Serotonin Transporter and COMT Polymorphisms as Independent Predictors of Health-Related Quality of Life in Patients with Panic Disorder

Eunho Kang,1* Ah Young Choe,2* Borah Kim,1 Jun-Yeob Lee,1 Tai Kiu Choi,3 Hae-Ran Na,4 and Sang-Hyuk Lee3

1Department of Psychiatry, Inwha Hospital, Pocheon, Korea; 2Seongnam Mental Health Care Center, Seongnam, Korea; 3Department of Psychiatry, CHA Bundang Medical Center, CHA University, Seongnam, Korea; 4Department of Psychiatry, CHA Gumi Medical Center, CHA University, Gumi, Korea; 5Department of Psychiatry, the Catholic University of Korea, Seoul, Korea

*Eunho Kang and Ah Young Choe contributed equally to this work and should be considered as co-first authors.

Received: 13 July 2015 Accepted: 15 February 2016

Address for Correspondence:
Sang-Hyuk Lee, MD
Department of Psychiatry, CHA Bundang Medical Center, CHA University, 11 Yatap-ro 60beon-gil, Bundang-gu, Seongnam, Korea
E-mail: sanghyuk.lee70@gmail.com

Funding: This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (2011-0023359) to S.H. Lee.

INTRODUCTION

Panic disorder (PD) is a common chronic condition associated with significant social morbidity and increased health care utilization (1,2). There is growing evidence that poor health-related quality of life (HRQOL) is noted in patients with PD (3-5) even in remission state (6). However, little is known about the factors affecting HRQOL in patients with PD. The authors examined whether 5-HTTLPR tri-allelic approach and Cathechol-O-methyltransferase (COMT) Val158Met polymorphism can predict HRQOL in patients with PD controlling for sociodemographic factors and disorder-related symptom levels. The sample consisted of 179 patients with PD consecutively recruited from an outpatient clinic and age- and gender ratio-matched 110 healthy controls. The SF-36 was used to assess multiple domains of HRQOL. Hierarchical multiple regression analysis was performed to determine the independent effect of the 5-HTTLPR and COMT Val158Met on the SF-36 in panic patients. Patients with PD showed lowered HRQOL in all sub-domains of the SF-36 compared to healthy controls. The 5-HTTLPR independently and additively accounted for 2.2% of variation (6.7% of inherited variation) of perceived general health and the COMT Val158Met independently and additively accounted for 1.5% of variation (5.0% of inherited variance) of role limitation due to emotional problems in patient group. The present study suggests that specific genetic polymorphisms are associated with certain domains of HRQOL and provides a new insight on exploring the factors that predict HRQOL in patients with PD.

Keywords: Quality of Life; Panic Disorder; 5-HTTLPR; COMT Val158Met

There is growing evidence of poor health-related quality of life (HRQOL) in patients with panic disorder (PD). However, little is known about the factors affecting HRQOL in patients with PD. The authors examined whether 5-HTTLPR tri-allelic approach and Cathechol-O-methyltransferase (COMT) Val158Met polymorphism can predict HRQOL in patients with PD controlling for sociodemographic factors and disorder-related symptom levels. The sample consisted of 179 patients with PD consecutively recruited from an outpatient clinic and age- and gender ratio-matched 110 healthy controls. The SF-36 was used to assess multiple domains of HRQOL. Hierarchical multiple regression analysis was performed to determine the independent effect of the 5-HTTLPR and COMT Val158Met on the SF-36 in panic patients. Patients with PD showed lowered HRQOL in all sub-domains of the SF-36 compared to healthy controls. The 5-HTTLPR independently and additively accounted for 2.2% of variation (6.7% of inherited variation) of perceived general health and the COMT Val158Met independently and additively accounted for 1.5% of variation (5.0% of inherited variance) of role limitation due to emotional problems in patient group. The present study suggests that specific genetic polymorphisms are associated with certain domains of HRQOL and provides a new insight on exploring the factors that predict HRQOL in patients with PD.

Keywords: Quality of Life; Panic Disorder; 5-HTTLPR; COMT Val158Met

There is growing evidence of poor health-related quality of life (HRQOL) in patients with panic disorder (PD). However, little is known about the factors affecting HRQOL in patients with PD. The authors examined whether 5-HTTLPR tri-allelic approach and Cathechol-O-methyltransferase (COMT) Val158Met polymorphism can predict HRQOL in patients with PD controlling for sociodemographic factors and disorder-related symptom levels. The sample consisted of 179 patients with PD consecutively recruited from an outpatient clinic and age- and gender ratio-matched 110 healthy controls. The SF-36 was used to assess multiple domains of HRQOL. Hierarchical multiple regression analysis was performed to determine the independent effect of the 5-HTTLPR and COMT Val158Met on the SF-36 in panic patients. Patients with PD showed lowered HRQOL in all sub-domains of the SF-36 compared to healthy controls. The 5-HTTLPR independently and additively accounted for 2.2% of variation (6.7% of inherited variation) of perceived general health and the COMT Val158Met independently and additively accounted for 1.5% of variation (5.0% of inherited variance) of role limitation due to emotional problems in patient group. The present study suggests that specific genetic polymorphisms are associated with certain domains of HRQOL and provides a new insight on exploring the factors that predict HRQOL in patients with PD.

Keywords: Quality of Life; Panic Disorder; 5-HTTLPR; COMT Val158Met
the role of 5-HTTLPR in psychiatric researches (21,24,25). In the present study, S or L allele was designated as S' whereas L allele as L'.

COMT is a major enzyme that metabolizes catecholamines including dopamine and norepinephrine and the enzymatic activity exhibits allelic variation according to the genetic locus COMT Val158Met (26,27). COMT Val allele encodes for valine, associated with high activity whereas the Met allele encodes for methionine at position 108/158. Research has shown that COMT Val158Met is associated with panic disorder (15).

Thus, the present study was to examine whether 5-HTTLPR and COMT Val158Met could be independent predictors of HRQOL in patients with PD controlling for sociodemographic data and illness-related symptomatology.

MATERIALS AND METHODS

Participants

The sample consisted of 179 panic patients with or without agoraphobia who met the diagnostic criteria in the Structured Clinical Interview for DSM-IV (SCID-IV) (28) by experienced psychiatrists. They were recruited consecutively at the Department of Psychiatry of CHA Bundang Medical Center. Age- and gender ratio-matched 110 healthy controls were recruited by local advertisement and referrals. All subjects were 18 to 70 years old, unrelated, and of Korean ancestry. Exclusion criteria included any history of schizophrenia, bipolar disorder, alcohol and substance abuse or dependence, mental retardation, and current or past serious medical or neurological disorders.

Measures

The SF-36 (12,29) was used to determine HRQOL in patients with PD. It consists of eight subscales: physical functioning (the ability to perform a range of physical activities), role physical (the impact of physical health on usual role activities), bodily pain, general health (overall perception of personal health), vitality (energy and fatigue), social functioning (interference of physical and emotional problems in social activities), role emotional (impact of emotional problems on usual role activities), and mental health (psychological distress and well-being). The raw scores of SF-36 were transformed to a 0 to 100 range with higher scores indicating better HRQOL. The Panic Disorder Severity Scale (PDSS) (30) was used to assess the overall panic-related symptoms. Depressive symptoms were determined by the Beck Depression Inventory (BDI) (31).

Genotyping

Genomic DNA was extracted from blood (stored frozen) using a G-DEXTM II Genomic DNA Extraction Kit (Intron Biotechnology, Seongnam, Korea). The genotyping was based upon analysis of primer extension products generated from previously amplified genomic DNA using a chip-based matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry platform (Sequenom, San Diego, CA, USA). Genotyping for the triallelic 5-HTTLPR was performed as previously described method (32) with slight modification. Traditional biallelic polymerase chain reaction (PCR) analysis yields an “S” 486 bp and an “L” 529 bp fragment. MSPI restriction enzyme digestion analysis were also performed and resulted in the following fragments: 340, 127, and 62 bp for the L allele, 297, 127, and 62 bp for the S allele, 174, 166, 127, and 62 bp for the L allele and 166, 131, 127, and 62 bp for the S allele. The COMT Val158Met was analyzed as previously described method (16).

Statistical analysis

Pearson correlation coefficients measured the linear relationship between the SF-36 subscales and age, education level, duration of illness, and clinical data. For binary measures, Student’s t-test was used to compare mean scores of the SF-36. For categorical variables with more than 2 levels, one-way analysis of variance (ANOVA) was used to compare the SF-36 scores. Hardy-Weinberg equilibrium was tested using χ² test. The Bonferroni correction was applied for the multiple tests according to the two genetic polymorphisms. Hierarchical multiple regression analysis was performed to examine whether 5-HTTLPR or COMT Val158Met could independently predict the subscales of SF-36 controlling for age, gender, and other variables that were statistically significant in bivariate analysis. Tests were two-tailed and alpha was set at 0.05. Data analysis was conducted by using SPSS version 20 software (SPSS, Inc., Chicago, IL, USA).

Ethics statement

All study procedures complied with CHA Bundang Medical Center institutional review board regulations (IRB number: 2011-164) and Declaration of Helsinki. After a complete description of the study was given to the subjects, written informed consent was obtained.

RESULTS

Table 1 displays sociodemographic and clinical features of the sample. Of the 179 patients with PD, 96 (53.6%) were female, with a mean age of 39.1 years (SD = 10.6), a mean education of 12.9 years (SD = 2.9). One-hundred seven patients (65.4%) were diagnosed as PD with agoraphobia. Patients with PD showed lowered HRQOL in all sub-domains of the SF-36 compared to healthy controls. Panic patients were less educated and had less amount of monthly income. More divorced/separated/widowed subjects were in patient group. Subjects in unemployed states were more in patient group than in normal control group.

In patients with PD, male gender was related with better function in terms of physical functioning, bodily pain, and vitality.
Age was positively correlated with the vitality, role-emotional, and mental health. Education was associated with better QOL of physical functioning, role-physical, and bodily pain. Employment status was associated with better QOL in all subscales of the SF-36 except for role-physical and role-emotional. Patients with higher monthly income reported better QOL except for role-emotional. Married patients reported better role-physical, vitality, social functioning, role-emotional, and mental health compared to those who had never married. Both the PDSS and BDI were negatively correlated with all domains of the SF-36 (Table 2).

The genotype frequencies in the 5-HTTLPR and COMT Val<sub>108</sub>Met in patient group were in Hardy-Weinberg equilibrium (SS' = 129 [72.1%]; S'L' = 46 [25.7%]; L'L' = 4 [2.2%], P = 1.0 and Val/Val = 94 [52.5%]; Met/Val = 73[40.8%]; Met/Met = 12 [6.7%], P = 0.91). Panic patients with 5-HTTLPR SS' showed a trend to be associated with poorer general health (corrected P = 0.076) compared to L' carriers. Patients with COMT Val/Val were significantly associated with poor role-emotional (corrected P = 0.032) (Table 2). In hierarchical multiple regression analysis, 5-HTTLPR SS' predicted poor general health (ΔR² = 0.022, P = 0.018). COMT Val/Val also predicted poor role-emotional (ΔR² = 0.015, P = 0.048) controlling for sociodemographic factors and disorder-related symptom levels (Table 3).

**DISCUSSION**

Patients with PD showed lowered HRQOL in all sub-domains of the SF-36 compared to healthy controls which is largely consistent with previous reports (3-5). In patient group, the tri-allelic approach of 5-HTTLPR independently and additively accounts for 2.2% of variation (6.7% of inherited variance) of general health (i.e. S'S' with poor HRQOL). The COMT Val<sup>108</sup>Met independently and additively accounts for 1.5% of variation (5.0% of inherited variance) of role-emotional (i.e., COMT Val/Val with poor HRQOL). To our knowledge, this is the first study to examine the independent effect of specific genetic polymorphisms on the HRQOL in patients with PD. In our data, socio-economic variables accounted for 7%-20% of each domains of the SF-36. Disorder-related symptom levels in terms of PDSS and economic variables accounted for 7%-20% of each domains of the SF-36. Disorder-related symptom levels in terms of PDSS and BDI scores explained 10%-25% additionally which is largely consistent with previous reports (3-5). In patient group, the tri-allelic approach of 5-HTTLPR independently and additively accounts for 2.2% of variation (6.7% of inherited variance) of general health (i.e. S’S’ with poor HRQOL). The COMT Val<sup>108</sup>Met independently and additively accounts for 1.5% of variation (5.0% of inherited variance) of role-emotional (i.e., COMT Val/Val with poor HRQOL). To our knowledge, this is the first study to examine the independent effect of specific genetic polymorphisms on the HRQOL in patients with PD. In our data, socio-economic variables accounted for 7%-20% of each domains of the SF-36. Disorder-related symptom levels in terms of PDSS and BDI scores explained 10%-25% additionally which is largely consistent with previous results (3,7).

The implications of the 5-HTTLPR in panic disorder have been inconsistent. Kim et al. (33) reported no association between the 5-HTTLPR and PD in a Korean sample. Recent data of ours also suggest that even tri-allelic approach shows no direct association between the 5-HTTLPR and PD in a Korean sample (34). Taken together, the present study suggests that the 5-HTTLPR is related with specific domains (i.e., perception of...
Table 2-1. Factors associated with health-related quality of life in patients with panic disorder

| Factors                  | Continuous variables | Dichotomous variables |
|--------------------------|-----------------------|------------------------|
|                          | r                     | P                      | Mean (SD) for | P | Mean (SD) for | P | Mean (SD) for | P | Mean (SD) for | P |
|                          | r                     | P                      | F              |   | r              | P | F              |   | F              |   | F              |   |
| Age                      | 0.081                 | 0.278                  | 0.135          | 0.071 | 0.044          | 0.556 | -0.012        | 0.873 |
| Education                | 0.215                 | 0.004                  | 0.193          | 0.010 | 0.254          | 0.001 | 0.125         | 0.095 |
| Length of illness        | -0.106                | 0.159                  | 0.032          | 0.675 | -0.046         | 0.540 | -0.070        | 0.348 |
| PDSS                     | -0.387                | < 0.001                | -0.414         | < 0.001 | -0.470        | < 0.001 | -0.429        | < 0.001 |
| BDI                      | -0.420                | < 0.001                | -0.417         | < 0.001 | -0.420        | < 0.001 | -0.503        | < 0.001 |
| Mean (SD)                |                       |                        |                |     |                |     |                |     |                |     |
| Job                      | 2.722                 | 0.007                  | 1.159          | 0.248 | 2.680          | 0.008 | 2.470         | 0.014 |
| Employed                | 74.5 (18.1)           |                        | 62.2 (29.3)    | 54.6 (29.3) | 42.0         | 0.204 | 34.5          | 18.6 |
| Unemployed              | 66.9 (18.4)           |                        | 56.8 (31.2)    | 44.3 (31.1) | 38.0         | 19.8  | 34.5          | 18.6 |
| Monthly household income |                        |                        |                |     |                |     |                |     |                |     |
| < $2,000                 | 59.6 (21.4)           | 0.011                  | 41.3 (28.0)    | 32.5 (29.1) | 30.4         | 0.204 | 34.5          | 18.6 |
| $2,000-$5,000            | 75.5 (16.5)           | 0.001                  | 61.1 (29.2)    | 49.5 (29.3) | 39.1         | 0.205 | 34.5          | 18.6 |
| ≥ $5,000                 | 76.4 (18.9)           | 0.001                  | 68.4 (29.3)    | 60.5 (28.5) | 44.1         | 0.171 | 34.5          | 18.6 |
| Marriage                 |                        |                        |                |     |                |     |                |     |                |     |
| Married                  | 72.2 (19.2)           | 0.011                  | 64.1 (28.2)    | 53.3 (30.8) | 39.8         | 0.205 | 34.5          | 18.6 |
| Never married            | 70.0 (19.3)           | 0.001                  | 50.9 (31.4)    | 42.4 (26.0) | 37.3         | 0.171 | 34.5          | 18.6 |
| Divorced/separated/widowed | 72.0 (18.5)       | 0.001                  | 54.6 (35.6)    | 44.4 (32.8) | 39.0         | 0.205 | 34.5          | 18.6 |
| s-HTTLPR*                | -1.238                | 0.434                  | -1.248         | 0.428 | -1.132        | 0.518 | -2.001        | 0.076 |
| S’S’                    | 70.6 (19.0)           | 0.011                  | 58.4 (30.5)    | 48.3 (31.0) | 37.2         | 0.171 | 34.5          | 18.6 |
| L’ carrier               | 74.4 (17.2)           | 0.001                  | 64.6 (28.8)    | 54.0 (27.6) | 44.1         | 0.171 | 34.5          | 18.6 |
| PDSS                     | -0.463                | < 0.001                | -0.551         | < 0.001 | -0.427        | < 0.001 | -0.586        | < 0.001 |
| BDI                      | -0.531                | < 0.001                | -0.509         | < 0.001 | -0.517        | < 0.001 | -0.645        | < 0.001 |
| Mean (SD)                |                       |                        |                |     |                |     |                |     |                |     |
| Val/Val                  | 68.6 (17.9)           | 0.001                  | 57.5 (29.1)    | 46.5 (30.9) | 38.9         | 0.171 | 34.5          | 18.6 |
| Met carrier              | 75.0 (18.7)           | 0.001                  | 63.0 (31.1)    | 53.7 (29.0) | 39.4         | 0.171 | 34.5          | 18.6 |
| PDSS, Panic Disorder Severity Scale; BDI, Beck Depression Inventory.
*The Bonferroni correction was applied for the multiple tests according to the two genetic polymorphisms.

*PDSS, Panic Disorder Severity Scale; BDI, Beck Depression Inventory.
*The Bonferroni correction was applied for the multiple tests according to the two genetic polymorphisms.
general health) of HRQOL rather than with psychopathology or symptoms in patients with PD. The COMT Val<sup>158</sup>Met was not associated with the symptomatology in terms of PDSS and BDI. Thus, the COMT Val<sup>158</sup>Met is also related with specific domain of HRQOL in terms of the SF-36 (i.e., role-emotional) rather than with symptoms in patients with PD. This is consistent with previous studies showing that the HRQOL is another different domain compared to symptoms in panic disorder (4).

Interestingly, our finding suggests that different domains of HRQOL in terms of the SF-36 have a different genetic basis. It is well known that the 5-HTTLPR is closely related with 5-HT neurotransmitter system and the COMT Val<sup>158</sup>Met with dopamine and norepinephrine system (17,26,27). Specifically, our finding means that increased serotonergic neurotransmission is associated with poor HRQOL in terms of general health while decreased catecholaminergic neurotransmission is associated with more role limitation due to emotional problems. Given that the magnitude of variance of the two genetic polymorphisms in our study was much smaller than proposed total variation of inheritance of the SF-36 (11), it is also plausible that there should be other genes that explain the rest of the variance in general health and role-emotional in patients with PD. On the other hand, it is also possible that there exist other genetic polymorphisms rather than 5-HTTLPR and COMT Val<sup>158</sup>Met that explain other domains of the SF-36.

Ethnicity and culture are important factors that should be considered. Although little is known about the ethnic or cultural effects on the profile of SF-36 in patients with PD, studies of other conditions suggest the possibility of different profile of the domains of SF-36 by different ethnicity or cultures (35,36). The previous studies (33,37) showed that the distribution as well as the roles of both 5-HTTLPR and COMT Val<sup>158</sup>Met in Korean panic patients are different from those in Westerners. However, in terms of the COMT Val<sup>158</sup>Met, we recently found that the frequency of COMT Val/Val is higher in the panic patient group than in normal controls (unpublished data, available at request), consistent with the results in Caucasians and contrary to the report by Woo et al. (37). Thus, further studies in other ethnic groups or cultures are warranted.

The present study has several limitations. First, our investigation about the relationship between the genetic factors and HRQOL was performed only in panic patients, not in healthy controls or other psychiatric illnesses. Thus, it is unclear whether the relationship between the 5-HTTLPR and COMT Val<sup>158</sup>Met and HRQOL in terms of the SF-36 is specific to PD. Second, our sample size was too small to examine the effect of the 5-HTTLPR L’ or COMT Met homozygotes on HRQOL. It is known that the frequencies of L or L’ allele as well as COMT Met allele in Asians (especially, in Korean and Japanese populations) are much less compared to those in Westerners (15,22,33). Third, we used the data reported by Romeis et al. (11) in which the subjects were middle-age, middle-class Caucasians, to calculate the portion of the genetic effect in terms of inheritance of the SF-36. Finally, the significant differences in education level and job status might have played as confounding factors for explaining the between group difference in HRQOL. Further studies on the heritability of SF-36 in patients with PD as well as in Asians are needed for more accurate calculation of the propor-

Table 3. Hierarchical multiple regression analysis of factors associated with quality of life in panic disorder patients

| Risk factors | General health | Role-emotional |
|--------------|----------------|----------------|
|              | β   | t    | P   | ΔR² | β   | t    | P   | ΔR² | P   |
| Step 1       |     |      |     |     |     |      |     |     |     |
| Age          | 0.017 | 0.236 | 0.814 | -0.117 | 1.336 | 0.183 |< 0.001 |
| Gender (ref: male) | 0.043 | 0.518 | 0.605 | -0.009 | -0.125 | 0.900 |< 0.001 |
| Job (ref: employment) | -0.179 | -2.112 | 0.036 | 0.315 | 3.060 | 0.003 |
| Monthly household income (ref: < 2,000) | 0.214 | 2.015 | 0.045 | 0.382 | 3.691 | < 0.001 |
| > 2,000-$5,000 | 0.275 | 2.577 | 0.011 | 0.315 | 3.060 | 0.003 |
| Marriage (ref: Divorced/ separated/widowed) | 0.135 | 1.078 | 0.283 | 0.347 | 1.078 | < 0.001 |
| Never married | -0.096 | -0.685 | 0.494 | 0.347 | 1.078 | < 0.001 |
| Step 2*      |     |      |     |     |     |      |     |     |     |
| PDSS         | -0.207 | -2.396 | 0.018 | -0.114 | -1.342 | 0.181 |< 0.001 |
| BDI          | -0.359 | -4.235 | < 0.001 | -0.378 | -4.496 | < 0.001 |
| 5-HTTLPR S’S’ (ref: L’ carrier) | -0.151 | -2.382 | 0.018 | 0.362 | 0.015 | < 0.001 |
| COMT Val/Val (ref: Met carrier) | -0.125 | -1.991 | 0.048 | 0.362 | 0.015 | < 0.001 |

PDSS, Panic Disorder Severity Scale; BDI, Beck Depression Inventory.
*Step 2 includes variables in step 1; Step 3 includes variables in step 2.

http://dx.doi.org/10.3346/jkms.2016.31.5.757
tion of variance in terms of inheritance by certain genetic polymorphisms.

In conclusion, the present study suggests that the 5-HTTLPR S’S’ independently predicts poor perceived general health (2.2% of total variation and 6.7% of variance in terms of inheritance) and COMT Val/Val are related with poor functioning in role-emotional (1.5% of total variation and 5.0% of variance in terms of inheritance) in terms of the SF-36 controlling for sociodemographic factors and disorder-related symptom levels in patients with PD. Our finding also shows that specific domains of the SF-36 are associated with the specific genetic polymorphisms that are closely related with specific neurotransmitter systems. In addition, the finding that the magnitude of explanation for HRQOL by symptom levels is not so large is consistent with the previous reports and suggests the need to include HRQOL in assessment of the patients. Finally, the total variance of prediction by sociodemographic factors, disorder-related symptoms, and the two genetic polymorphisms were all less than 40%, which warrants exploration of other factors that explain the HRQOL in patients with PD.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and design: Choe AY, Kim BR, Lee JY, Choi TK, Lee SH. Acquisition of data: Choe AY, Kim BR, Choi TK, Lee SH. Analysis and interpretation of data: Kang EH, Choe AY, Kim BR. First writing of manuscript: Kang EH, Choe AY. Revision of the manuscript: Kang EH, Choe AY, Na HR, Lee SH. Agree with the manuscript contents and conclusions: all authors.

ORCID

Eunho Kang  http://orcid.org/0000-0001-7393-9826
Ah-Young Choe  http://orcid.org/0000-0003-4293-244X
Borah Kim  http://orcid.org/0000-0001-9992-9669
Jun Yeob Lee  http://orcid.org/0000-0002-7677-0605
Tae Kiu Choi  http://orcid.org/0000-0003-0221-0573
Hae-Ran Na  http://orcid.org/0000-0002-7960-8603
Sang-Hyuk Lee  http://orcid.org/0000-0001-5985-624X

REFERENCES

1. Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2006; 63: 415-24.
2. Klerman GL, Weissman MM, Ouellette R, Johnson J, Greenwald S. Panic attacks in the community. Social morbidity and health care utilization. JAMA 1991; 265: 742-6.
3. Katerndahl DA, Reaini JP. Quality of life and panic-related work disability in subjects with infrequent panic and panic disorder. J Clin Psychiatry 1997; 58: 153-8.
4. Rapaport MH, Clarey C, Fayyad R, Endicott J. Quality-of-life impairment in depressive and anxiety disorders. Am J Psychiatry 2005; 162: 1711-8.
5. Sherbourne CD, Wells KB, Budd LL. Functioning and well-being of patients with panic disorder. Am J Psychiatry 1996; 153: 213-8.
6. Daviddoff J, Christensen S, Khalili DN, Nguyen J, IsHak WW. Quality of life in panic disorder: looking beyond symptom remission. Qual Life Res 2012; 21: 945-39.
7. Hollifield M, Katon W, Skipper B, Chapman T, Ballenger JC, Mannuzza S, Fyer AJ. Panic disorder and quality of life: variables predictive of functional impairment. Am J Psychiatry 1997; 154: 766-72.
8. Rubin HC. Rapaport MH, Levine B, Gladso JK, Rabin A, Auerbach M, Judd LL, Kaplan R. Quality of well being in panic disorder: the assessment of psychiatric and general disability. J Affect Disord 2000; 57: 217-21.
9. Katschnig H, Amering M, Stolk JM, Ballenger J. Predictors of quality of life in a long-term followup study in panic disorder patients after a clinical drug trial. Psychopharmacol Bull 1996; 32: 149-55.
10. Dimenäs ES, Dahlöf CG, Jern SC, Wåkland IK. Defining quality of life in medicine. Scand J Prim Health Care Suppl 1990; 1: 7-10.
11. Romeis JC, Heath AC, Xian H, Eisen SA, Scherrer JF, Pedersen NL, Fu Q, Bucholz KK, Goldberg J, Lyons MJ, et al. Heritability of SF-36 among middle-age, middle-class, male-male twins. Med Care 2005; 43: 1147-54.
12. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30: 473-83.
13. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993; 31: 247-63.
14. Caspi A, Harriri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. Am J Psychiatry 2010; 167: 509-27.
15. Domschke K, Deckert J, O’donovan MC, Glatt SJ. Meta-analysis of COMT val158met in panic disorder: ethnic heterogeneity and gender specificity. Am J Med Genet B Neuropsychiatr Genet 2007; 144B: 667-73.
16. Kim B, Yoo E, Lee JY, Lee KS, Choe AY, Lee JE, Kwack K, Yook KH, Choi TK, Lee SH. The effects of the catechol-O-methyltransferase val158met polymorphism on white matter connectivity in patients with panic disorder. J Affect Disord 2013; 147: 64-71.
17. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996; 274: 1527-31.
18. Strug LJ, Suresh R, Fyer AJ, Talati A, Adams PB, Li W, Hodge SE, Gilliam SC. Genetic variations in the serotonin transporter gene (SLC6A4) but not the promoter region (5-HTTLPR) and Panic Disorder: a systematic review and meta-analysis. Behav Brain Funct 2007; 3: 41.
19. Rotondo A, Mazzanti C, Dell’Osso L, Rucci P, Sullivan P, Bouanani S, Gorn-
nelli C, Goldman D, Cassano GB. Catechol o-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. Am J Psychiatry 2002; 159:23-9.

21. Zalsman G, Huang YY, Oquendo MA, Burke AK, Hu XZ, Brent DA, Ellis SP, Goldman D, Mann JJ. Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. Am J Psychiatry 2006; 163:1588-93.

22. Nakamura M, Ueno S, Sano A, Tanabe H. The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. Mol Psychiatry 2000; 5:32-8.

23. Kraft JB, Slager SL, McGrath PJ, Hamilton SP. Sequence analysis of the serotonin transporter and associations with antidepressant response. Biol Psychiatry 2005; 58:374-81.

24. Stein MB, Seedat S, Gelernter J. Serotonin transporter gene promoter polymorphism predicts SSRI response in generalized social anxiety disorder. Psychopharmacology (Berl) 2006; 187:68-72.

25. Neumeister A, Hu XZ, Luckenbaugh DA, Schwarz M, Nugent AC, Bonne O, Herscovitch P, Goldman D, Drevets WC, Charney DS. Differential effects of 5-HTTLPR genotypes on the behavioral and neural responses to tryptophan depletion in patients with major depression and controls. Arch Gen Psychiatry 2006; 63:978-86.

26. Lachman HM, Morrow B, Shprintzen R, Veit S, Parsia SS, Faedda G, Goldberg R, Kucherlapati R, Papoulis DE. Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. Am J Med Genet 1996; 67:468-72.

27. Chen J, Lipska BK, Halim N, Ma QD, Matsamotu M, Melhem S, Kolachana BS, Hyde TM, Herman MM, Apud J, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet 2004; 75:807-21.

28. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Washington, D.C.: American Psychiatric Press, 1996.

29. Nam BH, Lee SW. Testing the validity of the Korean SF-36 health survey. J Korean Soc Health Stat 2003; 28:3-24.

30. Lim YJ, Yu BH, Kim JH. Korean panic disorder severity scale: construct validity by confirmatory factor analysis. Depress Anxiety 2007; 24:95-102.

31. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:561-71.

32. Lonsdorf TB, Weike AI, Nikamo P, Schalling M, Hamm AO, Ohman A. Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder. Psychol Sci 2009; 20:198-206.

33. Kim H, Lim SW, Kim S, Kim JW, Chang YH, Carroll BJ, Kim DK. Monoamine transporter gene polymorphisms and antidepressant response in Koreans with late-life depression. JAMA 2006; 296:1609-18.

34. Choe AY, Kim B, Lee KS, Lee JE, Lee JY, Choi TK, Lee SH. Serotonergic genes (5-HTT and HTR1A) and separation life events: gene-by-environment interaction for panic disorder. Neuropsychobiology 2013; 67:192-200.

35. Trivedi MH, Rush AJ, Wisniewski SR, Warden D, McKinney W, Downing M, Berman SR, Farabough A, Luther JE, Nierenberg AA, et al. Factors associated with health-related quality of life among outpatients with major depressive disorder: a STAR*D report. J Clin Psychiatry 2006; 67:185-95.

36. Franco OH, Wong YL, Kandala NB, Ferrie JE, Dorn JM, Kivimäki M, Clarke A, Donahue RP, Manoux AS, Freudentheim JL, et al. Cross-cultural comparison of correlates of quality of life and health status: the Whitehall II Study (UK) and the Western New York Health Study (US). Eur J Epidemiol 2012; 27:255-65.

37. Woo JM, Yoon KS, Yu BH. Catechol O-methyltransferase genetic polymorphism in panic disorder. Am J Psychiatry 2002; 159:1785-7.