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Investigation into the Possible Genetic Role of Serotonin and Dopamine Transporters in Psychological Resilience

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Objectives Psychological resilience is the ability to cope with stress. The genetic background behind psychological resilience is not much known. The serotonin transporter and dopamine transporter are implicated in stress related psychology and emotional processing. The aim of this study is to investigate a possible genetic role of functional polymorphisms of serotonin and dopamine transporters for psychological resilience.

Methods A total of 951 healthy adult subjects were included. Psychological resilience was measured using Connor-Davidson Resilience Scale (CD-RISC). Genotyping was performed for *serotonin transporter gene* (*SERT*) promoter variable number tandem repeat (VNTR) and *dopamine transporter gene* (*DAT1*) 3'-untranslated region (UTR) VNTR. Genetic association analysis was conducted between genotypes and the CD-RISC score.

Results No genetic association was observed for *SERT* promoter VNTR or *DAT1* 3'-UTR VNTR with CD-RISC score. No genetic interaction between *SERT* promoter VNTR and *DAT1* 3'-UTR VNTR with CD-RISC score was detected.

Conclusions Either serotonin or dopamine transporter did not seem to play a significant role for psychological resilience in this sample.

Key Words CD-RISC · Dopamine · Gene · Psychological resilience · Serotonin.

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Introduction

Psychological resilience is a measure of the ability to cope with stress and adversity. It is a complex trait determined by multiple factors interacting with each other including genetic, biological, psychological, and environmental factors.[1-4] Psychological resilience is associated with positive affect and self-esteem,[5] and has been shown to moderate the relationship between environmental adversity and an individual's psychiatric symptoms. For example, the relationship between childhood maltreatment and current psychiatric symptoms was reported to be moderated by psychological resilience.[1] Psychological resilience is also associated with reduced psychopathology[6] and may act as a protective factor against the development of mood disorders.[7] However, there have been few studies regarding which genes are responsible for psychological resilience. Two genes in nitric oxide pathway, Nitric oxide synthase adapter protein (*NOS1AP*) and *NOS1* have been studied and single nucleotide polymorphisms (SNP) of these genes were associated with resilience.[8] Another genetic study on tumor necrosis factor alpha (*TNFα*) could not find association between a SNP rs1800629 and resilience.[9]

Serotonin has been strongly considered to be an important neurotransmitter depressive mood and stress. Especially, the repeat polymorphism in the promoter region of the *serotonin transporter gene (SERT)* is thought to be associated with depression and anxiety-related conditions.[2][10-12] Dopamine is associated with personality, emotionality, cognitive processing, and regulation of reward.[13-15] These characteristics are all related to stress management of human being in general. The variable number of tandem repeat (VNTR) polymorphism in the 3'-untranslated region (UTR) of *dopamine transporter gene* (*DAT1*) is known to much influential to *DAT1* function.[16]

Based on the above previously studied relationship between

serotonergic and dopaminergic neuronal pathways and mood as well as vulnerability to stress, we hypothesized a possible genetic role for the serotonin transporter and dopamine transporter on psychological resilience in general population. In this study, we aim to evaluate the possible role of 44bp VNTR at the promoter of the *SERT* and 40 bp VNTR at the 3'-UTR of the *DAT1* polymorphisms in Connor–Davidson Resilience Scale (CD-RISC) score in a group of healthy adult subjects. Up to our knowledge, these polymorphisms have not been studied for genetic association with psychological resilience.

Methods

Subjects

We selected subjects who had completed the CD-RISC from the pool of normal subjects who participated in our previous studies.[17)18)] All subjects were recruited from college students, nurses, and fire and public protection officers. Each subject completed a brief psychiatric interview performed by a psychiatric research nurse to evaluate current and past psychiatric illnesses. Subjects with a lifetime history of major psychiatric illness and/or brain trauma were excluded. All subjects were ethnically Korean. The final analyses of the present study included 951 subjects. It consists of 346 nurses, 391 college students, and 214 fire and public protection officers. All subjects understood the study purpose and signed a written informed consent form. The study protocol was approved by the Ethics Committee of Eulji General Hospital (201103-01).

Measurement of psychological resilience

To measure psychological resilience, we used the original version of the CD-RISC translated in Korean, which includes 25 items rated on a 5-point scale from 0−4. The maximum CD-RISC score is 100, and the higher the score the better the resilience.[19)] It is a self-administered scale that comprehensively asks about aspects of psychological resilience. A Korean version of CD-RISC has been developed and shown to have good reliability and validity.[17)20)]

Genotyping of the *SERT* promoter and *DAT1* 3'-UTR VNTR polymorphism

DeoxyriboNucleic Acid (DNA) was extracted from blood, and genotyping of *SERT* promoter VNTR and *DAT1* 3'-UTR VNTR polymorphisms was done as described in our previous publications.[18)21)] There have been S (short) , L (long) alleles for *SERT* and 5 different alleles (6, 7, 9, 10, 11R) for *DAT1* found. Genotypes were classified as SS, SL, and LL for *SERT* promoter VNTR and single copy of 10 repeat (10R), double copies of 10R, and no copy of 10R for *DAT1* 3'-UTR VNTR.

Statistical analysis

Age was found to be significantly correlated with CD-RISC total score ($r = -0.069$, $p < 0.033$), so an analysis of covariance (ANCOVA) was conducted to compare the scores of the three different genotype groups of each gene. Individual genetic roles of *SERT* promoter VNTR and *DAT1* 3'-UTR VNTR and their genetic interaction were analyzed. p-values < 0.05 were considered to indicate statistical significance. Hardy-Weinberg equilibrium was assessed by Chi-square goodness-of-fit test. SPSS 12.0 software (SPSS Inc., Chicago, IL, USA) was used for all analyses. Power calculations were performed by G*Power 3.19 (Heinrich Heine University, Dusseldorf, Germany).

Table 1. Number of subjects, age, CD-RISC total scores, and genotype and allele distribution

	Total	Male	Female
Number of subjects	951	442	509
Age			
Mean	25.86	27.85	24.14
SD	6.66	8.51	3.69
CD-RISC score			
Mean	63.63	66.24	61.38
SD	14.73	16.35	12.82
SERT promoter VNTR			
Genotypes (%)			
SS	619 (65.1)	304 (68.8)	315 (61.9)
SL	268 (28.2)	109 (24.7)	159 (31.2)
LL	64 (6.7)	29 (6.6)	35 (6.9)
Alleles (%)			
S	1506 (79.2)	717 (81.1)	789 (77.5)
L	396 (20.8)	167 (18.9)	229 (22.5)
DAT1 3'-UTR VNTR			
Genotypes (%)			
Single copy of 10R	139 (14.6)	63 (14.3)	76 (14.9)
Double copies of 10R	797 (83.8)	363 (83.5)	428 (84.1)
No copy of 10R	15 (1.6)	10 (2.3)	5 (1.0)
Alleles (%)			
6R	4 (0.2)	3 (0.3)	1 (0.1)
7R	64 (3.4)	38 (4.3)	26 (2.5)
9R	68 (3.6)	30 (3.4)	38 (3.7)
10R	1733 (91.1)	801 (90.6)	932 (91.6)
11R	33 (1.7)	12 (1.4)	21 (2.1)

CD-RISC scores are shown as mean (SD). *SERT* promoter VNTR genotypes are described as SS, SL, and LL. *DAT1* 3'-UTR VNTR genotypes are described according to number of copies of 10R allele. CD-RISC : Connor–Davidson resilience scale, *SERT* : *serotonin transporter gene*, VNTR : variable number tandem repeat, S : short allele (14R), L : long allele (16R), *DAT1* : *dopamine transporter gene*, UTR : untranslated region, R : repeat

Results

Information about the age, CD-RISC score, allele frequencies and genotype frequencies regarding gender was provided in Table 1. No association was detected between the CD-RISC total score and *SERT* promoter VNTR genotype, or between the CD-RISC total score and *DAT1* 3'-UTR VNTR genotype. Additionally, no significant interaction was observed between *SERT* promoter VNTR and *DAT1* 3'-UTR VNTR on CD-RISC score (Table 2). The mean age was 25.86 ± 6.66. The CD-RISC total score was 63.63 ± 14.73. Our sample was satisfied for *DAT1* 3'-UTR VNTR (χ^2 = 9.005, df = 2, p > 0.05), but was not satisfied for Hardy-Weinberg equilibrium for *SERT* promoter VNTR (χ^2 = 20.07, df = 2, p < 0.05). Power calculation estimated that our sample size has power of 0.80 under the assumption of small effect size (0.1) and α error probability 0.05.

Discussion

Psychological resilience is a complex phenotype that may include personality, self-image, mood, anxiety, and ability of adjustment.[5] It acts as a protective factor against maladjustment, stress vulnerability, and even psychiatric illnesses.[6][7] Serotonin and dopamine are well-studied neurotransmitters associated with mood disorders, and serotonin and dopamine transporters control serotonergic and dopaminergic neurotransmission. In the present study, we focused on the serotonin, and *DAT1,* and investigated their common functional polymorphisms (*SERT* promoter VNTR and *DAT1* 3'-UTR VNTR) for possible associations with psychological resilience.

Table 2. Comparison of CD-RISC score according to *SERT* promoter VNTR and *DAT1* 3'-UTR VNTR genotypes

	Total	Male	Female
SERT promoter VNTR			
SS	63.52 (14.87)	65.48 (16.44)	61.62 (12.93)
SL	63.71 (14.46)	67.93 (16.12)	60.81 (12.45)
LL	64.47 (15.09)	67.79 (16.25)	61.71 (13.68)
F	0.154	0.416	0.234
p-value	0.857	0.660	0.792
DAT1 3'-UTR VNTR			
Single copy of 10R	63.51 (14.18)	65.57 (16.28)	61.80 (12.02)
Double copies of 10R	63.58 (14.87)	66.27 (16.49)	61.26 (12.89)
No copy of 10R	67.53 (14.62)	69.10 (11.91)	64.40 (20.27)
F	0.570	0.213	0.190
p-value	0.566	0.808	0.827
SERT promoter VNTR***DAT1* 3'-UTR VNTR			
F	2.594	0.746	0.418
p-value	0.051	0.237	0.659

CD-RISC scores are shown as mean (SD). *SERT* promoter VNTR genotypes are described as SS, SL, and LL. *DAT1* 3'-UTR VNTR genotypes are described according to number of copies of 10R allele. *SERT* promoter VNTR***DAT1* 3'-UTR VNTR indicates tests of interactions between *SERT* promoter VNTR and *DAT1* VNTR. CD-RISC : Connor–Davidson resilience scale, *SERT* : *serotonin transporter gene*, VNTR : variable number tandem repeat, *DAT1* : *dopamine transporter gene*, S : short allele (14R), L : long allele (16R), 10R : 10 Repeat

The *SERT* (SLC6A4) gene is located at chromosome 17q11-12. A recent meta-analysis of 54 studies found that the S allele was linked with an increased risk of depression under conditions of stress.[12] A 44-bp insertion/deletion VNTR polymorphism is located upstream of the transcription initiation site, and the most common alleles are a long allele (16 repeats) and a short allele (14 repeats). The S allele has a lower transcriptional efficiency than the L allele,[22][23] and typically exhibits a greater degree of vulnerability to social stressors.[2][11]

The *DAT1* (or SLC6A3) is important in the regulation of dopamine levels in the brain.[24] *DAT1* has also been shown to play a role in the development of depression,[25][26] attention deficit hyperactivity disorder (ADHD), bipolar disorder, and substance use disorder.[27-29] It is located at chromosome 5p15. It has a common 40 bp VNTR polymorphism in its 3'-UTR, for which the most frequent allele in the population is 10R allele. The 10R allele is associated with an increased level of *DAT1* expression,[16][30][31] and is a risk-conferring allele for ADHD.[32] Additionally, the 10R/10R genotype is associated with higher *DAT1* density and lower dopamine expression in the synapse.[16] Several studies have investigated possible associations between *DAT1* 3'-UTR VNTR and psychiatric phenotypes, although the findings are heterogenous.[33][34]

There have been previously two other studies about CD-RISC for non-clinical subjects. The CD-RISC score (63.59 ± 14.77) in our study was slightly lower (65.9 ± 13.6) than that for the general population in the previous study.[20] Another recent study reported a 25-item CD-RISC score of 61.2 ±13.3 in 1794 hospital employees in Korea.[35] Altogether, it seems that CD-RISC score is getting lower with aging and hospital employees have tendency of low CD-RISC score.

Contrary to our hypothesis based on the known functional difference of specific polymorphic alleles, we found no significant association between *SERT* promoter VNTR or *DAT1* 3'-UTR VNTR and psychological resilience in our sample. This could be explained in many ways. First, the polymorphic sites may not be representative of the entire serotonin or *DAT1*, and alternative polymorphic sites in these genes may show significant associations with psychological resilience. Second, the complexity of the psychological resilience phenotype involves many aspects of brain function. Therefore, it is more likely that mul-

tiple genes with small to moderate effects interact together, and that any genetic effect of *SERT* promoter VNTR and/or *DAT1* 3'-UTR VNTR is too small to detect with our relatively small sample. In this study we tried to explore a possible interaction between *SERT* promoter VNTR and *DAT1* 3'-UTR VNTR, and found a marginally significant result ($p = 0.051$) (Table 2). This result may suggest a possible genetic interaction between these polymorphisms. However, this finding is inconclusive. Further study with large sample is definitely required. Third, serotonin and dopamine may not contribute sufficiently to psychological resilience to be detected as influential. It is possible that other neurotransmitters systems function individually and interactively, so these should be investigated for their possible association with psychological resilience in future studies.

Several limitations should be considered when interpreting the present results. First, the total sample size was not sufficiently large to provide appropriate statistical power and it may cause the deviation from Hardy-Weinberg equilibrium for *SERT* promoter VNTR. Another possible cause of deviation of Hardy-Weinberg equilibrium for *SERT* promoter VNTR would be the specific characteristics of our sample. Since subjects were recruited from college students, nurses, and fire and public protection officers, this sample would be genetically deviated from general population. Second, our non-clinical subjects did not represent the general population because it derived from nursing staff, nursing students, and fire and public protection officers. Finally, as mentioned above, we were unable to investigate multiple polymorphic sites because of limited resources, so we selected *SERT* promoter VNTR and *DAT1* 3'-UTR VNTR as well-known functional polymorphic sites. However, these were not representative of the entire DNA sequence.

In conclusion, the present findings suggest that the *SERT* promoter VNTR and/or *DAT1* 3'-UTR VNTR genotypes do not play a significant role in psychological resilience. However, it is likely that many genes interact together to affect the complex trait of psychological resilience, further studies on other candidate genes using larger samples are warranted to fully understand the possible common genetic influence on psychological resilience as a complex phenotype.

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Conflicts of interest

The authors have no financial conflicts of interest.

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