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Association of G-Protein β3 Subunit C825T Polymorphism with Seasonal Variations in Mood and Behavior

Yoon-Ju Nam[1*], Chul-Hyun Cho[1,2*], Leen Kim[1,2], and Heon-Jeong Lee[1,2,3] ✉

[1]Department of Psychiatry, Korea University College of Medicine, Seoul, Republic of Korea
[2]Korea University Chronobiology Institute, Seoul, Republic of Korea
[3]Department of Biomedical Science, Korea University College of Medicine, Seoul, Republic of Korea

Objective Seasonal affective disorder and seasonal changes in mood and behavior are associated with several genes that regulate circadian rhythms. In this study, we investigated the relationship between the C825T polymorphism of the G-protein β3 subunit and seasonal variations in mood and behavior in a young healthy Korean population.

Methods A total of 507 young Korean participants were recruited through a newspaper advertisement, and their seasonality was evaluated by the Korean version of the Seasonal Pattern Assessment Questionnaire to assess the global seasonality score (GSS). We analyzed the CC, CT, and TT genotypes and their association with the GSS score and subscales.

Results T allele carriers of the *GNB3* C825T polymorphism were more likely to score higher on body weight and GSS. In the female group, the T allele carriers obtained significantly high total GSS and its subscale scores for mood, body weight, energy level, and appetite; however, differences in genotypes and allele carriers were also observed in the male participants.

Conclusion These results suggested that *GNB3* C825T polymorphism plays a role in seasonal variations in mood, body weight, energy level, and appetite in a Korean population, particularly in females. **Psychiatry Investig 2018;15(2):200-204**

Key Words Seasonality, *GNB3*, Seasonal affective disorder, Genetic association.

INTRODUCTION

Seasonal affective disorder (SAD) is a condition that is related to seasonal mood changes recurring annually.[1] According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[2] depression with a seasonal pattern means having a depressive episode that begins and ends during a specific season annually for at least two years and more seasons of depression than seasons without depression over a lifetime. In general, SAD is accompanied with atypical depressive symptoms, including cravings for carbohydrates, hypersomnia, and prominent fatigue.[3] The pathophysiology of SAD is closely related to circadian rhythm changes, including abnormalities in core body temperature, cortisol levels, and diurnal variations of melanin levels.[4] Guanine nucleotide proteins (G-proteins) may play a role in circadian rhythm regulation.[5] Postmortem brain studies have also found that G-proteins are implicated in the pathophysiology of affective disorders and the mechanism of action of antidepressants and mood stabilizers.[6] Moreover, genetic variations in G-protein, which is probably involved in the endogenous circadian clock, may influence not only the circadian rhythm but also the mood in accordance with seasonal changes.[7]

G-proteins are important regulatory components in determining the specificity and temporal characteristics involved in signal transduction. These proteins are composed of α, β, and γ subunits, where both α and βγ subunits serve as transduction molecules.[8] A single nucleotide polymorphism (SNP) of C825T in the axon of 10 genes that encode the β3 subunit of the heterotrimeric G-proteins (*GNB3*) has been a topic of interest. The presence of the T-allele leads to a splice variant, Gβ3s, which is associated with an altered response to G-protein-activating agents in human cell lines and platelets.[9] *GNB3* C825T polymorphism is associated with various medical conditions, such as hypertension, obesity, and functional

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✉ **Correspondence:** Heon-Jeong Lee, MD, PhD
Department of Psychiatry, Anam Hospital, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, Seoul 02841, Republic of Korea
Tel: +82-2-920-5815, **Fax:** +82-2-929-7679, **E-mail:** leehjeong@korea.ac.kr

*These authors contributed equally to this work.

dyspepsia, and sildenafil response.[10-12] *GNB3* C825T polymorphism is also involved in psychiatric disorders, which is associated with the severity or treatment of major depressive disorders in a Korean population[13] and German case-control study participants.[14] In addition, *GNB3* C825T polymorphism was found to be associated with schizophrenia[15] and recurrent winter depression or seasonal affective disorder (SAD).[16-18] SAD has a strong genetic component,[18] which is similar to other types of affective disorders, and reduced levels of Gβ have been found in the leukocytes of patients with SAD.[18] In the present study, we aimed to investigate the association between *GNB3* C825T polymorphism and seasonal variations in mood and behaviors in a homogenous young healthy Korean population.

METHODS

Participants

A total of 507 healthy Korean adults aged between 18 and 35 years were recruited through a newspaper advertisement. Among the participants, 300 were men and 207 were women. Participants were diagnosed to be free of lifetime or current psychiatric disorders by an experienced psychiatrist through the mini-international neuropsychiatric interview. Participants with a family history of substance abuse or major psychiatric disorders (e.g., schizophrenia or mood disorders) were excluded. The participants were unrelated Korean adults who reside in Seoul and free of any major medical problems. All the participants provided an informed consent before enrolling in the study. Study protocols were approved by the Ethics Committee of Korea University (IEC 1067), and the study was conducted according to the Declaration of Helsinki. Other findings related to these participants have been previously reported.[19,20]

Assessment of seasonality

A Korean version of the Seasonal Pattern Assessment Questionnaire (SPAQ)[21] was provided to the participants to assess the global seasonality score (GSS). The GSS is a retrospective self-report that evaluates seasonal variations in sleep, appetite, mood, energy level, weight, and social behavior. The score of each item ranges from 0 (no change) to 4 (extremely marked change). Thus, the sum of the 6 items will range from 0 to 24. Given that the GSS is obtained by adding all 6 items, the sum of the items will range from 0 to 24. Participants also scored their degree of difficulty with seasonal changes from 0 to 5 (none, mild, moderate, marked, severe, or extremely severe, respectively). Based on Kasper's criteria,[22] the participants were categorized into the SAD group, subsyndromal SAD group, (both group categorized as seasonals), and non-seasonal group. Participants with SAD were defined as those with a GSS higher than 11 and a score above 2 on difficulty with seasonal changes. Participants with subsyndromal SAD were those with a GSS of 11 or higher and a score of 0 and 1 on difficulty with seasonal changes or those with a GSS of 11 or above and a score above 1 on difficulty with seasonal changes. The participants were categorized into winter or summer type according to the seasons (autumn and winter or spring and summer) when they feel worst. Individuals with summer-type SAD presented agitation, insomnia, decreased appetite, weight loss, and heat and humidity intolerance, whereas those with winter-type SAD experienced carbohydrate craving, hypersomnia, and fatigue.[23] The biological background of individuals with summer-type SAD is different from that of individuals with winter-type SAD.[24,25] Therefore, the group with a summer-type SAD (29 participants) were excluded. A total of 478 participants were evaluated.

Genotyping

Genomic DNA was extracted from leukocytes using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). Genotyping was performed via high-resolution melting curve analysis.[26] The polymerase chain reaction (PCR) was performed in a 20-μL reaction mixture and a 96-well CFX96 real-time PCR system (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The reaction mixture included 2 μL of genomic DNA; 200 mM of primer *GNB3*, forward primer 5′-GAT TTG TGG GAA CTT CTT GAG-3′, and reverse primer 5′-ATG AGG ACT GTT TGA TGT GT-3′; SsoFast EvaGreen Supermix (1×final concentration; BioRad Laboratories, Inc.); and sterile H_2O. The amplification protocol was as follows: initial denaturation at 98°C for 3 min, followed by 39 cycles of denaturation at 98°C for 10 s and 58°C for 20 s. After the initial denaturation at 95°C for 10 s and 65°C for 10 s, melting curves were generated from 65−95°C, in increments of 0.2°C at each cycle. Melting profiles were analyzed with Precision Melt Analysis software (BioRad Laboratories, Inc.).

Statistical analysis

The presence of Hardy–Weinberg equilibrium was tested with the χ^2 test for goodness of fit. The χ^2 test was also used to compare genotype differences between the seasonal and non-seasonal groups. The association between the continuous variables with the total GSS scores and subscores was evaluated via Student's t-test or one-way analysis of variance. To detect a variant with an effect size of 0.15 with 80% power, a total of 429 samples (df=2) or 349 (df=1) is required. Statistical analyses were carried out with SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). A probability value (p value) less than 0.05 was considered statistically significant.

RESULTS

According to the Kasper's criteria, 61 (12.0%; 47 with winter-type SAD and 14 with summer-type SAD) out of 507 participants were classified in the SAD category and 52 (10.3%; 37 with winter-type SAD and 15 with summer-type SAD) out of 507 participants were included in the subsyndromal SAD category. Therefore, 22.3% of the participants were considered seasonals. As previously mentioned, 29 participants with summer-type SAD were excluded. Thus, 478 out of 507 participants were evaluated. The genotype distribution of the *GNB3* C825T polymorphism in individuals with and without seasonal disorders are shown in Table 1. Among the 478 participants, the genotypes of the *GNB3* C825T polymorphism are C/C 155 (32.4%), C/T 243 (61.7%), and T/T 80 (20.3%). No significant differences were observed in the genotype distributions of the individuals with and those without seasonal disorder (n=84 and n=394, respectively) (χ^2= 3.224; p=0.199). The presence of T allele carriers (T/T and C/T) of the *GNB3* C825T polymorphism was not significantly observed in individuals with seasonal disorder compared with those without seasonal disorder (χ^2=2.565, p= 0.109). Table 2 shows the total GSS and scores for its 6 subitems of all the participants. The GSS and scores of the 6 subscales were not significantly different among the genotypes of the *GNB3* C825T polymorphism (F=1.412; p=0.245). However, T allele carriers of the *GNB3* C825T polymorphism were more likely to have a higher score on body weight and GSS in general. Based on the evaluation of the female group, significant differences were found in the total GSS and subscale scores (mood, body weight, energy level, and appetite) of the T allele carriers.

DISCUSSION

G-protein-mediated signal transduction is closely related with the pathogenesis of affective disorders that are influenced by monoaminergic neurotransmissions or phototransduction processes (which is more specific for SAD).[27,28] Previous studies by Avissar et al.[29] suggested that light therapy may have effects on SAD because it helps normalize the transducin (a G-protein in the retina) levels, which can reduce the symptoms of winter depression. Thus, the alteration of the G-protein signal transduction, including *GNB3* C825T polymorphism, could lead to the dysregulation of the response to light, causing seasonal alterations in mood and the pathophysiology of SAD.

Previous studies have found no association between *GNB3* C825T polymorphism and seasonal disorder.[17] In addition, bipolar disorder was suspected to be a confounding factor. On the contrary, Zill et al.[14] found that T-allele carriers were likely to experience the onset of SAD at an early age and obtain high rating scores for non-seasonal depression.

In the present study, the prevalence rates of SAD and subsyndromal SAD were 12.0% (9.3% with winter-type and 2.8% with summer-type) and 10.3% (7.3% with winter-type and 3% with summer-type), respectively. Unlike in Western countries,[20,30] the prevalence rate of the summer-type SAD and subsyndromal SAD were relatively high, which was consistent with other studies or researches conducted in Asian countries.[31,32] This phenomenon was formerly reported in Korean populations.[33,34] The high prevalence of summer-type SAD in eastern Asian countries, including Korea, could be due to the hot and humid climates. Since summer-type SAD is different from winter-type SAD[24,25] due to various factors including decreased light exposure, we excluded the participants with the summer-type seasonal disorder from the analysis.

In the current study, the GSS and scores of its subscales revealed genotypic differences in the *GNB3* C825T polymorphism. Compared with the participants with the C/C genotype, T allele carriers (with T/T and C/T genotypes) of the *GNB3* C825T polymorphism had higher GSS values and sub-

Table 1. Genotype distribution of the *GNB3* C825T polymorphism in individuals with and those without seasonal disorder

	C/C (%)	C/T (%)	T/T (%)	Genotype		T allele carrier vs. non-carrier
				χ^2	p value	p value
Total				3.224	0.199	0.109
Participants with seasonal disorder, N=84	21 (25.0)	45 (53.6)	18 (21.4)			
Participants without seasonal disorder, N=394	134 (34.0)	198 (50.3)	62 (15.7)			
Men				0.858	0.651	0.534
With seasonal disorder	14 (29.8)	23 (48.9)	10 (21.3)			
Without seasonal disorder	79 (34.5)	113 (49.3)	37 (16.2)			
Women				3.180	0.204	0.114
With seasonal disorder	7 (18.9)	22 (59.5)	8 (21.6)			
Without seasonal disorder	55 (33.3)	85 (51.5)	25 (15.2)			

Table 2. Global seasonal score and 6 subscores of the individuals with *GNB3* C825T polymorphism

	CC	CT	TT	ANOVA		T carrier vs. non-carrier
				F	p value	p value
Total						
GSS	4.69	5.53	5.24	2.106	0.123	0.049*
Sleep duration	0.91	1.09	0.96	2.097	0.124	0.087
Social behavior	0.60	0.63	0.60	0.073	0.930	0.788
Mood	0.90	1.05	0.96	1.211	0.299	0.167
Body weight	0.59	0.77	0.71	2.156	0.117	0.044*
Energy level	0.95	1.11	1.11	1.505	0.223	0.083
Appetite	0.74	0.87	0.86	0.965	0.382	0.166
Women						
GSS	4.26	6.16	5.36	4.866	0.009*	0.004*
Sleep duration	0.87	1.14	1.03	1.762	0.174	0.077
Social behavior	0.48	0.64	0.64	0.747	0.475	0.222
Mood	0.74	1.20	1.03	4.249	0.016*	0.006*
Body weight	0.61	0.97	0.70	4.160	0.017*	0.021*
Energy level	0.81	1.19	1.06	3.147	0.045*	0.016*
Appetite	0.74	1.07	0.91	2.439	0.090	0.043*
Men						
GSS	4.98	5.03	5.15	0.028	0.973	0.874
Sleep duration	0.94	1.05	0.91	0.673	0.511	0.473
Social behavior	0.68	0.63	0.57	0.230	0.795	0.558
Mood	1.00	0.94	0.91	0.146	0.865	0.605
Body weight	0.58	0.60	0.72	0.558	0.573	0.593
Energy level	1.04	1.05	1.15	0.213	0.808	0.786
Appetite	0.74	0.72	0.83	0.231	0.794	0.956

Data are reported as means. *p<0.005. GSS: global seasonality score

scale scores for body weight. These findings were more prevalent in the female group, with T allele carriers that have higher total GSS and subscale scores for mood, body weight, energy level, and appetite. Moreover, the T allele of the *GNB3* C825T polymorphism is associated with seasonal variations in mood and behavior, particularly in women. This result supports those of previous studies on the relationship between SAD and the *GNB3* C825T polymorphism genotypes.[16] However, no significant differences were observed between the seasonality (seasonals and non-seasonals) and genotypes in all groups, even in the female subgroup. This result could be explained by the definition of individuals with and those without SAD. Since seasonal disorders are classified as SAD and subsyndromal SAD, the criteria for the definition may not be supported. Further studies on the association between SAD alone and the genotypes should be conducted to support the hypothesis.

Another important point is that the *GNB3* C825T polymorphism is associated with seasonal variations only in women, which is not in accordance with the results of our previous studies that show significant differences in male medical students.[24] This result is probably due to the characteristics of the previous sample group, which consists of medical students. Medical students will be more likely to answer the question sensitively because of their knowledge on seasonal depression. In other words, if someone has prior knowledge on seasonal variation, he/she may have responded more sensitively to the questionnaire, which could be a confounding factor overestimating the correlation between the genes and seasonal disorders. In the case of women, they may possibly recognize seasonal changes more sensitively than men, even without prior knowledge.

Population stratification bias was not excluded. However, the Korean population is characterized by a relatively high degree of genetic homogeneity.[35] Therefore, population stratification bias is unlikely in our sample. Furthermore, our sample was composed of young individuals from the same homogenous ethnic group who reside in the same place. Therefore, several confounding factors were excluded in this study. In conclusion, the present study showed an association between the *GNB3* gene and seasonal variations in mood and behavior in a Korean population. Further studies with a larger sample size should be conducted to evaluate the possible association between genes, other than the *GNB3* genes, and seasonal variation in mood and behavior.

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