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. Gout is considered a major public health issue because it greatly impacts on quality of life. 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.

Serum uric acid (SUA) levels are influenced by both genetic and non-genetic factors, including obesity and the consumption of alcohol. Recent genome-wide association studies (GWAS) have identified several genes associated with SUA. 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. LRP2 encodes low-density lipoprotein receptor-related protein 2 (megalin), a member of the low-density lipoprotein receptor (LDLR) family. 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. 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. GLUT9 also affects glucose-stimulated insulin secretion in mouse pancreatic β cells. 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. 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.

Our previous studies have confirmed the associations with these polymorphisms, and we observed an interaction with alcohol consumption on SUA in our investigation of the LRP2 intron 1 polymorphism rs2544390. Because obesity is an important factor that determines SUA, 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, 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. 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. 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. Another study showed that SUA was significantly higher in those with a SLC2A9 TT genotype after adjustment for age, while those with an ABCG2 126X allele and those without an ABCG2 141Q allele had elevated SUA levels.

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/m²) 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). Genotyping details have been described elsewhere.

**Statistical analysis**

The adjusted odds ratio (OR) and 95% confidence interval (CI) of BMI ≥25.0 or 18.5–25.0 (versus <18.5) 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.
SERUM URIC ACID, BMI, AND LRP2 rs2544390

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.

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 gout1) but also a risk factor for cardiovascular disease,1,2 it’s 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 \textit{SLC2A12}, \textit{SLC2A9}, and \textit{ABCG2} because it enabled us to remove the influence of genetic traits closely related to SUA levels on the effect of the \textit{LRP2} polymorphism on SUA.

In conclusion, we observed significant interactions between \textit{LRP2} rs2544390 and BMI with respect to SUA levels among Japanese males and females with \textit{SLC22A12} 258WW, \textit{SLC2A9} rs11722228 C alleles, and \textit{ABCG2} 126QQ and 141Q alleles. The effect of BMI was significantly weaker among males with the \textit{TT} genotype and significantly stronger among females with the \textit{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.

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SERUM URIC ACID, BMI, AND LRP2 rs2544390

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