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Association between exonic polymorphism (rs629849, Gly1619Arg) of *IGF2R* gene and obesity in Korean population

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The aim of this study is to investigate the relationship between single nucleotide polymorphisms (SNPs) and susceptibility to obesity. A previous study suggested that insulin-like growth factors (IGFs) may affect obesity and that IGFs regulate cellular signals by receptors that include the insulin-like growth factor 1 receptor (IGF1R) and the insulin-like growth factor 2 receptor (IGF2R). In this research, the rs3743262 and rs2229765 SNPs of *IGF1R* gene and rs629849 and rs1805075 SNPs of *IGF2R* gene were genotyped in 120 overweight and obese patients with a BMI ≥ 23 kg/m^2 (Body Mass Index) and 123 healthy controls with a BMI of 18.5-23.0 kg/m^2. Genotyping of each SNP was performed by direct sequencing. Among tested SNPs in *IGF1R* and *IGF2R* genes, rs629849 SNP of *IGF2R* gene showed significant association with obesity (OR = 1.86, 95% CI = 1.02-3.40, *P* = 0.044 in codominant1 model; OR = 1.99, 95% CI = 1.10-3.57, *P* = 0.020 in dominant model; OR = 1.93, 95% CI = 1.13-3.31, *P* = 0.013 in log-additive model). And allele distribution between the control group and overweight/obese group also showed significant difference (OR = 1.93, 95% CI = 1.14-3.28, *P* = 0.015). In conclusion, these results indicate that rs629849 SNP of *IGF2R* might be contributed to development of obesity in the Korean population.

Keywords: Overweight, Obesity, *IGF1R*, *IGF2R*, Single nucleotide polymorphism

INTRODUCTION

Obesity is a growing medical problem in Korea (Lee et al., 2010; Mak et al., 2015; Paik et al., 2015). Obesity has been known to relate to many other diseases or bad conditions, such as cancer (Goday et al., 2015), stress (Mak et al., 2015), heavy alcohol drinking (Kim et al., 2014), and metabolic syndrome, which causes heart diseases (Byeon et al., 2015).

Many factors may affect the development of obesity, however, obesity shows complex relations of genetic and environmental factors (Apalasamy et al., 2015; Doo et al., 2015; Ghosh et al., 2014; Hruby et al., 2015). Many researchers have reported that various cytokines may influence the cellular signals affected by obesity (Kohlgruber et al., 2015; Wueest et al., 2015), among them, insulin-like growth factors (IGFs) are major axis linked to insulin and growth hormone (GH) (Coughlin et al., 2015; Savastano et al., 2014). They are major hormones affecting free fatty acid, plasma glucose, and adipose tissue, and that may show modified profiles in obesity (Oh et al., 2015). Additionally, IGF1 is released in liver by stimulation of GH, and IGF1 receptor signal may also affect insulin signal (Garwood et al., 2015), however, nutrition, exercise, stress, and body mass index (BMI) may affect the IGF and GH levels (Fontana et al., 2010; Glaser et al., 2010; Greer et al., 2011; Sherlock et al., 2007; Ubertini et al., 2008). Peet et al. reported IGF1 may be associated with beta-cell autoimmunity (Peet et al., 2015), and Salmon et al. reported that IGF1 level may be associated with obesity resistance (Salmon et al., 2015).

Above mentioned studies suggest that IGF may affect or be affected by obesity. IGFs may affect cellular signals through its receptors, the IGF1 receptor (IGF1R) and IGF2 receptor (IGF2R) (Kashyap, 2015; Zhu et al., 1997). IGF receptors have genetic variations that can affect various features in humans, such as cause

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the SHORT syndrome (Prontera et al., 2015), growth restriction (Begemann et al., 2015), and cancer responses to the receptor antibody therapies (Cao et al., 2014; Lee et al., 2015). However, there was no study directly reported on whether or not obesity and *IGF1R* gene or *IGF2R* gene is associated. Therefore, the relationship between obesity and the single nucleotide polymorphisms (SNPs) of *IGF1R* gene and *IGF2R* gene were investigated in this study.

MATERIALS AND METHODS

Study subjects

In the present study, a total of 243 subjects were analyzed (Table 1). These subjects were recruited among participants that examined a general health check-up program. Subjects with severe diseases such as stroke, psychiatric disorders, and cancers were excluded. The biochemical characteristics of individuals were measured such as fasting plasma glucose, fasted glycated hemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Body mass index (BMI) is calculated as weight (in kilograms) divided by the square of height (in meters). According to the classification of Korean Society for the Study of Obesity (underweight, BMI < 18; normal, BMI 18 to < 23; moderately obese, BMI 23 to < 25; obesity I, BMI 25 to < 30; obesity II, BMI ≥ 30), subjects were divided into two subgroups, the abnormal (overweight/obese) group (BMI ≥ 23) and the normal group (18 < BMI < 23).

SNP selection and genotyping

Peripheral bloods of all subjects were collected in EDTA or heparin tube. Genomic DNAs were extracted by QIAamp® DNA mini kit (QIAGEN, Valencia, CA, USA). We selected exonic rs3743262 (Thr766Thr) and rs2229765 (Glu1043Glu) SNPs of *IGF1R* gene (Cho et al., 2012) and rs629849 (Gly1619Arg) and rs1805075 (Asn2020Ser) SNPs of *IGF2R* gene. Genotype of each SNP was performed by direct sequencing (MACROGEN, Seoul, Korea).

Polymerase chain reaction (PCR) was employed using the specific primers. Conditions of PCR were 35 cycles at 94°C for 30 sec, 58°C for 30 sec, and 72°C for 30 sec, and 1 cycle at 72°C for 5 min for the final extension reaction. SeqManII software (DNASTAR, Madison, WI, USA) was used to determine the genotype.

Statistical analysis

SNPStats (http://bioinfo.iconcologia.net/index.php) and SPSS 18.0 (SPSS Inc., Chicago, IL, USA) were used to determine the odds ratio (OR), 95% confidence interval (CI), and *P*-value. Multiple logistic regression models (codominant1, codominant2, dominant, recessive, and log-additive models) were applied and age and gender as covariables were adjusted. When the numbers of subject were below 5, the *P*-values were recalculated by Fisher's exact test. The *P*-value below 0.05 was considered significant.

RESULTS

In the control group, the genotype distributions for all SNPs were in HWE [rs3743262 ($P = 0.33$) and rs2229765 ($P = 0.45$) SNPs of *IGF1R* gene and rs629849 ($P = 1.00$) and rs1805075 ($P = 0.84$) SNPs of *IGF2R* gene]. The genotype frequencies of the polymorphisms were compared between the control group and the overweight/obese group by using logistic regression models with adjustment for age and gender. The genotype distributions of rs3743262 and rs2229765 SNPs of *IGF1R* gene and rs629849 and rs1805075 SNPs of *IGF2R* gene in each group were shown in Table 2. Among tested SNPs in *IGF1R* and *IGF2R* genes, rs629849 SNP of *IGF2R* gene showed significant association with obesity [OR = 1.86, 95% CI = 1.02-3.40, $P = 0.044$ in codominant1 model (G/G genotype versus G/A genotype); OR = 1.99, 95% CI = 1.10-3.57, $P = 0.020$ in dominant model (G/G genotype versus G/A genotype+A/A genotype); OR = 1.93, 95% CI = 1.13-3.31, $P = 0.013$ in log-additive model (G/G genotype versus G/A genotype versus A/A genotype)], respectively. And allele distribution between the control group and overweight/obese group also showed significant difference (OR = 1.93, 95% CI = 1.14-3.28, $P = 0.015$). However, three SNPs did show any significant association with development of obesity.

In haplotype analysis, we analyzed haplotype using Haploview 4.2. There were four haplotypes (CG, TA, CA, and TG haplotype) in *IGF1R* gene and three haplotypes (GA, GG, and AA haplotype) in *IGF2R* gene. Among haplotypes, AA haplotype in *IG-*

Table 1. Clinical data of subjects included in the study

Clinical indicator	Overweight/obesity (n = 120)	Control (n = 123)
Age (yr)	43.3 ± 14.2	35.3 ± 11.3
Male/Female	87/33	45/78
Fasting plasma glucose (mg/dL)	90.9 ± 22.0	85.3 ± 6.6
HbA1c (%)	5.8 ± 0.7	5.5 ± 0.5
Total cholesterol (mg/dL)	190.7 ± 33.0	171.0 ± 26.4
HDL-C (mg/dL)	49.6 ± 10.7	54.9 ± 11.8
LDL-C (mg/dL)	288.2 ± 53.6	261.4 ± 45.7

HbA1c, Fasted glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. Genetic analysis of exonic polymorphisms in *IGF1R* and *IGF2R* genes between overweight/obesity and control subjects

SNPs	Genotype Allele	Control	Overweight/obese	Models	OR (95% CI)	*P*	Fisher' exact *P*
		n (%)	n (%)				
IGF1R	C/C	50 (40.6)	51 (42.5)	Codominant1	0.93 (0.55-1.58)	0.80	
rs3743262	C/T	61 (49.6)	58 (48.3)	Codominant2	0.90 (0.36-2.22)	0.82	
Thr766Thr	T/T	12 (9.8)	11 (9.2)	Dominant	0.93 (0.56-1.54)	0.77	
				Recessive	0.93 (0.40-2.21)	0.88	
				Log-additive	0.94 (0.63-1.40)	0.77	
	C	161 (65.4)	160 (66.7)		1		
	T	85 (34.6)	80 (33.3)		0.95 (0.65-1.38)	0.78	
IGF1R	G/G	48 (39)	44 (36.7)	Codominant1	1.06 (0.62-1.81)	0.84	
rs2229765	G/A	66 (53.7)	64 (53.3)	Codominant2	1.45 (0.56-3.78)	0.44	
Glu1043Glu	A/A	9 (7.3)	12 (10.0)	Dominant	1.11 (0.66-1.86)	0.70	
				Recessive	1.41 (0.57-3.47)	0.46	
				Log-additive	1.14 (0.76-1.72)	0.52	
	G	162 (65.9)	152 (63.3)		1		
	A	84 (34.1)	88 (36.7)		1.12 (0.77-1.62)	0.56	
IGF2R	G/G	99 (80.5)	81 (67.5)	Codominant1	1.86 (1.02-3.40)	**0.044**	
rs629849	G/A	23 (18.7)	35 (29.2)	Codominant2	4.89 (0.54-44.61)	0.16	0.18
Gly1619Arg	A/A	1 (0.8)	4 (3.3)	Dominant	1.99 (1.10-3.57)	**0.020**	
				Recessive	4.21 (0.46-38.16)	0.15	0.21
				Log-additive	1.93 (1.13-3.31)	0.013	
	G	221 (89.8)	197 (82.1)		1		
	A	25 (10.2)	43 (17.9)		1.93 (1.14-3.28)	**0.015**	
IGF2R	A/A	52 (42.3)	57 (47.5)	Codominant1	0.75 (0.44-1.29)	0.30	
rs1805075	A/G	57 (46.3)	47 (39.2)	Codominant2	1.04 (0.46-2.34)	0.92	
Asn2020Ser	G/G	14 (11.4)	16 (13.3)	Dominant	0.81 (0.49-1.34)	0.41	
				Recessive	1.20 (0.56-2.58)	0.64	
				Log-additive	0.93 (0.64-1.35)	0.71	
	A	161 (65.4)	161 (67.1)		1		
	G	85 (34.6)	79 (32.9)		0.93 (0.64-1.35)	0.70	

SNP, Single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table 3. Haplotype analysis of exonic polymorphisms in *IGF1R* and *IGF2R* genes between overweight/obesity and control subjects

Gene	Haplotype	Frequency	Control		Overweight/obese		Chi Square	*P*
			+	-	+	-		
IGF1R	CG	0.535	133.8	112.2	126.1	113.9	0.166	0.68
	TA	0.228	56.8	189.2	54.1	185.9	0.02	0.89
	CA	0.126	27.2	218.8	33.9	206.1	1.037	0.31
	TG	0.111	28.2	217.8	25.9	214.1	0.056	0.81
IGF2R	GA	0.523	136	110	118	122	1.822	0.18
	GG	0.337	85	161	79	161	0.145	0.70
	AA	0.14	25	221	43	197	6.07	**0.0138**

IGF1R, Insulin-like growth factor 1 receptor; IGF2R, insulin-like growth factor 2 receptor.

F2R gene showed significant difference between the control group and the overweight/obese group ($P = 0.0138$) (Table 3).

DISCUSSION

In the present study result, the two SNPs (rs3743262 and rs2229765) in *IGF1R* gene did not show any relationship with obesity, also, a SNP (rs1805075) in *IGF2R* gene did not showed any relationship. However, only one SNP (rs629849) of *IGF2R* gene was associated with obesity. Minor allele frequency (MAF) of rs629849 in our study was 0.1 in the control group. MAF of rs629849 in NCBI dbSNP (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=629849) was 0.0968. Therefore MAF in the control group is consistent with MAF in NCBI dbSNP. Significant associations are shown in the allele frequency, co-dominant model, dominant model, and log-additive model, respectively. In all of

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them, ORs were positive in the minor allele (A). Therefore, it suggests that the minor allele "A" of the rs629849 in the *IGF2R* gene may be associated with development of obesity.

IGF2R is a multifunctional receptor that possesses binding sites for diverse ligands, including IGF2, retinoic acid, TGF-beta (TGFB1), urokinase-type plasminogen activator receptor (UPAR), and mannose-6-phosphate (M6P) (Killian et al., 1999). Additionally, IGF2R is involved in lysozyme reaction and cytotoxic T cell apoptosis (Kornfeld et al., 1989; Motyka et al., 2000). Which means IGF2R may have wide range of signal transduction, however, Le Stunff et al. reported that increased expression of mutated insulin(INS) and *IGF2* gene may predispose offspring to postnatal fat deposition (Le Stunff et al., 2001). And Rodriguez et al. reported that certain haplotype composed by the gene region of IGF2-INS-thyroid hormone (TH) is related with obesity (Rodriguez et al., 2004). Also, IGF2-INS region is associated with past famine history in individuals (Tobi et al., 2009). Interestingly, IGF2R has degradation function of IGF2, which is known as mitogen (Yoon et al., 2012). Rezgui, studied the correlation of "A" allele and receptor function, however, the researchers concluded that it showed no direct effect and they suspected the linkage between other intronic polymorphisms.

In previous study, rs629849 of *IGF2R* gene was significantly associated with higher level of circulating IGF2 level in "A" allele homozygote woman (Hoyo et al., 2012). The authors concluded that "A" homozygote in rs629849 of *IGF2R* gene may modulate IGF2 level in sex-specific manner, and it may affect colorectal cancer risk as a mitogen effect of IGF2. Additionally, rs629849 of IGF2R gene was associated with advanced stage of oral cancer, that "GG "genotype showed ORs of 0.32 compared to "A" allele carriers (Yoon et al., 2012). The previous research results are, consistent with ours that the minor "A" allele may tribute to the obesity development.

In conclusion, though it was marginal relation in this study, we suggest that having "A" allele of rs629849 of *IGF2R* gene may be associated with development of obesity in the Korean population.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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