Relation of the DGKH genotype with openness to experience, a premorbid personality trait of bipolar disorder

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Introduction

Diacylglycerol kinases (DGK)

- Phosphorylates diacylglycerol to produce phosphatidic acid, which is an important lipid second messenger regulating several signaling proteins (**Fig. 1**) (Goto et al, 2006; Kanoh et al, 1990; Sakai and Sakane, 2012)
- Plays an important role in various intracellular signaling pathways by regulating diacylglycerol and phosphatidic acid levels

DGKη gene (DGKH)

- Abundantly expressed in the brain (Klauck et al, 1996)
- DGKH polymorphisms have a strong association with bipolar disorder in several GWASs (Baum et al, 2008 ; Yosifova et al, 2011)
- Higher DGKH mRNA levels in post-mortem brains of bipolar patients (Moya et al, 2010)
- A/G polymorphism located in the intron 3 of DGKH (rs9525580)
 - Higher DGKH mRNA levels in the A allele than in the G allele in human peripheral blood
 - A allele: risk allele for bipolar disorder (Baum et al, 2008; Kittel-Schneider et al, 2016; Yosifova et al, 2011)

Bipolar disorder and premorbid personality

- NEO Personality Inventory-Revised (NEO PI-R)
 - Neuroticism, extraversion, openness to experience, agreeableness, conscientiousness (Costa and McCrae, 1992)
- Higher openness to experience and higher neuroticism in euthymic bipolar disorder compared to healthy controls or population norms (Nowakowska et al, 2005; Barnett et al, 2011; Schouws et al, 2015)

Purpose

- Hypothesis: “the A/G polymorphism of DGKH is related to premorbid personality traits of bipolar disorder, especially openness to experience and neuroticism”
- To examine the relation of the DGKH genotype with broad dimensions of personality

Methods

Subjects

- 319 healthy Japanese (244 males and 75 females, age $\pm$ SD = 23.8 $\pm$ 2.2 years)
- No Axis I or II disorders(DSM-IV), no serious physical diseases
- Approved by Ethics Committee of Yamagata University School of Medicine, and written informed consent to participate from all subjects

Personality Assessment

- Japanese version of NEO PI-R (Shimonaka et al, 1999)

Genotyping: PCR-RFLP method

Statistical analysis

- Analysis of covariance with age and sex as covariates
- Significance: p<0.05

Results

- NEO PI-R scores and DGKH genotypes of the subjects (**Table 1**)
- Significantly higher openness to experience in the group with the A allele compared to that without the A allele (**Table 2**)
- No significant differences in scores of neuroticism, extraversion, agreeableness, conscientiousness between the two groups (**Table 2**)

Discussion

Phase I

- A allele of the DGKH polymorphism $\Leftrightarrow$ higher scores of openness to experience
 - DGKH: most promising candidate gene for bipolar disorder (Baum et al, 2008; Moya et al, 2010; Yosifova et al, 2011)
 - Openness to experience: most characteristic premorbid personality of bipolar disorder (Nowakowska et al, 2005; Barnett et al, 2011; Schouws et al, 2015)

Phase II

- Emotional dysregulation of bipolar disorder $\Leftrightarrow$ structural and functional abnormalities in neural systems including the amygdala (Blond et al, 2012; Townsend and Altshuler, 2012)
- Openness to experience $\Leftrightarrow$ Amygdala activity in function MRI (Kunisato et al, 2011; Morawetz et al, 2014)
- A allele of the DGKH polymorphism $\Leftrightarrow$ increased volume of amygdala (Kittel-Schneider et al, 2015)

- Influence of the DGKH genotype on openness to experience possibly by modulating amygdala activity

Phase III

- No association between the DGKH genotype and other NEO PI-R dimensions including neuroticism
- Possible involvement of other bipolar-risk gene such as the CACNA1C and the serotonin transporter gene in other personality traits (Lasky-Su et al, 2005; Ferreira et al, 2008; Munafo et al, 2009; Erk et al, 2010; Jiang et al, 2013)

Conclusion

- Association of a bipolar-risk allele of DGKH with higher openness to experience, providing further evidence for the implication of this gene in the etiology of bipolar disorder.

Table 1 NEO PI-R scores and DGKH genotypes of the subjects.

NEO PI-R score	mean $\pm$ SD			
Neuroticism	101.0 $\pm$ 21.4			
Extraversion	100.1 $\pm$ 19.0			
Openness to experience	114.0 $\pm$ 13.4			
Agreeableness	105.9 $\pm$ 15.5			
Conscientiousness	99.3 $\pm$ 18.7			
DGKH genotype	n			
GG	218			
GA	89			
AA	12			

Table 2 Effects of the DGKH genotype on NEO PI-R scores.

	GG	GA+AA	F	P
Neuroticism	102.3 $\pm$ 21.2	98.2 $\pm$ 21.8	2.030	0.155
Extraversion	99.5 $\pm$ 18.8	101.5 $\pm$ 19.4	1.059	0.304
Openness to experience	112.8 $\pm$ 12.7	116.6 $\pm$ 14.6	5.208	0.023
Agreeableness	104.9 $\pm$ 16.1	108.0 $\pm$ 13.9	3.099	0.079
Conscientiousness	99.2 $\pm$ 17.9	99.4 $\pm$ 20.3	0.058	0.809

Conflicts of interest: None.