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Genetic association of liver X receptor beta rs2695121 polymorphism with obesity-related traits in a northeastern Iranian population

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Abstract

Background: Liver X receptor Beta (LXRβ), located in an obesity susceptible region, has been shown to be involved in the metabolism of lipid and carbohydrates. Previous human genetic studies have suggested genetic variability of LXRβ could be associated with human obesity. Therefore, we hypothesized that LXRβ gene rs2695121 polymorphism may be associated with the risk of obesity in a northeastern Iranian population.

Methods: A TaqMan allelic discrimination assay was used to genotype LXRβ rs2695121 polymorphism in this cross-sectional study of 168 obese, 209 overweight and 76 normal-weight subjects recruited from Mashhad city in Iran. Logistic regression analyses were used to analyze alleles and genotypes distribution. Anthropometrics and clinical variables among different genotype carriers were compared by univariate analyses. All statistical analysis was performed using SPSS v.16.0.

Results: Allelic and genotypic associations with obesity were not significant for the rs2695121 variant even after adjustment for age and gender (OR=1.17, 95% CI=0.46-2.91), p=0.586). Moreover, haplotype analysis using data from the other variant (rs17373080) of LXRβ revealed no significant association (p=0.88). However, among the clinical and metabolic parameters tested, systolic and diastolic blood pressures were found nominally associated with the genotype CT (p=0.031 and p=0.017 respectively).

Conclusion: This study failed to demonstrate any association between the rs2695121 variant of LXRβ and obesity neither alone nor when considered with rs17373080. However, its association with blood pressure may influence one's susceptibility to obesity, supporting further studies in a larger population.

Keywords: Liver X receptor-β; Obesity; Polymorphism; rs2695121

1. Introduction

Liver X receptor beta (LXRβ) is a member of the nuclear hormone receptor superfamily which modulates transcription of many target genes involved in cholesterol, lipid and carbohydrate metabolism (1-3). This ligand-dependent transcription factor is encoded by the nuclear receptor 1 type H2 (NR1H2) gene located on chromosome 19 and is ubiquitously expressed at moderate to high levels in almost all tissues (4). The transcriptional activity of LXRβ is depended on the exposure of oxidized cholesterol and subsequent heterodimerization with the retinoid X receptor (RXR). Activated LXR–RXR heterodimers promote adipogenesis and lipid accumulation in adipocytes by transcriptional regulation of sterol regulatory binding transcription factor 1 (SREBP1C), the master regulator of TG synthesis, and several target genes including FAS and stearoyl-CoA desaturase 1 in the SREBP1C pathway (5-8).

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The lipogenic actions of LXRs have presented them as potential pharmaceutical targets for the treatment of metabolic disorders such as diabetes, metabolic syndrome, obesity, and atherosclerosis (9). Targeted disruption (knockout) of the LXRβ gene in mice have revealed a strong association with defects in the cardiovascular system, homeostasis and metabolism and the nervous system (10). Based on having an important role in regulating the lipid and carbohydrate metabolism, genetic variations in LXRβ may contribute in mediating susceptibility to obesity and modulating serum lipids and glucose levels. One of the common variations within the NR1H2 gene is rs2695121, which is identified by C to T substitution in intron 2. This SNP was associated with several metabolic-related disorders including high blood pressure, metabolic syndrome, type 2 diabetes and also preeclampsia (11-13). A 2006 study by Dahlman reported evidence of the association between LXRβ rs2695121 polymorphism and obesity phenotypes (13). Whereas, other subsequent reports have been inconsistent (14). However, no reported data exists for the association of this SNP with the risk of obesity and related metabolic traits in an Iranian population. Based on the proposed involvement of LXRβ in the regulation of lipid and carbohydrate homeostasis, the present cross-sectional study was designed to assess the potential association of LXRβ rs2695121 variant with obesity and related metabolic traits in a northeastern Iranian population.

2. Material and Methods

2.1. Subjects

In this cross-sectional study, a total of 453 genetically unrelated adult subjects of both genders, ranging from 18 to 60 years of age, were enrolled from our previous study in which the relationship of two LXRα SNPs with obesity was investigated on individuals who were randomly selected from participants of a cohort study of metabolic syndrome and cardiovascular disease risk factors performed in Mashhad as a second largest city in Iran (15). The World Health Organization-body mass index (WHO-BMI) was calculated as a weight to height ratio (kg/m^2), and a BMI of 18.5-24.99, 25-29.99 and $\geq$30 kg/m^2 were taken as cut-off values defining normal weight, overweight and obesity, respectively. With this in mind, all subjects were classified into three groups: 209 subjects as overweight, 168 subjects as obese, and 76 healthy individuals as normal weight. Before participating voluntarily in research work, informed written consent was obtained from all participants. After that, a complete physical assessment and anthropometric measurements were performed by trained health workers. Blood samples were drowned after a fasting period, and data on age, sex, geographical birthplace, ethnicity, past medical and family history, and dietary habits were collected. All subjects with a history of stroke, MI (Myocardial infarction), endocrinological abnormalities, diabetes mellitus, alcohol consumption, heart, liver and/or renal disease, or those who were under high blood pressure medication and lipid or glucose lowering treatment were excluded from the study. This research project was approved by the Ethical Committee of the Shahid Beheshti University of Medical Sciences (SBUMS: Research Project No. 648).

2.2. Anthropometric and Biochemical measurements

Anthropometric and clinical measurements were measured according to international standard procedures as described in details in our previous studies (11, 15, 16). In brief, all parameters including height, weight, waist circumference (WC), hip circumference (HC), waist/hip ratio, systolic blood pressure (SBP) and diastolic blood pressure (DBP), total cholesterol (TC), high- density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting blood glucose (FBG) and serum C-reactive protein (CRP) were measured.

2.3. Genotyping

Genomic DNA was isolated from the peripheral blood sample with a FlexiGene DNA Kit (Qiagen) in accordance with the manufacturer's instructions. Genotyping of single nucleotide polymorphisms (SNPs) was performed by allelic discrimination assays using TaqMan probes (C_16059177_10; Applied Biosystems, USA). Allelic discrimination was performed on Applied Biosystems 7500 real-time PCR System. The following conditions were used for the polymerase chain reaction: initial denaturation step at 95°C for 10 minutes, and 40 cycles of 92°C for 15 seconds and 60°C for 1 minute. Approximately 10% of the samples were re-genotyped to ensure reproducibility and accuracy.

2.4. Statistical analysis

All statistical analysis was performed using SPSS v.16.0 (SPSS Inc., Chicago, Illinois., USA). The descriptive statistics were determined for all variables and are presented as mean (SD) for the normally distributed variables (or as the median [IQR] for non-normal variables). The chi-square or Fisher's exact tests were applied to evaluate differences in allele and genotype distribution among the examined groups. It was also used to assess any deviation

from the Hardy-Weinberg equilibrium (HWE) for the study SNP. Independent-samples t-test was used to compare the means of demographic and clinical variables between independent groups. Analyses of variance (ANOVA) followed by the Bonferroni post hoc test, was performed to compare anthropometric traits for differences between genotype groups. Using data from our previous report regarding the other common variant (rs17373080) of LXRβ gene (17), haplotype frequencies for two sites and any potential relationship with excess weight were estimated using the SNPStats program (18). Logistic regression analyses were used to calculate the odds ratios (ORs) with 95% confidence interval (CI) of each related parameter, both in crude or adjusted for age and gender. All the analyses were two-sided and statistical significance was set at p-value of < 0.05.

3. Results

3.1. Characteristics of the Populations

The baseline characteristics of the total genotyped samples, stratified by BMI status, are presented in Table 1. In total, 168 obese, 209 overweight and 76 normal-weight subjects were successfully genotyped and analyzed. As expected, all people in normal BMI group exhibited a significantly lower level of WC, HC and waist/hip ratio than the two other groups ($p<0.0001$). A very strong positive correlation was found between BMI and WC and HC (Rho=0.820; $p<0.0001$ and Rho=0.771; $p<0.0001$ respectively). There were no significant differences in the levels of mean age, serum TC and LDL-C, between the overweight/obese and normal subjects ($p>0.05$ for all).

Table 1. Demographic and clinical characteristics of the study population

Characteristics	Normal (n=76)	Overweight (n=209)	Obese (n=168)	p-value
Gender (M/F)	25/51	87/122	43/125	0.005
Age (years)	48.30±8.00	47.76±7.07	48.23±7.08	0.767
Weight (kg)	59.42±7.64	72.33±9.08	82.54±10.02	0.001
Height (cm)	160.37±9.53	161.72±8.95	158.58±8.38	0.003
BMI (kg/m^2)	23.04±1.57	27.56±1.37	32.78±2.65	0.001
Waist circumference (cm)	83.45±9.66	92.40±8.73	102.65±8.71	0.001
Hip circumference (cm)	95.16±5.02	101.48±4.98	110.67±7.84	0.001
W/H ratio	0.88±0.08	0.91±0.07	0.93±0.07	0.001
Glucose (mmol/l)	4.49±0.95	4.65±0.93	4.89±1.14	0.009
HDL-C (mmol/l)	1.12±0.28	1.02±0.21	1.03±0.21	0.002
LDL-C (mmol/l)	3.12±1.03	3.17±0.82	3.16±0.86	0.864
TC (mmol/l)	4.74±1.08	4.96±1.00	5.05±0.97	0.085
TG (mmol/l)	1.53±1.11	1.83±1.11	1.90±1.08	0.048
SBP (mmHg)	116.22±14.41	121.40±17.06	124.01±19.30	0.006
DBP (mmHg)	74.66±10.90	79.92±11.01	81.49±11.13	0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; W/H, waist/hip; TC, total cholesterol; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein cholesterol; TG, triglycerides. Values were expressed as mean ±SD.

3.2. Genotypic and allelic frequencies

The allelic and genotypic frequencies of the investigated SNP in the entire study group are summarized in Table 2. The distribution of genotypes was in accordance with HWE ($p>0.05$). As shown in Table 2, allelic and genotypic associations of LXRβ rs2695121 variant were not significant with excess weight. These results maintained statistical insignificancy even after adjustment for gender and age. Additionally, further gender-based association analysis did not modify the results. We also examined association of different genotypes of LXRβ rs2695121 with anthropometric and obesity-related metabolic and found no statistically significant differences (Table 3). However, SBP and DBP were significantly higher in subjects with the TC and TT genotypes ($p=0.031$, $p=0.017$ respectively). Using the data combinations of two SNPs in LXRβ gene (rs2695121-rs17373080), we then explored the haplotype frequencies and D' and r^2 values for degree of linkage disequilibrium (LD) (Table 4). According to the results of haplotype-based analysis associating the two SNPs, three haplotypes including CG, TC, and CC were found to be more common. The overall haplotype frequencies, compared with the most common haplotype (CG), were not statistically different among the studied groups. Haploblock analysis revealed these two SNPs were in strong LD ($D'=0.981$, $r^2=0.518$ in the overweight group and $D'=0.972$, $r^2=0.550$ in the obese group respectively).

Table 2. Genotype distributions and Allele frequencies of LXRβ SNP in the control and overweight/obese groups

Variables		Normal	Overweight	Obese	†OR (95% CI)	p	†OR (95% CI)	p
Genotype	rs2695121	76	209	168	Overweight vs. normal		Obese vs. normal	
	CC	36 (47.4)	91 (43.5)	69 (41.1)		-		-
	CT	32 (42.1)	96 (45.9)	81 (48.2)	1.00	0.546	1.00	0.914
	TT	8 (10.5)	22 (10.5)	18 (10.7)	1.19 (0.68-2.07)	0.854	1.32 (0.74-2.35)	0.586
Allele	C allele	104 (68.4)	278 (66.5)	219 (65.2)	1.08 (0.44-2.66)	-	1.17 (0.46-2.91)	-
	T allele	48 (31.5)	140 (33.5)	117 (34.8)	1.00	0.667	1.00	0.483

X^2-test and Logistic regression were used. OR, odds ratio; CI, confidence interval. †Adjusted for Age and Sex.

Table 3. Associations of the LXRβ rs2695121 variant with anthropometric and metabolic parameters

Characteristics	rs2695121			
	CC	CT	TT	p
n (%)	197 (43.1)	211 (46.2)	49 (10.7)	-
Weight (kg)	73.68±12.07	74.08±12.26	74.45±12.26	0.695
Height (cm)	160.8±9.3	159.9±8.7	160.1±7.7	0.873
BMI (kg/m^2)	28.4±3.8	28.9±4.0	29.1±4.6	0.456
WC (cm)	93.7±11.6	95.6±10.7	94.7±11.3	0.184
HC (cm)	103.4±8.2	104.2±8.4	104.4±9.6	0.684
W/H ratio	0.91±0.08	0.92±0.07	0.91±0.07	0.147
Glucose (mmol/l)	4.69±0.95	4.75±1.14	4.53±0.68	0.337
HDL-C (mmol/l)	1.02±0.24	1.05±0.23	1.08±0.22	0.282
LDL-C (mmol/l)	3.12±0.90	3.21±0.85	3.20±0.66	0.732
TC (mmol/l)	4.89±1.03	5.00±1.00	5.02±0.86	0.628
TG (mmol/l)	1.79±1.06	1.79±1.08	1.85±1.31	0.918
SBP (mmHg)	119.7±17.2	123.3±18.0	120.7±17.1	0.031
DBP (mmHg)	78.4±11.3	81.2±10.4	78.2±13.7	0.017

Values are expressed as mean ± Sd. Bold values represent significant p-value. Adjusted for age and gender.

Table 4. Haplotype frequencies associating LXRβ rs2695121-rs17373080 polymorphisms in the study population and linkage disequilibrium statistics.

Gene	Haplotype	Frequency			
		Controls	Overweight	Obese	p-value
LXRβ	CG	0.36	0.37	0.38	0.88
	TC	0.32	0.31	0.34	
	CC	0.33	0.30	0.27	
	TG	0.006	0.00	0.004	
LD	D′	1.00	0.981	0.972	
	r^2	0.502	0.518	0.550	

The degree of linkage disequilibrium (LD) between the two variants is shown as D′ and r^2 for each group.

4. Discussion

To our knowledge, this study constitutes the first report on the possible association of LXRβ gene rs2695121 variant with excess weight and obesity-related metabolic traits in an Iranian population. Our results indicated this SNP was not identified as an independent risk factor for obesity. Further, haplotype analysis with another SNP (rs17373080) of the same gene, revealed no significant evidence of relationship with the risk of overweight/obesity or related phenotypes. In all, our results provide evidence that LXRβ may not be involved in the development of obesity. However, other studies have reported inconsistent data. In particular, in one study conducted by Dahlman and colleagues on Swedish obese women, the two SNPs of the LXRβ gene including LB44732G>A and rs2695121, were found to be nominally associated with obesity-related phenotypes (13). Nevertheless, consistent with them at the rs2695121 locus, our results showed the CT genotype was more common in overweight/obese groups (48%) than in the control group (42%), which implicates an increased risk of susceptibility to excess weight (OR=1.32, 95% CI, 0.74-2.35, p=0.914). In another study by Solaas et al, characterizing the impact of genetic variability of the LXRβ gene on various metabolic phenotypes in three independent samples, two polymorphisms of LXRβ

(rs17373080 and rs2695121) were shown to be associated with insulin and HOMA-IR values in adult subjects in which G allele of rs17373080 has been reported as a risk allele for overweight/obesity (14). However, in line with our results, two above mentioned studies reported no association of rs2695121 or rs17373080 with BMI as a continuous trait in their larger samples. Although our results do not support the possible association of LXRβ gene with increased risk of obesity and related phenotypes, we cannot exclude this possibility for several reasons: first, there is sufficient evidence suggesting that LXRs are critically involved in cholesterol homeostasis, and lipid metabolism (19), and their effect on obesity has also been examined in both human and animal models (20-23). They all indicated a modulatory role for LXRs in many metabolic and inflammatory pathways that are potentially contributing to the development of various metabolic disorder, especially obesity. However, the in vivo contribution of LXR-dependent gene expression in the setting of obesity is still unclear. It is also worth noting that other SNPs located within the same gene without a strong LD with these two polymorphisms (rs17373080, rs2695121) may be associated with the risk of disease development. Second, although rs2695121 genotypes did not show any association with obesity, the CT genotype was associated with SBP and DBP (p=0.031 and p=0.017 respectively) as one of the obesity-related metabolic parameters, indicating the possible role of LXRβ in pathophysiology of obesity. Due to the relatively small sample size, the statistical power of this study may be insufficient to pick up a significant association. It should be noted that, a well-defined sampling strategy with an ethnically homogenous population is one of the main strengths of the present study which avoided possible bias due to individual selection. Finally, if lifestyle factors such as dietary intake and physical activity were taken into account, it might be able to better control the impact of probable confounding factors and compensatory mechanisms, and reveal the subtle effect of LXRβ on excess weight.

5. Conclusions

To our knowledge, this is the first study investigating the role of LXRβ rs269512 polymorphism with excess weight in an Iranian population. In conclusion, our results can not reveal any association between rs2695121 polymorphism of LXRβ gene and obesity/overweight except for blood pressure as an obesity-related phenotype. Our negative results should be interpreted in light of the limitations of the study and given the related small sample size. Since existing data is supporting the role of genetic variability of LXRβ in obesity, further investigations in other larger populations are required to investigate the association of LXRβ gene polymorphisms, to provide more evidence for the biological role of LXRβ in etiology of obesity and other metabolic disorders.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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