Korean J Physiol Pharmacol
Vol 12: 125−129, June, 2008

Matrix Metallopeptidase 2 Gene Polymorphism is Associated with Obesity in Korean Population

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The aim of this study was to determine whether single nucleotide polymorphisms (SNPs) of matrix metallopeptidase 2 (MMP2) are associated with obesity. MMP2 is an enzyme with proteolytic activity against matrix and nonmatrix proteins, particularly basement membrane constituents. To identify the relationship between polymorphisms of MMP2 and overweight/obese, we genotyped 5 SNPs (rs17242319, rs1053605, rs243849, rs2287074, and rs10775332) of the coding region of MMP2 using the Golden Gate assay on an Illumina BeadStation 500 GX. One hundred and forty two overweight/obese (BMI ≥23) and 145 normal (BMI 18 to <23) subjects were analyzed. SNPStats, Haploview, HapAnalyzer, SNPAnalyzer, and Helixtree programs were used for the analysis of genetic data. A linkage disequilibrium (LD) block was discovered among the 5 SNPs selected, including rs17242319, rs1053605, rs243849, and rs2287074. Of the 5 polymorphisms, 2 synonymous SNPs [rs17242319 (Gly226Gly) and rs10775332 (Phe602Phe)] were found significant associations with overweight/obese. Recently, rs1132896 replaced rs17242319 as a new number (SNP database, BUILD 129). In haplotype analysis using Haploview, a haplotype (haplotype: CCCA) containing a meaningful polymorphism (rs17242319) was found to be significantly different. The results suggest that MMP2 may be associated with overweight/obese in Korean population.

Key Words: Body mass index, Linkage disequilibrium, Matrix metallopeptidase 2, Obesity, Single nucleotide polymorphism

INTRODUCTION

It is now clear that obesity is associated with low-grade inflammation. Various proinflammatory cytokines such as interleukin (IL)1, IL6, interferon gamma, and tumor necrosis factor (TNF) alpha are synthesized and released in human adipocytes (Clement & Langin, 2007; Mehta & Farmer, 2007). Obesity is also one of worldwide health problems, and is closely related to several diseases such as hyperlipidemia and hypertension. The numbers of reports on pathophysiology and mechanism of obesity have recently increased (Bajaj et al, 2003). It is well-known that environmental and genetic factors may be involved in the pathogenesis of obesity. Environmental factors such as diet and stress resulted in the increase of prevalence of obesity during relatively short time interval (Aranceta et al, 2007). Fat deposition in peripheral tissues is related to the signaling of the central nervous system (CNS) (Cota et al, 2007; Migrenne et al, 2007), and molecules to signal the peripheral fuel status also are known, to transmit the signal to the CNS (Wynne et al, 2005). Several studies showed the contribution of genetic factor to the etiology of obesity (Barsh et al, 2000; Martinez-Hernandez et al, 2007). Family and twin studies have shown that genetic factors are related to susceptibility of obesity (Dong et al, 2005; Wilson et al, 2006).

Type IV collagenase (72 kD) is officially designated as matrix metallopeptidase 2 (MMP2), and also known as gelatinase (Nagase et al, 1992). MMP2 cleaves type IV collagen, the major structural component of basement membrane. According to NCBI (http://www.ncbi.nlm.nih.gov/sites/entrez), MMP2 is located on chromosome 16. In Ensembl Gene View (Ensembl ID, ENSG00000087245), it covers 27.51 kb, spanning from 54,070,589 to 54,098,101 as the foreword direction. This complete mRNA is 3,533 bp long, and has 13 exons. The protein has 660 amino acid residues with pI of 5.1, and it contains a cleavable signal peptide domain from 1 to 29 amino acids (MEALMARGALTGPLRALCLLGCLLSHAAA). MMP2 is expressed in blood, brain, kidney, lung, heart, and colon. MMP2 protein is secreted, and cleavage of a signal sequence is required for its activity (http://www.ncbi.nlm.nih.gov/sites/entrez). Although MMP2 has important roles in several signal pathways including inflammation, the genetic association of

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ABBREVIATIONS: BMI, body mass index; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; LD, linkage disequilibrium; MMP2, Matrix metallopeptidase 2; OR, odds ratio; SNP, single nucleotide polymorphism.

MMP2 with development of obesity is not yet known. In the present study, 5 coding SNPs of MMP2 in 142 healthy controls and 145 obesity (overweight/obese) subjects were examined to investigate the possible relationship between MMP2 and obesity.

METHODS

Subjects

This study was approved by the Ethics Committee of the Medical Research Institute, College of Medicine, Kyung Hee University, Seoul, and Republic of Korea. Blood samples were obtained from unrelated Korean subjects with informed written consent. One hundred forty two overweight/obese subjects and 145 healthy individuals were recruited from Kyung Hee University Medical Center. Patients with hypertension, hyperlipidemia, diabetes, stoke, and neuropsychiatric diseases were excluded. All studies were conducted according to the Declaration of Helsinki guidelines. Body mass index (BMI) was defined as weight in kilogram divided by the square of height in meter (kg/m^2). Obese subjects with BMI over 23 and control subjects (BMI 18 to <23) were selected according to 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).

Extraction of DNA from blood

Blood samples for DNA extraction were collected in ethylenediamine tetraacetic acid (EDTA) tube from all subjects. Genomic DNA was extracted from whole blood of each subject using a commercially available Qiagen DNA Extraction kit (Qiagen, Tokyo, Japan)., and stored at $-20^{\circ}C$ before use.

SNP selection and genotyping

We selected 5 SNPs (rs17242319, rs1053605, rs243849, rs2287074, and rs10775332) in the MMP2 gene region using the following websites: Human SNP websites (http://www.ensembl.org; www.ncbi.nlm.nih.gov/SNP). The SNPs with unknown heterozygosity and minor allele frequency (below 5%) were excluded. Finally, the 5 coding SNPs were all synonymous polymorphisms [rs17242319 (exon 5, Gly226Gly), rs1053605 (exon 5, Thr250Thr), rs243849 (exon 7, Asp383Asp), rs2287074 (exon 9, Thr460Thr), and rs10775332 (exon 12, Phe602Phe)]. SNP genotyping was carried out using the Golden Gate assay on an Illumina BeadStation 500 GX (Illumina Inc., San Diego, USA), according to the protocol supplied. Each oligonucleotide (bead type) represents a specific SNP locus. Each Golden Gate genotyping is the result of the mean intensity of 30 replicates, resulting in accuracy call rates (all $>99\%$).

Statistical analysis

For the case-control association study, Hardy-Weinberg equilibrium (HWE) for all SNPs was assessed using SNPstats (http://bioinfo.iconcologia.net/index.php) (Solé et al, 2006). A linkage disequilibrium (LD) block of polymorphisms was tested using Haploview 3.32 (Barrett et al, 2005). The haplotypes and their frequencies were calculated by the EM algorithm (Stephens et al, 2001). To analyze odds ratio (OR), 95% confidence intervals (CI), and p value, SNPStats, SNPAnalyzer (ISTECH Inc., Goyang, Korea), and Helixtree (Golden Helix Inc., MT, USA) were also used. For all statistical tests, the significant level was set at 0.05. The power of sample size was calculated using G*Power computer software (Faul et al, 2007).

RESULTS

We investigated whether MMP2 is related to obesity by genotyping the 5 SNPs selected in Korean population. There were significant differences in the polymorphisms of SNPs (rs1724319 and rs10775332) between obese subjects and controls using the logistic analysis of codominant, dominant, and recessive models.

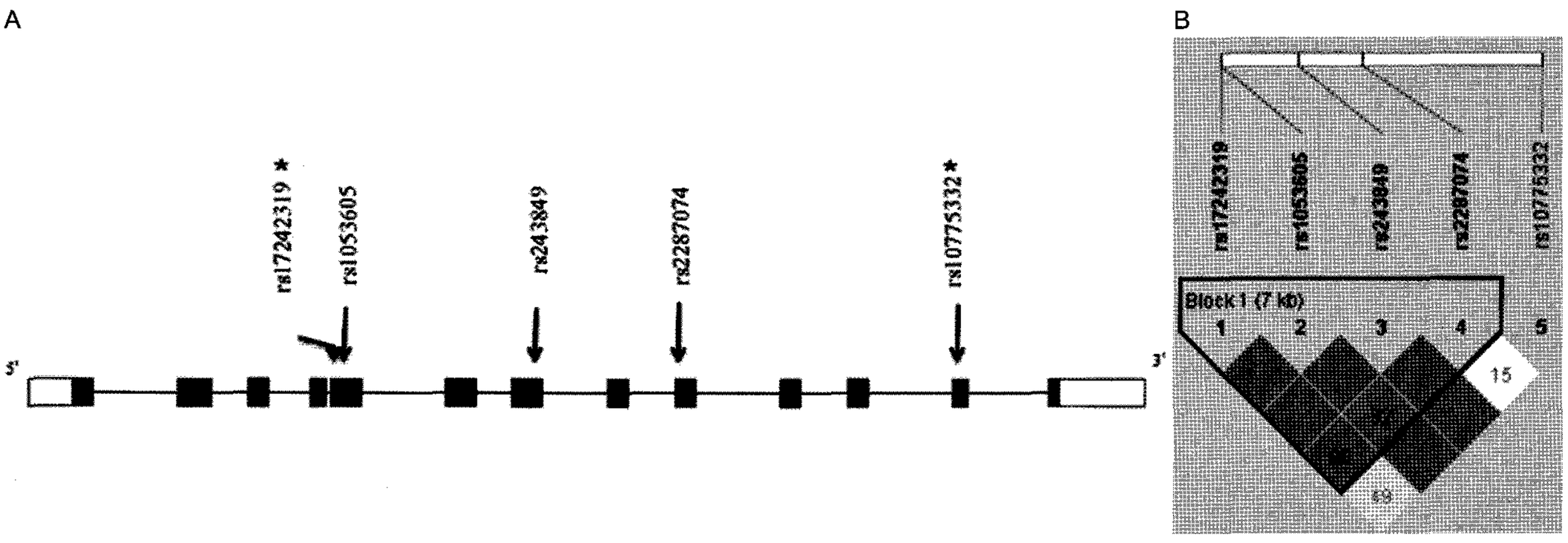

Fig. 1. Gene map and linkage disequilibrium (LD) in matrix metallopeptidase 2 (MMP2) gene. (A) Gene map of single nucleotide polymorphisms (SNPs) in MMP2 on chromosome 16. Exons are marked with box. The coding region is black-boxed and untranslation regions are white-boxed. Asterisk (*) indicates a significant SNP. Arrow indicates the location of each SNP. EX, exon. (B) LD coefficient ($|D'|$) and LD blocks among SNPs of MMP2. Block 1 consists of rs17242319, rs1053605, rs243849, and rs2287074.

In the MMP2 gene containing various SNPs, the selected 5 SNPs (rs1724319, rs1053605, rs243849, rs2287074, and rs10775332) were examined. In the recent SNP database (BUILD 129), rs1132896 replaced rs17242319 as a new number. The positions of 5 SNPs are marked on the MMP gene region (Fig. 1A). The genotype distributions of MMP2 gene polymorphisms in the overweight/obese and control groups are shown in Table 1. In the control group, the genotype distributions of the 5 SNPs were in HWE [rs1724319 (p=0.29), rs1053605 (p=0.78), rs243849 (p=0.52), rs2287074 (p=1.00), and rs10775332 (p=0.94), respectively]. Of the 5 SNPs, two polymorphic SNPs [rs1724319: odds ratio (OR)=1.64, 95% confidence interval (CI)=1.06-2.54, p=0.023 in the codominant model, and OR=1.70, 95% CI=1.02-2.82, p=0.041 in the dominant model; rs10775332: OR=3.97, CI=1.08-14.56. p=0.022 in the recessive model] were associated with the development of overweight/obese. The rare allele of rs17242319 (rare allele, C) and rs10775332 (rare allele, A) increased the risk of obesity. The rest of the SNPs (rs1053605, rs243849, and rs2287074) were not statistically associated with overweight/obese (Table 1). We identified haplotype (ht) 1, 2, 3, and 4 which comprised the four polymorphisms (rs1724319, rs1053605, rs243849, rs2287074, frequency>0.01) and accounted for 99.9% of all the observed haplotypes (Table 2). They were in a linkage disequilibrium (LD) block according to Solid spine of LD block definition (Fig. 1B). The LD block contained a significant SNP (rs17242319). Haplotype association was tested using Haploview 3.32, and the result showed that the haplotype (CCCA) had a significant association between the control and overweight/obese groups (frequency=0.1618, Chi Square=4.858, p=0.027). Genotype frequencies of the selected SNPs in each population are shown in Table 3. Three SNPs (rs1724319, 1053605, and 2287074) are similar to those of Chinese, whereas others (rs243849 and 10775332) are similar to those Japanese (Table 3). Taken together, the results suggest that MMP2 affects the susceptibility to the development of obesity in Korean population.

Table 1. Logistic regression analysis and genotype frequency of matrix metallopeptidase 2 (MMP2) polymorphisms in control and overweight/obesity subjects

SNP Locus	Protein residue	Genotype	Control n=145 (%)	Overweight/obesity n=142 (%)	Codominant OR (95% CI)	p	Dominant OR (95% CI)	p	Recessive OR (95% CI)	p
rs17242319 (rs1132896) Exon 5	Gly226 Gly	G/G	109 (75.2)	91 (64.1)	**1.64 (1.06~2.54)**	**0.023**	**1.70 (1.02~2.82)**	**0.041**	2.83 (0.73~10.88)	0.110
		G/C	33 (22.8)	43 (30.3)						
		C/C	3 (2.1)	8 (5.6)						
rs1053605 Exon 5	Thr250Thr	C/C	106 (73.1)	114 (80.3)	0.73 (0.43~1.22)	0.230	0.67 (0.38~1.16)	0.150	2.06 (0.18~22.94)	0.550
		C/T	38 (26.2)	26 (18.3)						
		T/T	1 (0.7)	2 (1.4)						
rs243849 Exon 7	Asp383Asp	C/C	97 (66.9)	100 (70.4)	0.88 (0.56~1.38)	0.570	0.85 (0.52~1.40)	0.520	1.02 (0.20~5.15)	0.980
		C/T	45 (31.0)	39 (27.5)						
		T/T	3 (2.1)	3 (2.1)						
rs2287074 Exon 9	Thr460Thr	G/G	74 (51.0)	70 (49.3)	1.08 (0.76~1.56)	0.660	1.07 (0.67~1.70)	0.770	1.23 (0.53~2.84)	0.630
		G/A	60 (41.4)	59 (41.5)						
		A/A	11 (7.6)	13 (9.2)						
rs10775332 Exon 12	Phe602Phe	C/C	76 (52.4)	74 (52.1)	1.19 (0.80~1.76)	0.390	1.01 (0.64~1.61)	0.960	**3.97 (1.08~14.56)**	**0.022**
		C/T	66 (45.5)	57 (40.1)						
		T/T	3 (2.1)	11 (7.8)						

Genotype distributions are shown as number (%). Odds ratio (OR), 95% confidence interval (CI), and p values were from logistic regression analysis with codominant, dominant, and recessive models controlling age and gender as covariates. SNP, single nucleotide polymorphism.

Table 2. Haplotype analysis of matrix matrix metallopeptidase 2 (MMP2) polymorphisms in control and overweight/obesity subjects

	Haplotype	Freq	Control		Overweight/obesity		Chi Square	p
			+	−	+	−		
ht1	GCCG	0.5366	155.0	135.0	152.1	131.9	0.001	0.974
ht2	GCTG	0.1633	49.8	240.2	45.0	239.0	0.183	0.669
ht3	CCCA	0.1618	37.1	252.9	55.6	228.4	4.858	**0.028**
ht4	GTCA	0.1083	37.0	253.0	25.2	258.8	2.259	0.133

Each haplotype with a frequency of more than 0.1 is shown. ht:haplotype. Haplotype1, 2, 3, and 4 consist of rs17242319, rs1053605, rs243849, and rs2287074. p-values of haplotype association were calculated using Haploview 3.32.

Table 3. Genotype frequencies of matrix metallopeptidase 2 (MMP2) polymorphisms in each population

SNP	Genotype	Control	Overweight/obesity	HapMap-CEU	HapMap-HCB	HapMap-JPT
				European	Chinese	Japanese
rs17242319	G/G	0.752	0.641	0.309	**0.757**	0.575
(rs1132896)	G/C	0.228	0.303	0.527	**0.243**	0.350
	C/C	0.021	0.056	0.164	**0.000**	0.075
rs1053605	C/C	0.731	0.803	0.867	**0.756**	0.705
	C/T	0.262	0.183	0.117	**0.244**	0.295
	T/T	0.007	0.014	0.017	**0.000**	0.000
rs243849	C/C	0.669	0.704	0.767	0.600	**0.667**
	C/T	0.310	0.275	0.233	0.333	**0.289**
	T/T	0.210	0.021	0.000	0.067	**0.044**
rs2287074	G/G	0.510	0.493	0.254	**0.511**	0.432
	G/A	0.414	0.415	0.492	**0.489**	0.386
	A/A	0.076	0.092	0.254	**0.000**	0.182
rs10775332	C/C	0.524	0.521	0.200	0.578	**0.467**
	C/T	0.455	0.401	0.600	0.311	**0.489**
	T/T	0.021	0.078	0.200	0.111	**0.044**

From database (http://www.ncbi.nlm.nih.gov/sites/entrez).

DISCUSSION

Although the role of MMP2 in the regulation of weight has previously been reported, no genetic study concerning the association between MMP2 and obesity has been yet reported. In this study, we found that MMP2 is associated significantly with overweight/obese subjects in Korean population.

In a Saudi family with idiopathic multicentric osteolysis, Martignetti et al, (2001) found that affected members revealed a G-to-A transition in codon 101 (exon 2) of the MMP2 gene, predicting replacement of an arginine by histidine (Arg101His). They also found a Try244Tyr mutation of the MMP2 gene. The mutation might have effects on the deletion of catalytic site and fibronectin type II-like and hemopexin binding domains (Martignetti et al, 2001). In an Italian patient with Winchester syndrome, Zankl et al, (2005) found a homozygous Glu404Lys mutation in exon 8 of the MMP2 gene. The glutamic acid at codon 404 is located at the catalytic domain of the protein, as its carboxyl group catalyzes 2 proton transfers (Hangauer et al, 1984; Morgunova et al, 1999). Since Lambert et al, (1989) first reported 2 sisters with Winchester syndrome, Rouzier et al, (2006) found a homozygous 3 bp deletion (1488delTGG) in exon 8 of the MMP2 gene, resulting in a loss of the third alpha-helix site of the catalytic domain of the protein. Zhou et al, (2007) suggest that the genetic polymorphisms or haplotype in the MMP2 promoter (rs243865, -1306 and rs2285053, -735) may play a role in mediating the susceptibility to nasopharyngeal carcinoma in Chinese populations. Gremlich et al, (2007) reported that fetal MMP2 C-1306T mutation rate was higher within the intrauterine growth retardation (IUGR) than appropriate for gestational age (AGA) population. The risk of IUGR occurrence is increased both in CT (OR=3.603, 95% CI=1.577-8.231, p=0.004) and TT carriers (OR=3.391, 95% CI=0.786-14.630, p=0.102), compared to the normal CC genotype. Hinterseher et al, (2006) revealed that the entire coding region and three parts of the promoter of the MMP2 gene failed to show an association between genetic polymorphisms and abdominal aortic aneurysm (AAA). On the other hand, Zhou et al, (2007) observed a 2-fold (OR, 2.12; 95% CI, 1.64-2.72) or 1.6-fold (OR, 1.57; 95% CI, 1.27-1.95) excess risk of developing lung cancer for the -1306CC or -735CC genotype carriers compared with non-carriers, respectively, Miao et al, (2003) found that subjects with the CC genotype had >3-fold increased risk for developing GCA, compared with those with the variant CT or TT genotype, and Yu et al, (2002) demonstrated a significant association between the MMP2 -1306C/T polymorphism and the risk of developing lung cancer.

In conclusion, the results in the present study revealed that SNPs and haplotype in the MMP2 gene were significantly associated with overweight/obese subjects, suggesting that MMP2 may be involved in the regulation of weight balance. To our knowledge, this is the first report to assess the association genetic study between MMP2 polymorphisms and obesity in Korean population. Since no other association studies concerning the association of MMP2 gene with obesity have been reported, more studies on the role of MMP2 in the development of obesity are needed.

ACKNOWLEDGEMEMT

This study was supported by a grant of the Small and Medium Business Administration (S5107A11901) and partially by the Governance Program of Kyung Hee University.

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