SHORT COMMUNICATION

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ASSOCIATIONS BETWEEN BODY MASS INDEX AND SERUM URIC ACID LEVELS IN A JAPANESE POPULATION WERE SIGNIFICANTLY MODIFIED BY *LRP2* rs2544390

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ABSTRACT

The genome-wide association study identified associations between the *LRP2* polymorphism rs2544390 and serum uric acid (SUA) levels in a Japanese population. Our previous study on the *LRP2* rs2544390 polymorphism identified an interaction between SUA and alcohol consumption. Here, we investigated an interaction with body mass index (BMI) using the same dataset. Subjects were 3,742 health checkup examinees (2,544 males and 1,198 females) aged 35–69 years. Those with the *SLC22A12 258WW* genotype, *SLC2A9* rs11722228 *C* allele, and *ABCG2 126QQ* genotype and *141Q* allele were selected for analysis to remove the strong influences of these genetic traits. In males, the odds ratio of BMI ≥25.0 relative to BMI <18.5 for hyperuricemia (SUA ≥7 mg/dL and/or under medication for hyperuricemia) was 6.58 (95% confidence interval [CI], 0.84–51.32) for *CC,* 10.08 (2.38–42.83) for *CT*, and 2.53 (0.54–11.78) for *TT*. The interaction was 0.59 (p=0.029) from the model including BMI (<25.0 and ≥25.0), genotype (*CC/CT* and *TT*), and the multiplicative interaction term between BMI ≥25.0 and the *TT* genotype. In females, the odds ratio of BMI ≥25.0 relative to BMI <18.5 for high SUA (≥5 mg/dL and/or under medication for hyperuricemia) was 6.35 (95%CI, 1.68–24.08) for *CC,* 4.55 (1.85–11.18) for *CT*, and 5.93 (1.97–17.90) for *TT*. The interaction term was significant in the opposite direction for females (OR=2.75, p=0.011). The association between BMI and SUA was therefore modified by the *LRP2* polymorphism in this Japanese population.

Key Words**:** *LRP2* rs2544390, Body mass index, Serum uric acid levels

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INTRODUCTION

Hyperuricemia is the most important risk factor for the development of gout, and is also a risk factor for cardiovascular disease.[1,2] Gout is considered a major public health issue because it greatly impacts on quality of life.[3,4] According to the Comprehensive Survey of Living Conditions undertaken by the Ministry of Health, Labour and Welfare of Japan, an average of 14.9 per 1,000 men visited a hospital or clinic for treatment of gout in Japan in 2010.[5]

Serum uric acid (SUA) levels are influenced by both genetic and non-genetic factors, including obesity and the consumption of alcohol.[6] Recent genome-wide association studies (GWAS) have identified several genes associated with SUA.[7] Of these, polymorphisms in *SLC22A12*, *SLC2A9*, and *ABCG2* genes were found to be associated with SUA in a GWAS of 14,700 Japanese individuals. Moreover, this study also showed that the *T* allele of the *LRP2* intron 1 polymorphism (rs2544390) on chromosome 2q24-31 was associated with a higher SUA.[8] *LRP2* encodes low-density lipoprotein receptor-related protein 2 (megalin), a member of the low-density lipoprotein receptor (LDLR) family.[9] *LRP2* is expressed in the epithelia of renal proximal tubules, the epididymis, and thyroid cells, and is considered to play central roles in the reabsorption of proteins and endocytosis.[10] *SLC22A12* encodes urate transporter 1 (URAT1) while *SLC2A9* encodes glucose transporter 9 (GLUT9). Both molecules play a role in the reabsorption of uric acid in renal tubules.[11-13] GLUT9 also affects glucose-stimulated insulin secretion in mouse pancreatic β cells.[14] *ABCG2* encodes the ATP-binding cassette subfamily G member 2 (ABCG2), which inhibits the penetration of toxins into the brains and fetus and prevents their absorption from the intestinal lumen.[15] It is also known as a breast cancer resistance protein that plays a role in multi-drug resistance. Polymorphisms *ABCG2 Q126X* (rs72552713) and *Q141K* (rs2231142) have been shown to influence the risk of hyperuricemia through reduction of the uric acid transportation activity.[16-18]

Our previous studies have confirmed the associations with these polymorphisms,[16,19,20] and we observed an interaction with alcohol consumption on SUA in our investigation of the *LRP2* intron 1 polymorphism rs2544390.[21] Because obesity is an important factor that determines SUA,[6] the present study aimed to investigate the interaction between *LRP2* rs2544390 and BMI on SUA levels using the same dataset as our previous work.

MATERIALS AND METHODS

Subjects and data collection

As described previously,[20] subjects were derived from 5,018 health checkup examinees aged 35–69 years in a health checkup center in Hamamatsu, Japan, who participated in the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study) between 2006–2007.[22] Written informed consent was obtained from all participants. Subjects with serum creatinine levels ≥2.0 mg/dL (n=5) or missing data of height (n=1) were excluded from the analysis. Those subjects with the *SLC22A12 258WW* genotype, *SLC2A9* rs11722228 *C* allele, and *ABCG2 126QQ* genotype and *141Q* allele were selected for further analysis to remove the strong influences of these genetic traits.[11,16,17,19,20] The selection of genotypes was based on findings from previous studies. For example, SUA levels were greatly reduced in individuals with even one *SLC22A12 258X* allele.[19] Another study showed that SUA was significantly higher in those with a *SLC2A9 TT* genotype after adjustment for age,[20] while those with an *ABCG2 126X* allele and those without an *ABCG2 141Q* allele had elevated SUA levels.[16]

A self-administered questionnaire was employed to determine subjects' lifestyles. Drinking

frequency was divided into the following groups: every day, 5–6 times/week, 3–4 times/week, 1–2 times/week, 1–3 times/month, and no-drinking. BMI (kg/m^2) was calculated from subjects' weight and height measured at the health checkup. Peripheral blood was drawn in the morning from the participants following overnight fasting. SUA was measured enzymatically by a uricase method using an auto-analyzer.

Genotyping

DNA was extracted from buffy coat samples stored at −80°C using a BioRobot® M48 (QIAGEN, Tokyo, Japan). *LRP2* rs2544390 in intron 1 was genotyped by PCR with confronting two-pair primers (PCR-CTPP).[23] Genotyping details have been described elsewhere.[21]

Statistical analysis

The adjusted odds ratio (OR) and 95% confidence interval (CI) of BMI ≥25.0 or 18.5–25.0 (versus <18.5)[24] by sex and *LRP2* genotype were estimated using an unconditional logistic regression model. Drinking frequency (every day, 5–6 times/week, 3–4 times/week, 1–2 times/week, 1–3 times/month, or non-drinker) and age (30–39, 40–49, 50–59, or 60–69 years) were adjusted using dummy variables. Males with SUA ≥7 mg/dL and/or under medication for hyperuricemia were classified as 'high SUA'; other males were classified as 'normal', and the OR for 'high SUA' was calculated. In women, the OR for high SUA (≥7 mg/dL) was not calculated because only 18 females had such high SUA levels. Instead, females with SUA ≥5 mg/dL and/or under medication for hyperuricemia were classified as 'SUA ≥5'; other females were classified as 'normal', and the OR for 'SUA ≥5' was estimated. Because individuals with BMI <18.5 and 'high SUA' (for men) or 'SUA ≥5' (for women) were uncommon, we also attempted analyses by sex with BMI classified into tertiles. Interactions between the polymorphism and BMI were assessed by incorporating the genotype (*CC*, *CT*, or *TT*), BMI (<18.5, 18.5–25.0 or ≥25.0) and their four multiplicative interaction terms in the abovementioned logistic models. Additionally, the OR of BMI ≥25 (versus BMI <25) was estimated for the *TT* genotype and in the combined *CC* and *CT* genotypes in both males and females, and the interaction between BMI and genotype in this categorization was assessed with a multiplicative interaction term in the multivariable model. Statistical analyses were performed using STATA software, version 11 (STATA, College Station, TX, USA).

RESULTS

A total of 3,742 participants (2,544 males and 1,198 females) had *SLC22A12 258WW*, *SLC2A9* rs11722228 *C* allele, and *ABCG2 126QQ* and *141Q* allele (mean age ± SD, 50.29 ± 8.73 years). Age–drinking frequency-adjusted ORs and 95% CIs of BMI for high SUA according to the rs2544390 genotype are shown in Tables 1–4.

In males, the OR of BMI ≥25.0 relative to BMI <18.5 was 6.58 (95% CI, 0.84–51.32) for the *CC* genotype, 10.08 (95% CI, 2.38–42.83) for the *CT* genotype, and 2.53 (95% CI, 0.54–11.78) for the *TT* genotype (Table 1). Even when BMI was classified into tertiles, the OR of the highest BMI group relative to the lowest was smaller for the *TT* genotype. The OR was 3.07 (95% CI, 1.83–5.16), 3.01 (95% CI, 2.18–4.16), and 1.78 (95% CI, 1.09–2.90) for the *CC*, *CT*, and *TT* genotypes, respectively. The interaction from the model including BMI with two categories (<25.0 and ≥25.0), and the genotype with two categories (*CC/CT* and *TT*) was significant between BMI ≥25.0 and the *TT* genotype (OR for interaction, 0.59; p=0.029) (Table 2, footnote).

In females with the *CC*, *CT*, or *TT* genotypes, the OR of BMI ≥25.0 for SUA ≥5 was signifi-

Table 1 Age–drinking frequency-adjusted odds ratio (OR) and 95% confidence intervals (95% CI) of BMI for high SUA among Japanese males with *SLC22A12 258WW*, *SLC2A9* rs11722228 *C* allele, *ABCG2 126QQ* and *141Q* allele by *LRP2* rs2544390 genotype

Genotype	BMI	Serum uric acid		OR	95% CI
		Normal (%)	High (%)		
CC	<18.5	14 (2.8)	1 (0.8)	1	(Reference)
	18.5–25.0	378 (74.3)	76 (57.9)	2.81	(0.36–21.73)
	≥25.0	117 (23.0)	55 (41.4)	6.58	(0.84–51.32)
CT	<18.5	31 (3.2)	2 (16.0)	1	(Reference)
	18.5–25.0	735 (75.3)	199 (37.0)	4.20	(1.004–17.69)
	≥25.0	209 (21.6)	136 (47.0)	10.08	(2.38–42.83)
TT	<18.5	12 (2.7)	2 (1.4)	1	(Reference)
	18.5–25.0	333 (74.6)	99 (69.0)	1.78	(0.39–8.10)
	≥25.0	102 (22.8)	43 (29.7)	2.53	(0.54–11.78)

Interaction OR from the model including age, drinking frequency, BMI, genotype, and four interaction terms were: 1.54 (p=0.73, 95% CI 0.12–18.8) between 18.5≤BMI<25.0 and *CT* genotype, 0.61 (p=0.71, 95% CI 0.48–7.82) between 18.5≤BMI<25.0 and *TT* genotype, 1.58 (p=0.73, 95% CI 0.13–19.20) between BMI≥25.0 and *CT* genotype, and 0.37 (p=0.45, 95% CI 0.03–4.79) between BMI≥25.0 and *TT* genotype.

Table 2 Age–drinking frequency-adjusted odds ratio (OR) and 95% confidence intervals (95% CI) of BMI for high SUA among Japanese males with *SLC22A12 258WW*, *SLC2A9* rs11722228 *C* allele, *ABCG2 126QQ* and *141Q* allele by *LRP2* rs2544390 genotype and BMI level

Genotype	BMI	Serum uric acid		OR	95% CI
		Normal (%)	High (%)		
CC/CT	<25.0	1,158 (78.1)	278 (59.2)	1	(Reference)
	≥25.0	326 (22.0)	191 (40.7)	2.43	(1.94–3.03)
TT	<25.0	345 (77.2)	101 (70.1)	1	(Reference)
	≥25.0	102 (22.8)	43 (29.9)	1.43	(0.93–2.17)

Interaction OR from the model including age, drinking frequency, BMI, genotype, and a multiplication interactive term was 0.59 (p=0.029, 95% CI 0.37–0.95) between BMI≥25.0 and *TT* genotype.

Table 3 Age–drinking frequency-adjusted odds ratio (OR) and 95% confidence intervals (95% CI) of BMI for SUA ≥5 among Japanese females with *SLC22A12 258WW*, *SLC2A9* rs11722228 *C* allele, *ABCG2 126QQ* and *141Q* allele by *LRP2* rs2544390 genotype

Genotype	BMI	Serum uric acid		OR	95% CI
		Normal (%)	SUA ≥5 (%)		
CC	<18.5	25 (12.1)	3 (3.8)	1	(Reference)
	18.5–25.0	153 (74.3)	52 (65.8)	2.63	(0.74–9.21)
	≥25.0	28 (13.6)	24 (30.4)	6.35	(1.68–24.08)
CT	<18.5	47 (10.7)	7 (4.2)	1	(Reference)
	18.5–25.0	332 (75.3)	119 (70.8)	2.33	(1.01–5.36)
	≥25.0	62 (14.1)	42 (25.0)	4.55	(1.85–11.18)
TT	<18.5	29 (12.8)	6 (7.7)	1	(Reference)
	18.5–25.0	179 (79.2)	46 (59.0)	0.89	(0.33–2.39)
	≥25.0	18 (8.0)	26 (33.3)	5.93	(1.97–17.90)

Interaction OR from the model including age, drinking frequency, BMI, genotype, and four interaction terms were: 0.58 (p=0.84, 95% CI 0.19–3.85) between 18.5≤BMI<25.0 and *CT* genotype, 0.35 (p=0.20, 95% CI 0.07–1.72) between 18.5≤BMI<25.0 and *TT* genotype, 0.71 (p=0.67, 95% CI 0.14–3.54) between BMI≥25.0 and *CT* genotype, and 0.93 (p=0.93, 95% CI 0.17–5.22) between BMI≥25.0 and *TT* genotype.

Table 4 Age–drinking frequency-adjusted odds ratio (OR) and 95% confidence intervals (95% CI) of BMI for SUA ≥5 among Japanese females with *SLC22A12 258WW*, *SLC2A9* rs11722228 *C* allele, *ABCG2 126QQ* and *141Q* allele by *LRP2* rs2544390 genotype and BMI level

Genotype	BMI	Serum uric acid		OR	95% CI
		Normal (%)	SUA ≥5 (%)		
CC/CT	<25.0	557 (86.1)	181 (73.3)	1	(Reference)
	≥25.0	90 (13.9)	66 (26.7)	2.25	(1.55–3.25)
TT	<25.0	208 (92.0)	52 (66.7)	1	(Reference)
	≥25.0	18 (8.0)	26 (33.3)	6.56	(3.22–13.34)

Interaction OR from the model including age, drinking frequency, BMI, genotype, and a multiplication interactive term was 2.75 (p=0.011, 95% CI 1.26–6.01) between BMI≥25.0 and *TT* genotype.

cantly higher relative to BMI <18.5, at 6.35 (95% CI, 1.68–24.08), 4.55 (95% CI, 1.85–11.18), and 5.93 (95% CI, 1.97–17.90), respectively (Table 3). In the analysis dividing BMI into tertiles, the OR of the highest BMI group relative to the lowest was 2.45 (95% CI, 1.27–4.74), 3.60 (95% CI, 2.19–5.94), and 4.44 (95% CI, 2.10–9.37) for the *CC*, *CT*, and *TT* genotypes, respectively. The interaction between BMI ≥25.0 and the *TT* genotype was found to be significant (OR for interaction, 2.75; p=0.011) (Table 4, footnote).

DISCUSSION

To the best of our knowledge, no studies have yet examined the interaction between the *LRP2* polymorphism in intron 1 (rs2544390) and BMI with respect to SUA. In this study, the effect of BMI was significantly greater among males with *CC/CT* genotypes compared to males with the *TT* genotype. By contrast, the effect of BMI was significantly stronger among females with the *TT* genotype.

Because hyperuricemia is not only a major cause of gout[1)] but also a risk factor for cardiovascular disease,[1,2)] its prevention is considered an important issue in public health practice. Thus, our current findings may be particularly useful to identify individuals who are predisposed to hyperuricemia associated with obesity.

No detailed biological mechanisms have been reported about the influence of the *LRP2* polymorphism on the effect of BMI on SUA levels. However, the female hormone estrogen decreases SUA.[25)] From the present study findings, we suggest that the influence of the *LRP2* polymorphism differs between males and females because of differences in estrogen activity. Estradiol reduces SUA through renal clearance,[26)] so the observed SUA increase in females could be explained by the menopause or other age-related factors.[27)] Additionally, alcohol consumption increases SUA,[6)] and drinking habits differ between males and females. Moreover, a significant interaction was reported between drinking and the *LRP2* genotype for high SUA among Japanese males.[21)] Although we considered drinking habits in calculating the OR, alcohol consumption might also have affected the observed gender differences in our findings. Furthermore, because hematocrit values appear to be associated with SUA,[28)] gender differences in hematocrit might have impacted the current results.

One of the limitations of this study is that the reference value of SUA differed between males and females. In addition, the number of individuals with a BMI <18.5 or ≥25.0 was relatively small, and, especially in males, only 15–30 people had a BMI <18.5 after classification according to genotype. Our study findings should therefore be confirmed in a larger sample size. However,

we restricted our analysis to individuals with selected genotypes of *SLC22A12*, *SLC2A9*, and *ABCG2* because it enabled us to remove the influence of genetic traits closely related to SUA levels on the effect of the *LRP2* polymorphism on SUA.

In conclusion, we observed significant interactions between *LRP2* rs2544390 and BMI with respect to SUA levels among Japanese males and females with *SLC22A12 258WW*, *SLC2A9* rs11722228 *C* alleles, and *ABCG2 126QQ* and *141Q* alleles. The effect of BMI was significantly weaker among males with the *TT* genotype and significantly stronger among females with the *TT* genotype, such that the interactions were in the opposite direction between genders.

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CONFLICT OF INTEREST

The authors have declared that they have no conflicts of interest.

REFERENCES

1) Roddy E, Choi HK. Epidemiology of Gout. *Rheum Dis Clin North Am*, 2014; 40(2): 155–175.
2) Fenech G, Rajzbaum G, Mazighi M, Blacher J. Serum uric acid and cardiovascular risk: State of the art and perspectives. *Joint Bone Spine*, 2014 (impress)
3) Scire CA, Manara M, Cimmino MA, Govoni M, Salaffi F, Punzi L, Monti MC, Carrara G, Montecucco C, Matucci-Cerinic M, Minisola G. KING Study Collaborators; Gout impacts on function and health-related quality of life beyond associated risk factors and medical conditions: results from the KING observational study of the Italian Society for Rheumatology (SIR). *Arthritis Res Ther*, 2013; 15(5): R101.
4) Hirsch JD, Terkeltaub R, Khanna D, Singh J, Sarkin A, Shieh M, Kavanaugh A, Lee SJ. Gout disease-specific quality of life and the association with gout characteristics. *Patient Relat Outcome Meas*, 2010; 2010: 1–8.
5) http://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa10/toukei.html (accessed Mar 2nd, 2014)
6) Saag KG, Mikuls TR. Recent advances in the epidemiology of gout. *Curr Rheumatol Rep*, 2005; 7: 235–241.
7) Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, Perola M, Mangino M, Albrecht E, Wallace C, Farrall M, Johansson A, Nyholt DR, Aulchenko Y, Beckmann JS, Bergmann S, Bochud M, Brown M, Campbell H; EUROSPAN Consortium, Connell J, Dominiczak A, Homuth G, Lamina C, McCarthy MI; ENGAGE Consortium, Meitinger T, Mooser V, Munroe P, Nauck M, Peden J, Prokisch H, Salo P, Salomaa V, Samani NJ, Schlessinger D, Uda M, Völker U, Waeber G, Waterworth D, Wang-Sattler R, Wright AF, Adamski J, Whitfield JB, Gyllensten U, Wilson JF, Rudan I, Pramstaller P, Watkins H; PROCARDIS Consortium, Doering A, Wichmann HE; KORA Study, Spector TD, Peltonen L, Völzke H, Nagaraja R, Vollenweider P, Caulfield M; WTCCC, Illig T, Gieger C. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet,* 2009; 5: e1000504.
8) Kamatani Y, Matsuda K, Okada Y, Kubo M, Hosono N, Daigo Y, Nakamura Y, Kamatani N. Genome-wide association study of hematological and biochemical traits in a Japanese population. *Nat Genet*, 2010; 42: 210–215.
9) Cabezas F, Lagos J, Cespedes C, Vio CP, Bronfman M, Marzolo M-P. Megalin/LRP2 expression is induced by peroxisome proliferator-activated receptor-alpha and -gamma: implications for PPARs' roles in renal function. *PLoS One,* 2011; 6: e16792.
10) Ooka S, Matsui T, Nishioka K, Kato T. Autoantibodies to low-density-lipoprotein-receptor-related protein 2 (LRP2) in systemic autoimmune diseases. *Arthritis Res Ther*, 2003; 5(3): R174–80.
11) Taniguchi A, Kamatani N. Control of renal uric acid excretion and gout. *Curr Opin Rheumatol,* 2008; 20:

192–197.
12) Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, Hosoyamada M, Takeda M, Sekine T, Igarashi T, Matsuo H, Kikuchi Y, Oda T, Ichida K, Hosoya T, Shimokata K, Niwa T, Kanai Y, Endou H. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature,* 2002; 417(6887): 447–52.
13) Matsuo H, Chiba T, Nagamori S, Nakayama A, Domoto H, Phetdee K, Wiriyasermkul P, Kikuchi Y, Oda T, Nishiyama J, Nakamura T, Morimoto Y, Kamakura K, Sakurai Y, Nonoyama S, Kanai Y, Shinomiya N. Mutations in glucose transporter 9 gene *SLC2A9* cause renal hypouricemia. *Am J Hum Genet*. 2008; 83(6): 744–51.
14) Evans SA, Doblado M, Chi MM, Corbett JA, Moley KH. Facilitative glucose transporter 9 expression affects glucose sensing in pancreatic beta-cells. *Endocrinology*, 2009; 150(12): 5302–10.
15) Doyle LA, Yang W, Abruzzo LV, Krogmann T, Gao Y, Rishi AK, Ross DD. A multidrug resistance transporter from human MCF-7 breast cancer cells. *Proc Natl Acad Sci U S A*, 1998; 95(26): 15665–70.
16) Matsuo H, Takada T, Ichida k, Nakamura T, Nakayama A, Ikebuchi Y, Ito K, Kusanagi Y, Chiba T, Tadokoro S, Takada Y, Oikawa Y, Inoue H, Suzuki K, Okada R, Nishiyama J, Domoto H, Watanabe S, Fujita M, Morimoto Y, Naito M, Nishio K, Hishida A, Wakai K, Asai Y, Niwa K, Kamakura K, Nonoyama S, Sakurai Y, Hosoya T, Kanai Y, Suzuki H, Hamajima N, Shinomiya N. Common defects of ABCG2, a high-capacity urate exporter, cause gout: a functional-based genetic analysis in a Japanese population. *Sci Transl Med*, 2009; 1: 141–148.
17) Yamagishi K, Tanigawa T, Kitamura A, Köttgen A, Folsom AR, Iso H. The rs2231142 variant of the *ABCG2* gene is associated with uric acid levels and gout among Japanese people. *Rheumatology*, 2010; 49: 1461–1465.
18) Woodward OM, Köttgen A, Coresh J, Boerwinkle E, Guggino WB, Köttgen M. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. *Proc Natl Acad Sci*, 2009; 106(25): 10338–42.
19) Hamajima N, Naito M, Hishida A, Okada R, Asai Y, Wakai K. Serum uric acid distribution according to *SLC22A12* W258X genotype in a cross-sectional study of a general Japanese population. *BMC Med Genet*, 2011; 12: 33.
20) Hamajima N, Okada R, Kawai S, Hishida A, Morita E, Yin G, Wakai K, Matsuo H, Inoue H, Takada Y, Asai Y, Mori A, Naito M. Significant association of serum uric acid levels with *SLC2A9* rs11722228 among a Japanese population. *Mol Genet Metab*, 2011; 103: 378–382.
21) Hamajima N, Naito M, Okada R, Kawai S, Yin G, Morita E, Higashibata T, Tamura T, Nakagawa H, Matsuo H, Mori A, Wakai K. Significant interaction between *LRP2* rs2544390 in intron 1 and alcohol drinking for serum uric acid levels among a Japanese population. *Gene*, 2012; 503:131–136.
22) Asai Y, Naito M, Suzuki M, Tomoda A, Kuwabara M, Fukuda Y, Okamoto A, Oishi S, Ikeda K, Nakamura T, Misu Y, Katase S, Tokumasu S, Nishio K, Ishida Y, Hishida A, Morita E, Kawai S, Okada R, Wakai K, Tamakoshi A, Hamajima N. Baseline data of Shizuoka area in the Japan Multi-institutional Collaborative Cohort Study (J-MICC Study). *Nagoya J Med Sci*, 2009; 71: 137–144.
23) Hamajima N, Saito T, Matsuo K, Kozaki K, Takahashi T, Tajima K. Polymerase chain reaction with confronting two-pair primers for polymorphism genotyping. *Jpn J Cancer Res,* 2000; 91: 865–868.
24) http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (accessed Dec 2nd, 2013)
25) Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in US women – the Third National Health and Nutrition Examination Survey. *Arthritis Res Ther,* 2008; 10: R116.
26) Mumford SL, Dasharathy SS, Pollack AZ, Perkins NJ, Mattison DR, Cole SR, Wactawski-Wende J, Schisterman EF. Serum uric acid in relation to endogenous reproductive hormones during the menstrual cycle: findings from the BioCycle study. *Hum Reprod*, 2013; 28(7): 1853–62.
27) Ishii S, Miyao M, Mizuno Y, Tanaka-Ishikawa M, Akishita M, Ouchi Y. Association between serum uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women. *Osteoporos Int*, 2014; 25(3): 1099–105.
28) Jefferson JA, Escudero E, Hurtado ME, Kelly JP, Swenson ER, Wener MH, Burnier M, Maillard M, Schreiner GF, Schoene RB, Hurtado A, Johnson RJ. Hyperuricemia, hypertension, and proteinuria associated with high-altitude polycythemia. *Am J Kidney Dis*, 2002; 39(6): 1135–42.