele of NC_000001.10:g.209875254G>A polymorphism appears to be protective against hypertension.

Key words: Metabolic syndrome; single nucleotide polymorphism; 11 beta- hydroxysteroid dehydrogenase type 1

Introduction

Metabolic syndrome (metS) is a prediabetic syndrome, with the prevalence of 35% in the world (www.idf.org). The International Diabetes Federation (IDF) defines metS as a condition where, abdominal obesity is represented by higher waist circumferences (> 80 cm in women and > 90 cm in men), in addition to any two of these abnormalities: Triglycerides > 150 mg/dl, high density lipoprotein (HDL) < 40 mg/dl in males and < 50 mg/dl in

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females, blood pressure > 130/85 mmHg and fasting blood sugar (FBS) > 100mg/dl. [1]

Overexpression of 11beta- hydroxysteroid dehydrogenase type 1 (HSD11B1) and cortisol excess in metabolically active tissues plays a major role in metS pathophysiology.[2] Patients with metS exhibit insulin resistance (IR), higher levels of blood sugar and higher lipids due to excess of cortisol generation by 11β-HSD1.[3] Overexpression of HSD11B1 in mice exhibited many features of metS[4]. Masuzaki, H et al., have provided evidence that HSD11B1 overexpression led to obesity that was further exaggerated by a high -fat diet. These mice also exhibited pronounced insulin- resistant diabetes and, hyperlipidemia selectively in adipose tissue to an extent similar to adipose tissue in obese humans.[5] Moreover, pharmacological inhibition of 11β-HSD1 in diabetic mice reportedly lowered blood glucose and improved insulin sensitivity.[6,7]

The 11beta- hydroxysteroid dehydrogenase type 1 (HSD11B1) gene plays a crucial role in regulating the 11β-HSD1 activity against cortisol excess and IR.[3] Polymorphisms in this gene can develop diabetes and prediabetic conditions.[8-10] The two single nucleotide polymorphisms (SNPs); NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A of HSD11B1 gene were selected based on minor allele frequency (MAF>0.01) and literature studies. While the NC_000001.10:g.209875254G>A SNP in HSD11B1 modifies transcription factor binding site and, the NC_000001.10:g.209880259T>G in the third intron acts as intronic enhancers[8]. Genetic association studies have reported that these polymorphisms are involved in different IR-related conditions, such as type 2 diabetes (T2D), metS, and polycystic ovary syndrome.[8-12] Despite the prominent role of cortisol excess in metabolic abnormalities, the associations of HSD11B1 gene polymorphisms with metS have not yet been intensively studied.

The current study investigated the association between HSD11B1 polymorphisms and metS in South Indian cohort.

Materials and Methods

Ethics Statement

The study was approved by the Manipal University Ethics Committee. All the patients and control subjects signed the written informed consent before the commencement of the study.

Subjects, anthropometric and biochemical analysis

This hospital- based case -controlled genetic association study included 613 (204 metS and 409 control) subjects. MetS subjects were defined according to the IDF diagnostic criteria[13] by the general medicine physician in the inpatient treatment unit at Kasturba Medical College (KMC) hospital, Mangalore. The control subjects were recruited from those who attended the KMC hospital for a routine health check-up, without the family history of diabetes, and who had a FBS ≤ 100 mg/dl. Any patients with diabetes, malignancy, inflammation, and endocrine disorders were excluded from this study.

Anthropometric (weight, waist circumference (WC) and blood pressure (BP)) data were collected. The WC was measured at the midpoint between the distal rib and the iliac crest.[14] Body mass index (BMI) was calculated from weight and height values.[15] Systolic and diastolic blood pressure (SBP/DBP) were measured using sphygmomanometer. All biochemical data (FBS, postprandial blood sugar (PPBS), lipids such as total cholesterol (TC), HDL, low- density lipoprotein (LDL), and triglycerides (TGs) were measured following manufacturer's manual using 917 Hitachi auto-analyser.[16,17]

Genomic DNA extraction and SNP genotyping

Genomic DNA was extracted from the peripheral venous blood of each participant using a

commercially available genomic DNA purification kit (Bioserve Biotechnologies, Hyderabad, India) according to the instructions of the manufacturer. We selected two SNPs in the HSD11B1 gene (NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A) based on previous indications, that were studied with risk factors for T2D with a minor allele frequency > 0.5. Genotyping of SNPs was performed with amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) using two pairs of primers.

The primers used for NC_000001.10:g.209880259T>G were as follows:

Outer forward primer:
5'-TTTCTGCTGTATCACTGCAGGTGGTATC-3'
Outer reverse primer:
5'-CAGCTACAGTCAGGACCACGTAACTGAG-3'
Inner forward primer:
5'-AGAATGGGAAAGGTATCAACCCCAAAT-3'
Inner reverse primer:
5'-CCTGCAAGAGATGGCTATATTAAGAAACCC-3'

The primers used for NC_000001.10:g.209875254G>A were as follows:
Outer forward primer:
5'-CTCCTCACATTTTTGCCATCTCCTATCA-3'
Outer reverse primer:
5'-ACAGTGAACAGTTCACTCCACTCCTTGC-3'
Inner forward primer:
5'-GTGCTTGATTCCATTTATTCTGGGGG-3'
Inner reverse primer:
5'-CCAGGAATTCTCTCTGATTTGATCATGCT-3'

The ARMS-PCR was conducted in a final volume of 25µl, containing 50 ng of template DNA, 4 mM each dNTPs, 10 pm/µl of forward and reverse outer primers, 10 pm/µl of forward and reverse inner primers, and 1 U of Taq DNA polymerase in the buffer supplied by the manufacturer (New England Biolabs, USA). After initial denaturation at 95°C for 5 min, 35 cycles were run at 95°C, 60°C (NC_000001.10:g.209880259T>G) or 58°C (NC_000001.10:g.209875254G>A) and 72°C for 1 min each, followed by one cycle of final extension at 72°C for 10 min using PCR (Master cycler thermal cycler). PCR products were then separated by agarose gel electrophoresis at 100 V for 30 minutes and the bands were visualized under UV gel documentation system (Uvitec, UK). Positive and negative controls were used with each PCR run in order to confirm the precision of the genotyping outcome.

Statistical Analysis

Clinical parameters were presented as mean ± standard deviation. All the statistical tests were performed using SPSS v. 20 (IBM SPSS Inc., Chicago, IL, USA).[18] Statistical power was calculated using a web browser program, Genetic Power Estimator (http://osse.bii.a-star.edu.sg/). The Hardy-Weinberg equilibrium (HWE) was determined using Pearson's λ2 test for each SNPs. The odds ratio (OR) and 95% CI were calculated to find the genetic association with metS. Two sample t-test was used for the comparison of clinical parameters between genotypes of two SNPs. One-way analysis of variance (ANOVA) was used for the comparison of clinical parameters between the diplotypes of two SNPs. The p values < 0.05 were considered statistically significant.

Results

In the South Indian cohort, 58.8% were women and 41.2% were men, and their average age was 55.92 ± 12.03 years. The most common metS component was higher blood sugar (52.59%), followed by lower HDL levels (52.33%), and hypertension was the last common metS component (17.37%) (Table 1). The BMI, WC, BP, FBS, and TGs were significantly higher in metS cases than controls (p<0.001). HDL was significantly lower in cases than control (p<0.001). There was no significant difference in TC and LDL levels between cases and controls (Table 2).

Table 1: Characteristics of the South Indian cohort

Women	58.8%
Men	41.2%
Age	55.9212.03
Waist circumference	50.24%
BP (>130/85 mmHg)	17.37%
TGs (>150 mg/dl)	30.88%
Glucose (>100 mg/dl)	52.59%
HDL	52.33%

Age = mean ± standard deviation, Waist circumference (> 90 cm men or > 80 cm women), HDL (< 40 men or < 50 mg/dl women).

Table 2: Clinical characteristics of the metS and control subjects.

Phenotype	metS	Control	P value
Age (Years)	55.9212.03	13.17	0.245
BMI (Kg/m^2)	27.784.66	24.343.03	<0.001**
WC (cm)	95.5411.06	87.429.84	<0.001**
SBP (mmHg)	141.9914.72	124.9711.03	<0.001**
DBP (mmHg)	85.1610.59	78.625.98	<0.001**
FBS (mg/dl)	124.8145.10	97.619.65	<0.001**
PPBS (mg/dl)	175.4285.61	102.6525.11	<0.001**
TC (mg/dl)	200.3749.30	193.7139.73	0.184
HDL (mg/dl)	41.319.49	51.9214.04	<0.001**
LDL (mg/dl)	130.2740.67	126.7636.18	0.2
TGs (mg/dl)	167.9972.34	109.4748.54	<0.001**

Data are shown as mean standard deviation. **Significant P value <0.001. BMI, body mass index; WC, waist circumference;

SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; PPBS, Postprandial blood sugar; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TGs,triglycerides; metS, metabolic syndrome.

Genotyping of DNA samples in duplicate by ARMS-PCR showed 100% concordance. For TT genotype of NC_000001.10:g.209880259T>G, two bands of 383 bp (amplicon size for two outer primers) and 185 bp (amplicon size for T allele-specific inner forward primer) were generated. For TG genotype of NC_000001.10:g.209880259T>G, three bands of 383 bp, 185 bp, and 255 bp (amplicon size for G allele-specific inner reverse primer) were generated. Similarly, for GG genotype of NC_000001.10:g.209875254G>A, the two bands of 300 bp (amplicon size for two outer primers) and 199 bp (amplicon size for G allele-specific inner forward primer) were generated. For GA genotype of NC_000001.10:g.209875254G>A three bands of 300 bp, 199 bp, and 160 bp (amplicon size for A allele specific inner reverse primer) were generated.

The genotype distributions of NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A polymorphisms of the HSD11B1 gene were in HWE among the cases and the controls (p>0.05). The South Indian cohort included 613 subjects with 204 metS (33%) and 409 controls (67%). The frequency of G allele and TG genotype of NC_000001.10:g.209880259T>G SNP were significantly higher in cases than in controls. However, the A allele frequency and GA genotype frequency of NC_000001.10:g.209875254G>A polymorphism did not show significant differences between cases and controls (Tables 3). We observed positive association between metS and NC_000001.10:g.209880259T>G polymorphism (Allelic OR=2.13, CI=1.56-2.91), p<0.0001). However, no association was observed between NC_000001.10:g.209875254G>A polymorphism and metS (Allelic OR=1.26, CI=0.85-1.85, p=0.23) in South Indian cohort (Table 3).

We observed significantly higher PPBS and lower HDL levels in controls with TG genotype of NC_000001.10:g.209880259T>G compared to those with wild TT genotype (Table 4). NC_000001.10:g.209875254G>A polymorphism was not associated with metS. However, this SNP appears to have the negative association with BP. The controls with polymorphic GA genotype of NC_000001.10:g.209875254G>A had significantly lower DBP compared to those with wild GG genotype (p=0.001) (Table 4). Since cases were on medications, assessment of the association of HSD11B1 SNPs with clinical parameters was not performed.

Diplotype analyses show that, the control subjects with the combination of TG genotype of NC_000001.10:g.209880259T>G and GG genotype of NC_000001.10:g.209875254G>A has significantly higher BP, blood sugar, and TGs. The control subjects with the combination of TG genotype of NC_000001.10:g.209880259T>G and GA genotype of NC_000001.10:g.209875254G>A had significantly higher TC and LDL levels (Table 5).

Discussion

The HSD11B1 gene encodes the cortisone reductase 11β-HSD1 enzyme, which has a pivotal role in glucocorticoid metabolism.[2, 18] Variations in the transcription enhancer site of the third intron

Table 3: Genotype and allele frequencies of NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A polymorphisms in the South Indians

	Allele frequency				Genotype frequency			
	(HSD11B1) NC_000001.10:g.209880259T>G		(HSD11B1) NC_000001.10:g.209875254G>A		(HSD11B1) NC_000001.10:g.209880259T>G		(HSD11B1) NC_000001.10:g.209875254G>A	
	T	G	G	A	TT	TG	GG	GA
metS (n=204)	0.77	0.23	0.89	0.11	0.54	0.46	0.77	0.23
Control(n=409)	0.88	0.12	0.91	0.09	0.75	0.25	0.81	0.19
OR (CI)	2.13 (1.56-2.91)		1.26 (0.85-1.85)		2.62 (1.84-3.74)		1.29 (0.86-1.95)	
P value	<0.0001		0.23		<0.0001		0.21	

OR, odds ratio; CI, confidence interval; metS, metabolic syndrome.

Table 4: Association of HSD11B1 polymorphisms with clinical components in control cohort

Phenotype	(HSD11B1) NC_000001.10:g.209880259T>G			(HSD11B1) NC_000001.10:g.209875254G>A		
	TT (n=307)	TG (n=101)	p	GG (n=332)	AG (n=76)	p
BMI (kg/m²)	24.21 ± 3.28	24.73 ± 3.35	0.427	24.40 ± 3.43	24.07 ± 2.67	0.07
WC (cm)	86.87 ± 9.69	89.11 ± 10.16	0.224	87.71 ± 9.86	86.17 ± 9.73	0.287
SBP (mmHg)	123.95 ± 10.36	128.15 ± 12.42	0.148	126.20 ± 11.26	119.34 ± 7.76	0.417
DBP (mmHg)	78.43 ± 6.5	79.21 ± 3.89	0.147	79.44 ± 5.81	74.89 ± 5.34	0.001*
FBS (mg/dl)	97.25 ± 10.33	98.67 ± 7.26	0.195	97.99 ± 9.77	96.19 ± 9.14	0.345
PPBS (mg/dl)	99.34 ± 22.01	111.53 ± 30.58	0.029*	105.64 ± 25.51	91.21 ± 20.06	0.287
TC (mg/dl)	189.37 ± 36.58	206.75 ± 45.94	0.827	195.77 ± 41.79	186.42 ± 30.71	0.113
HDL (mg/dl)	53.02 ± 15.38	48.56 ± 7.96	0.009*	52.64 ± 14.93	49.38 ± 10.06	0.092
LDL (mg/dl)	122.75 ± 34.38	138.37 ± 39.01	0.357	127.93 ± 37.8	122.36 ± 29.3	0.384
TGs (mg/dl)	103.47 ± 45.43	127.22 ± 53.38	0.773	110.18 ± 54.00	106.98 ± 20.44	0.545

Data expressed as mean ± standard deviation. *Significant p value <0.05. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; PPBS, Postprandial blood sugar; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TGs, triglycerides.

Table 5: Association of the combination of NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A polymorphisms with clinical components in control cohort

Phenotype	(HSD11B1) NC_000001.10:g.209880259T>G, (HSD11B1) NC_000001.10:g.209875254G>A				p
	TG, GA (n=15)	TG, GG (n=86)	TT, GA (n=61)	TT, GG (n=246)	
BMI (kg/m²)	23.87 ± 2.82	24.88 ± 3.41	24.13 ± 2.66	24.23 ± 3.41	0.369
WC (cm)	86.13 ± 9.78	89.64 ± 10.19	86.2 ± 9.81	87.04 ± 9.68	0.115
SBP (mmHg)	124.75 ± 6.01	128.63 ± 13.02	118.28 ± 7.66	125.36 ± 10.47	<0.001**
DBP (mmHg)	78.58 ± 2.77	79.5 ± 4.03	74.16 ± 5.44	79.48 ± 6.32	<0.001**
FBS (mg/dl)	92.07 ± 8.15	100.18 ± 6.17	97.4 ± 9.13	97.21 ± 10.67	0.025*
PPBS (mg/dl)	90.14 ± 24.76	116.35 ± 30.00	91.55 ± 19.00	101.49 ± 22.41	0.001*
TC (mg/dl)	207.4 ± 21.41	206.47 ± 53.21	175.93 ± 29.47	192.64 ± 37.49	0.008*
HDL (mg/dl)	48.47 ± 5.18	48.63 ± 8.96	49.83 ± 11.79	53.79 ± 16.08	0.128
LDL (mg/dl)	139 ± 22.72	138.11 ± 44.36	113.15 ± 28.75	124.92 ± 35.25	0.023*
TGs (mg/dl)	109.6 ± 21.86	134.56 ± 60.76	105.67 ± 19.94	102.93 ± 49.82	0.007*

Data expressed as mean ± standard deviation. **Significant p value <0.001, *Significant p value <0.05. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; PPBS, Postprandial blood sugar; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TGs, triglycerides.

(NC_000001.10:g.209880259T>G) and promoter region (NC_000001.10:g.209875254G>A) of HSD11B1 may modulate the HSD11B1 transcription and expression levels[9].

Though previous studies assessed the association of HSD11B1 polymorphisms with several insulin resistance related conditions, including abdominal obesity, dyslipidaemia, hypertension, polycystic ovary syndrome, and T2D[2,11,12], none of the studies gave sufficient evidence. All previous studies gave conflicting association of HSD11B1 gene polymorphisms with metS. MetS is a major public health problem. Recently, the role of glucocorticoid excess in the pathophysiology of this entity has been widely reported. Our present investigation of the involvement of HSD11B1 (NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A) polymorphisms in the metS susceptibility within a South Indian cohort attending tertiary care hospital revealed that, the NC_000001.10:g.209880259T>G polymorphism was associated with metS. In accordance with our finding, a previous study reported that, the combination of NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A polymorphisms showed positive association with metS in South European women.[9] The frequency

of HSD11B1 NC_000001.10:g.209880259T>G genotype observed in our study is similar to the findings of Asian study which reported a 33.7% prevalence of NC_000001.10:g.209880259T>G genotype in Koreans with metS[10]. However, there was no significant difference in the frequency of TG genotype between cases and controls (p=0.197) in Koreans. As a result, there was no association of NC_000001.10:g.209880259T>G polymorphism with metS in their study. Moreover, their cases and controls were not age-matched. Unlike our study, the number of controls used by them was significantly lower than cases. Similarly, there was no association of NC_000001.10:g.209880259T>G and NC_000001.10:g.209875254G>A gene polymorphisms with metS in Bosnians, Euro Brazilians, and American Indians[19-21]. Reason for this discrepancy may be the use of different ethnic groups, inadequate sample size and lack of matching control samples.

The G allele carriers of NC_000001.10:g.209880259T>G had significantly higher PPBS and lower HDL levels. Similarly, previous study on South European women reported that the G allele carriers of NC_000001.10:g.209880259T>G had significantly higher blood sugar (p=0.006) and lower HDL (p=0.011) than T allele carriers[9]. The effect of HSD11B1 on blood sugar and lipid seems to be mediated by excess cortisol production due to HSD11B1 overexpression. In concordance with our study, an Asian study showed significantly higher values DBP (p=0.014) in A allele carriers of NC_000001.10:g.209875254G>A than those with wild G allele among Koreans[10]. Similarly, A allele carriers of NC_000001.10:g.209875254G>A had significantly higher values of DBP in American Indians[21] and South European women[9] compared to those with wild G allele. Since hypertension is a multifactorial condition, the influence of HSD11B1 polymorphism on BP may not be straightforward and may be modified by environmental as well as other genetic factors.

Our study reveals that, the NC_000001.10:g.209875254G>A polymorphism may be protective against hypertension due to the significantly lower BP in the carriers of this SNP compared to wild genotype. However, this SNP does not seem to be protective against high cholesterol values.

The sample size used in our study to assess the association of HSD11B1 polymorphism with metS is larger than all the previous studies. The study used two SNPs after assessing rare allele frequencies (>5%) and was based on the studies of literature. However, other SNPs may also influence metS in the study cohort. So further studies must assess the association of other SNPs with metS and associated components. Clinical analysis of the cases was not possible due to the use of medications by the majority of cases. Future studies must use medication naive subjects.

Supporting the study results, selective drug designing to inhibit the HSD11B1 over expression may help to reverse the abnormal clinical profile of metS subjects with HSD11B1 NC_000001.10:g.209880259T>G gene polymorphism.

Conclusions

The present study provides evidence that, NC_000001.10:g.209880259T>G polymorphism of the HSD11B1 gene is associated with high risk of metS, hyperglycaemia, blood pressure and low levels of HDL. NC_000001.10:g.209875254G>A polymorphism of HSD11B1 seems to pose a lower risk of hyperglycaemia and hypertension. Further studies with larger sample size are necessary to confirm these data.

Conflicts of interest

Authors declare no conflict of interest.

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