SPANDIDOS PUBLICATIONS

The -1438A/G polymorphism in the 5-hydroxytryptamine receptor 2A gene is related to hyperuricemia, increased γ-glutamyl transpeptidase and decreased high-density lipoprotein cholesterol level in the Japanese population: A prospective cohort study over 5 years

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Abstract. This prospective cohort study in Japanese workers examined the relationship between the -1438A/G polymorphism in the 5-hydroxytryptamine receptor 2A gene and the development of positive findings for various lifestyle-related disorders. This study over the 5-year period, 1997-2002, included observations of several disorders in cohorts ranging between 560-1023 for males and 477-735 for females who had negative findings for each disorder at baseline. The criteria for development of the disorders were: hypertension, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or taking antihypertensive medication; overweight, body mass index (BMI) ≥25 kg/m^2; obesity, BMI ≥30 kg/m^2; new onset of cerebral stroke; metabolic abnormalities, glycosylated hemoglobin A1c >6.0%, total cholesterol ≥240 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, uric acid >7.0 mg/dl, γ-glutamyl transpeptidase ≥60 IU/l in males and ≥30 IU/l in females. Pooled logistic regression analyses were performed using the -1438A/G genotype and other potential factors as covariates. The odds ratios to AA genotype were significant for uric acid (GG, 0.52; AG, 0.59), obesity (AG, 0.24) in males and for high-density lipoprotein cholesterol (GG, 0.11; AG, 0.36), γ-glutamyl transpeptidase (GG, 0.53; AG, 0.62) and total cholesterol (GG, 1.84) in females. The present study is the first prospective cohort investigation to demonstrate that the -1438G allele has a protective effect against the development of a range of cardiovascular and metabolic disorders. This study indicates that the -1438A/G polymorphism is an independent factor for various disorders in the general Japanese population and suggests that targeting of this polymorphism may be beneficial for preventing these disorders in Japan.

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Introduction

In recent years, many genetic variations have been identified that are associated with congenital hereditary diseases and acquired chronic diseases such as hypertension and diabetes mellitus. These chronic diseases are considered to be polygenic and have multifactorial traits. For example, the development of these diseases may be influenced by various genes that interact reciprocally with a combination of host factors such as lifestyle and environmental factors. However, as genetic variants may protect against one disease whilst promoting another, it is necessary to analyze associations between polymorphisms and a number of different diseases and to evaluate the findings from a comprehensive point of view.

5-Hydroxytryptamine (5-HT, serotonin) is a monoamine neurotransmitter found in both the central and peripheral nervous systems, and is essential for a variety of physiological functions such as platelet aggregation, smooth muscle contraction and central nervous system functions including appetite, pain perception, mood and anxiety (1,2). The 5-HT receptor 2A (HTR2A) is one of the different subtypes of 5-HT receptor that mediate the various functions of 5-HT (2). HTR2A is thought to be involved in platelet aggregation, vascular and non-vascular smooth muscle contraction, perception, and emotion (3), with a common synonymous variant 102T/C of the gene having been described and shown to be associated with a variety of psychiatric disorders (4-8). A -1438A/G polymorphism in the promoter region of *HTR2A* has also been related to schizophrenia (9), anorexia nervosa

(10) and major depressive (11), obsessive-compulsive (12) and seasonal affective disorders (13). In addition to psychiatric disorders, several clinical studies using the HTR2A selective antagonists, ketanserin and sarpogrelate (14), have shown the HTR2A is also implicated in the pathogenesis of a wide variety of cardiovascular diseases. Recent studies have also reported associations between variants in *HTR2A* and physical diseases with the 102T/C polymorphism being related to hypertension (15), decreased high-density lipoprotein cholesterol (HDL-C) (16) and irritable bowel syndrome (17). As the -1438A/G polymorphism is in complete linkage disequilibrium with T102C (18,19), it is considered a possible candidate for pathogenic polymorphisms. On the basis of this evidence we considered it likely that the -1438A/G polymorphism may influence various lifestyle-related disorders.

The majority of earlier studies in this area have been case-control designs carried out on patients and controls. From an epidemiological point of view, in order to determine the influence of genetic polymorphisms in the occurrence of a specific disease it is necessary to undertake large-scale studies in the general population. This requirement prompted us to undertake a follow-up study on the relationship between the -1438A/G polymorphism in the *HTR2A* gene and the development of positive findings for a variety of lifestyle disorders. We consider that a longitudinal study of this type had the potential to detect epidemiological cause-and-effect relationships. The study used pooled logistic regression analysis to examine whether polymorphism in the gene was associated independently with the disorders when factors such as age, body mass index (BMI), lifestyle and biochemical data were taken into account.

Materials and methods

Subjects. This prospective cohort study included observations made over a 5-year period from 1997 to 2002. The target subjects were 3834 males and 2591 females who worked in 1997 at a zipper and sash factory in the Hokuriku district of Japan. All workers in this company underwent a legally required health check-up that included measurement of height, weight, and blood pressure, analysis of blood samples and a self-administered questionnaire. The workers were also asked to estimate their alcohol intake based on gou, a traditional Japanese drinking unit corresponding to 25 g of ethanol. The amount of ethanol consumption per week was calculated for all participants, who were then assigned to one of the following 5 groups: non-drinkers, <100 g/week, 100-199 g/week, 200-299 g/week, and ≥300 g/week. Smoking habits were classified as non-smoker, ex-smoker, smoking <20 cigarettes/day or ≥20 cigarettes/day, while habitual exercise was classified as absent, light (light exercise at least once a week without shortness of breath or palpitations), moderate (strenuous exercise for >20 min once or twice a week, with shortness of breath, palpitations and perspiration) or heavy (strenuous exercise >20 min more than twice a week, with shortness of breath, palpitations and perspiration). After excluding workers with missing data or those who had not provided written, informed consent for the analyses, the target subjects consisted of 1452 males and 1169 females. Subjects who had health examinations with complete data within the next year (1998) were also included in the study. Subjects who had a positive finding for any of the variables were subsequently excluded from the statistical analysis of that variable. This resulted in the size of the cohorts ranging from 560-1023 in males and from 477-735 in females (Table I). The ethics review boards of Kanazawa Medical University and the Graduate School of Medicine, Chiba University approved the study protocol.

Laboratory and clinical measurements. In 1997, buffy coat preparations were obtained from blood samples collected from each subject. The *HTR2A* -1438A/G genotype was determined by the direct polymerase chain reaction (20) using Ampdirect (Shimadzu, Kyoto, Japan) buffers following restriction fragment length polymorphism with *Msp*I (New England Biolabs, MA), an enzyme that cleaves the -1438G allele into 2 fragments (21). On the basis of evidence from a previous study (21) the primers used were 5'-TTGTGCAGA TTCCCATTAAGG-3' and 5'-CTAGCCACCCTGAGCC TATG-3'.

Blood pressure was measured once in the right arm after 5 min of rest in a seated position by well-trained nurses using a standard mercury sphygmomanometer. The measurements was taken between 9 a.m. and 3 p.m. throughout the study period, with measurements within 30 min of consuming a meal or undertaking heavy physical activity being avoided. The standard mercury sphygmomanometers were checked and calibrated every year. Mean blood pressure (mean BP) was calculated by multiplying the diastolic blood pressure (DBP) by two, adding the systolic blood pressure (SBP) and then dividing this sum by three. BMI and the levels of hematocrit, platelet count, alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), total serum cholesterol (TC), HDL-C, glycosylated hemoglobin A1c (HbA1c), creatinine and uric acid (UA) were also measured at part of the legally-required annual health examination. All these tests were carried out by comprehensive clinical testing laboratories that were authorized by official certification organizations. Because of this comprehensive quality control of all the clinical test processes we consider that the accuracy and reliability of the measurements were assured. The development of positive findings for hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg or initiation of antihypertensive medication) (22), overweight (≥25 kg/m^2) (23), obesity (≥30 kg/m^2) (23), HbA1c (>6.0%) (24), TC (≥40 mg/dl) (25), HDL-C (<40 mg/dl) (25), UA (>7.0 mg/dl) (26), GGT (≥60 IU/l in males, ≥30 IU/l in females) and cerebral stroke (new onset of cerebral infarction, subarachnoid hemorrhage or intracerebral hemorrhage) were treated as endpoints during the period of follow-up. While 2 male and 2 female subjects were diagnosed as hypertensive simply by the initiation of antihypertensive medication, no other subjects were diagnosed as having positive findings on the basis of taking medication. As the measurement of HDL was restricted to subjects aged >34 years, the number of subjects in that cohort was less than for the other target variables. A medical history including cerebral stroke was obtained during the annual health examination using a self-administered questionnaire. The responses to this questionnaire were confirmed by individual interviews conducted by occupational physicians.

The number of subjects and person-years observed for each variable in the study.

Sex	Hypertension	Overweight	Obesity	HbA1c	TC	HDL	UA	GGT	Cerebral stroke
Males									
No. of subjects examined	878	810	1023	973	936	560	882	939	1041
No. of subjects who developed	154	103	14	38	144	71	135	193	8
positive findings (%)	(17.5)	(12.7)	(1.4)	(3.9)	(15.4)	(12.7)	(15.3)	(20.6)	(0.8)
Total person-years of observation	3011	3016	3953	3811	3398	1795	3194	3399	4035
Incidence rate per 1000 person-years	51.1	34.2	3.5	10.0	42.4	39.6	42.3	56.8	2.0
Mean observed years per person	3.43	3.72	3.86	3.92	3.63	3.21	3.62	3.62	3.88
Age at entry	37.8±9.6	37.6±10.0	38.1±9.9	37.8±9.8	37.7±9.9	44.6±5.8	38.2±9.9	37.5±9.9	38.0±9.9
(mean ± standard deviation)									
Females									
No. of subjects examined	692	608	714	712	662	477	715	716	735
No. of subjects who developed	63	38	15	8	99	30	5	100	0
positive findings (%)	(9.1)	(6.3)	(2.1)	(1.1)	(15.0)	(6.3)	(0.7)	(14.0)	(0.0)
Total person-years of observation	2383	2157	2579	2614	2213	1600	2632	2483	2669
Incidence rate per 1000 person-years	26.4	17.6	5.8	3.1	44.7	18.8	1.9	40.3	0.0
Mean observed years per person	3.44	3.55	3.61	3.67	3.34	3.35	3.68	3.47	3.63
Age at entry	38.5±9.2	38.4±9.1	38.9±9.2	38.8±9.2	38.0±9.1	44.2±5.2	38.8±9.2	38.6±9.2	38.7±9.2
(mean ± standard deviation)									

Statistical analyses. In the univariate analyses, the genotypic and allelic frequencies of the -1438A/G polymorphism in *5HT2RA*, at the entry year were compared between the subjects who developed positive findings for each disorder and those who remained negative using the Chi-square test (genotypes) and Fisher's exact test (alleles).

In the multivariate analyses, pooled logistic regression was used to evaluate the influence of the -1438A/G genotype on the development of each positive finding. The following factors were used as a common set of covariates: alcohol consumption, smoking habits, habitual exercise, age, BMI, mean BP, hematocrit, platelet count, ALT, GGT, creatinine, TC, UA and HbA1c. The following variables were excluded from the relevant analytical model: mean BP (hypertension), BMI (overweight, obesity), HbA1c (HbA1c), TC (TC, HDL-C), UA (UA), GGT (GGT). The period of observation continued only as long as the subjects received an annual health check. The dummy variables for genotypes and other categorical variables were constructed in the analyses. The analyses were performed with SPSS 12.0J (SPSS Japan Inc., Tokyo, Japan) with P-values <0.05 being considered statistically significant.

Results

Subject population characteristics. Table I shows the number of subjects and cumulative person-years recorded in the analyses. The total person-years of observation ranged between 1795-4035 for males and 1600-2669 for females, with the mean observed years per person being 3.21-3.92 and 3.34-3.68 for males and females, respectively. Table II summarizes the frequencies of the genotypes and alleles grouped according to gender and development of positive findings. In males, the allelic frequencies for HbA1c and UA, and the genotypic frequencies for UA and GGT differed significantly between the subjects with positive and negative findings. For HbA1c, the -1438G allele was found more frequently in subjects who developed a positive finding compared to subjects who remained negative. For UA, the -1438A allele and AA genotype were found more frequently in subjects who developed a positive finding than in subjects who remained negative, while for GGT, the AA and GG genotypes were more frequent in subjects who developed positive findings than in those who remained negative. In females, the allelic frequencies for HDL-C, and genotypic frequencies for HDL-C and GGT differed significantly between the positive and negative subjects. For HDL-C, the A allele and AA genotype were more frequent in the positive subjects than in those who remained negative, while for GGT, only the AA genotype was more frequent in the positive subjects. No significant differences in these frequencies between positive and negative subjects were observed for any of the other variables. Multivariate analysis for cerebral stroke was not carried out in females because no subject developed this condition, while the GG genotype and AG genotype were combined in the analyses for cerebral stroke in males and UA in females, as no subject with the GG genotype developed either condition.

Development of positive findings. The results of the pooled logistic regression analysis are summarized in Table III. After adjustment for the effects of other potential covariates, there was a significant, negative association in males between the GG and AG genotypes for UA and the AG genotype for obesity and the development of positive findings. Compared to the AA genotype, the odds ratios and 95% confidence intervals (95% CI) for a positive finding of UA in male subjects with the GG and AG genotypes were 0.52 (0.31-0.86) and

Table II. Frequencies of genotype and allele grouped according to gender and the development of positive findings for each variable.

Sex	Positive finding	Geno-type	Hyper-tension (%)	Overweight (%)	Obesity (%)	HbA1c (%)	TC (%)	HDL (%)	UA (%)	GGT (%)	Cerebral stroke (%)
Males	Not developed	AA	195 (26.9)	195 (27.6)	270 (26.8)	256 (27.4)	220 (27.8)	128 (26.2)	189 (25.3)	199 (26.7)	283 (27.4)
		AG	367 (50.7)	362 (51.2)	517 (51.2)	479 (51.2)	396 (50.0)	251 (51.3)	388 (51.9)	393 (52.7)	522 (50.5)
		GG	162 (22.4)	150 (21.2)	222 (22.0)	200 (21.4)	176 (22.2)	110 (22.5)	171 (22.9)	154 (20.6)	228 (22.1)
	Developed	AA	45 (29.2)	22 (21.4)	7 (50.0)	5 (13.2)	36 (25.0)	18 (25.4)	49 (36.6)	57 (29.5)	3 (37.5)
		AG	78 (50.6)	55 (53.4)	3 (21.4)	21 (55.3)	78 (54.2)	40 (56.3)	60 (44.8)	82 (42.5)	5 (62.5)
		GG	31 (20.1)	26 (25.2)	4 (28.6)	12 (31.6)	30 (20.8)	13 (18.3)	25 (18.7)	54 (28.0)	0 (0.0)
		P-value	0.766	0.358	0.066	0.100	0.648	0.667	0.025	0.026	0.196
	Not developed	A	757 (52.3)	752 (53.2)	1057 (52.4)	991 (53.0)	836 (52.8)	507 (51.8)	766 (51.2)	791 (53.0)	1088 (52.7)
		G	691 (47.7)	662 (46.8)	961 (47.6)	879 (47.0)	748 (47.2)	471 (48.2)	730 (48.8)	701 (47.0)	978 (47.3)
	Developed	A	168 (54.5)	99 (48.1)	17 (60.7)	31 (40.8)	150 (52.1)	76 (53.5)	158 (59.0)	196 (50.8)	11 (68.8)
		G	140 (45.5)	107 (51.9)	11 (39.3)	45 (59.2)	138 (47.9)	66 (46.5)	110 (41.0)	190 (49.2)	5 (31.3)
		P-value	0.490	0.179	0.448	0.046	0.848	0.720	0.020	0.457	0.220
Females	Not developed	AA	157 (25.0)	140 (24.6)	177 (25.3)	180 (25.6)	149 (26.5)	107 (23.9)	181 (25.5)	148 (24.0)	188 (25.6)
		AG	319 (50.7)	294 (51.6)	354 (50.6)	352 (50.0)	283 (50.3)	226 (50.6)	353 (49.7)	318 (51.6)	368 (50.1)
		GG	153 (24.3)	136 (23.9)	168 (24.0)	172 (24.4)	131 (23.3)	114 (25.5)	176 (24.8)	150 (24.4)	179 (24.4)
	Developed	AA	20 (31.7)	12 (31.6)	6 (40.0)	1 (12.5)	21 (21.2)	14 (46.7)	1 (20.0)	36 (36.0)	0
		AG	31 (49.2)	14 (36.8)	5 (33.3)	4 (50.0)	48 (48.5)	12 (40.0)	4 (80.0)	42 (42.0)	0
		GG	12 (19.0)	12 (31.6)	4 (26.7)	3 (37.5)	30 (30.3)	4 (13.3)	0 (0.0)	22 (22.0)	0
		P-value	0.422	0.212	0.341	0.582	0.263	0.018	0.331	0.037	n.a.
	Not developed	A	633 (50.3)	574 (50.4)	708 (50.6)	712 (50.6)	581 (51.6)	440 (49.2)	715 (50.4)	614 (49.8)	744 (50.6)
		G	625 (49.7)	566 (49.6)	690 (49.4)	696 (49.4)	545 (48.4)	454 (50.8)	705 (49.6)	618 (50.2)	726 (49.4)
	Developed	A	71 (56.3)	38 (50.0)	17 (56.7)	6 (37.5)	90 (45.5)	40 (66.7)	6 (60.0)	114 (57.0)	0
		G	55 (43.7)	38 (50.0)	13 (43.3)	10 (62.5)	108 (54.5)	20 (33.3)	4 (40.0)	86 (43.0)	0
		P-value	0.224	1.000	0.582	0.326	0.123	0.011	0.753	0.067	n.a.

n.a., not available.

0.59 (0.39-0.87), and for a positive finding of obesity in male subjects with the AG genotype were 0.24 (0.06-0.98). In females, there was a significant, negative association between the GG and AG genotypes and the development of positive findings for HDL-C and GGT, and a significant, positive association between the GG genotype and the development of positive findings for TC. Compared to the AA genotype, the odds ratios and 95% CI for positive findings of HDL-C in female subjects with the GG genotype and AG genotype were 0.11 (0.03-0.42) and 0.36 (0.15-0.84), respectively, and for a positive finding of GGT in female subjects with the GG and AG genotypes were 0.53 (0.30-0.94) and 0.62 (0.38-0.99), respectively. The odds ratio and 95% CI for positive findings of TC in female subjects with the GG genotype was 1.84 (1.02-3.29) compared to subjects with the AA genotype.

Discussion

In the present study, prospective and multivariate analysis using pooled logistic regression revealed that the GG and AG genotypes were independent protective factors for the development of positive finding of UA in males. On the other hand, in females, the GG and AG genotypes were significant protective factors for positive findings of HDL-C and GGT. Our data also showed a negative association between obesity and the AG genotype in males and a positive association between the GG genotype and increased TC. Taken together, these results show that the G allele has protective effects against the development of these various disorders. Conversely, the A allele generally had harmful effects on the same disorders. To our knowledge, this is the first demonstration that the -1438A/G polymorphism in the *HTR2A* gene may influence multiple physical disorders. These results also provide convincing evidence that there is a gender difference in this influence of the -1438A/G polymorphism on these lifestyle-related diseases.

Important features of this study included the fact that it was a prospective cohort study with a long follow-up period of 5 years. In contrast, earlier studies that have investigated the association between polymorphisms of *HTR2A* and physical disorders such as hypertension or dyslipidemia have been cross-sectional in nature.

The second feature of our study was the method of statistical analysis. We used pooled logistic regression analyses in which each examination interval of 1 year was treated as a mini follow-up study. The advantage of this method was that it allowed evaluation of repeated measurements of lifestyle and blood-sampling data that may have changed over time in multivariate models. This method of analysis has been adopted more frequently in recent years (27) and has been validated

The results of the pooled logistic regression analysis on the development of positive finding for each variable.

		Males				Females			
			95% confidence intervals				95% confidence intervals		
Genotype (/AA)	Dependent variables	Odds ratio	Lower limit	Upper limit	P-value	Odds ratio	Lower limit	Upper limit	P-value
GG	Hypertension	0.85	0.52	1.37	0.500	0.61	0.28	1.29	0.195
	Overweight	1.50	0.83	2.71	0.178	1.04	0.45	2.41	0.924
	Obesity	0.73	0.19	2.75	0.641	0.66	0.17	2.56	0.546
	HbA1c	2.83	0.97	8.27	0.058	3.79	0.37	38.64	0.261
	TC	0.99	0.60	1.65	0.980	1.84	1.02	3.29	0.042
	HDL-C	0.89	0.42	1.89	0.764	0.11	0.03	0.42	0.001
	UA	0.52	0.31	0.86	0.011	n.a.	n.a.	n.a.	n.a.
	GGT	1.13	0.75	1.69	0.571	0.53	0.30	0.94	0.029
AG	Hypertension	0.91	0.61	1.34	0.622	0.79	0.43	1.43	0.433
	Overweight	1.26	0.76	2.10	0.373	0.54	0.24	1.21	0.136
	Obesity	0.24	0.06	0.98	0.047	0.38	0.10	1.44	0.155
	HbA1c	2.17	0.80	5.91	0.129	1.72	0.18	16.64	0.641
	TC	1.18	0.78	1.79	0.428	1.33	0.78	2.26	0.298
	HDL-C	1.05	0.58	1.90	0.882	0.36	0.15	0.84	0.018
	UA	0.59	0.39	0.87	0.009	n.a.	n.a.	n.a.	n.a.
	GGT	0.75	0.52	1.09	0.132	0.62	0.38	0.99	0.046
AG+GG	UA	n.a.	n.a.	n.a.	n.a.	0.64	0.06	7.19	0.716
	Cerebral stroke	0.38	0.08	1.92	0.242	n.a.	n.a.	n.a.	n.a.

The odds ratios were adjusted for other covariates included into the model. n.a., not available.

by D'Agostino *et al* (28). Other studies on this gene polymorphism have used univariate analyses only (15,17), or alternatively have been multivariate studies on a smaller number of factors than the present study (16). We therefore consider that the design of our study would have resulted in improved epidemiological accuracy.

Another notable feature of our study was that data were collected from >1500 Japanese workers who represented the general Japanese population to a greater extent than hospital outpatients. From an epidemiological point of view it is important to establish genotypic distribution and the association of polymorphisms with target diseases in the general population. Taken together, we consider that this study is highly informative from an epidemiological perspective.

Choi *et al* (16) measured the frequency of the 102T/C polymorphism in 648 Korean patients who were admitted to hospital for diagnostic coronary angiography. Using multivariate analysis adjusted for age, BMI, smoking status, history of diabetes mellitus, hypertension and coronary heart diseases they showed that the 102CC genotype of the *HTR2A* gene was associated with lower HDL-C levels. As previous studies have reported that the 102C allele and -1438G are in genetic linkage (18,19), their result was equivalent to the -1438G allele being related to lower HDL-C levels, a finding directly opposite to our results. With regards to hypertension, Liolitsa *et al* (15) investigated 342 hypertensive subjects aged >75 years and 319 community-based control subjects group living in the UK and found that the 102C allele was more frequent in hypertensive female subjects. In contrast, we did not detect a significant relationship with hypertension in our study, possibly as a consequence of ethnic differences between the study cohorts. It should also be noted that the participants enrolled in the studies of both Choi *et al* (16) and Liolitsa *et al* (15) were hospital patients. From an epidemiological point of view, such a sampling method may have resulted in significant selection bias, and preferably both case and control subjects should be enrolled randomly from the general population. We consider therefore, that selection bias may explain the discrepancies between the results our study and and previous studies. In order to improve sensitivity it is also desirable to incorporate other factors in multivariate analysis of the data such as alcohol consumption, and habitual exercise.

With regard to the development of UA and GGT, the present study is the first to demonstrate a potential association between these variables and the -1438A/G polymorphism in the *HTR2A* gene. We consider that the significant result in our prospective follow-up study provides additional important information on the etiology of these disorders.

Recently an investigation on the functional effects of -1438A/G using two reporter gene assays showed that the -1438A/G polymorphism has the potential to modulate *HTR2A* promoter activity (29). As a result, promoter activity was greater with the A allele than in the G allele. Those findings suggested that the -1438A/G polymorphism was responsible for the associations between both polymorphisms and those phenotypes (29). Higher promoter activity of the A allele may yield a larger number of HTR2A and increased sensitivity to 5-HT. However, the etiological mechanism of

this effect has yet to be clarified in detail. Our study does not exclude the possibility that other variants around the -1438A/G polymorphism may influence a wide range of cardiovascular and metabolic disorders in the Japanese population. Therefore, future detailed investigations are necessary on the etiology of these changes and whether haplotypes of -1438A/G and other *HTR2A* variants are associated with these disorders.

In conclusion, this study indicates clearly that the -1438A/G polymorphism is an independent factor for decreased HDL-C and increased UA and GGT in the general Japanese population, and suggests that targeting of this polymorphism may be beneficial when attempting to prevent such disorders in this population.

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