Association Between *OLIG2* Gene SNP rs1059004 and Negative Self-Schema Constructing Trait Factors Underlying Susceptibility to Depression

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Recent evidence has indicated that the disruption of oligodendrocytes may be involved in the pathogenesis of depression. Genetic factors are likely to affect trait factors, such as characteristics, rather than state factors, such as depressive symptoms. Previously, a negative self-schema had been proposed as the major characteristic of constructing trait factors underlying susceptibility to depression. Thus, the association between a negative self-schema and the functional single nucleotide polymorphism (SNP) rs1059004 in the *OLIG2* gene, which influences *OLIG2* gene expression, white matter integrity, and cerebral blood flow, was evaluated. A total of 546 healthy subjects were subjected to genotype and psychological evaluation using the Beck Depression Inventory-II (BDI-II) and the Brief Core Schema Scale (BCSS). The rs1059004 SNP was found to be associated with the self-schema subscales of the BCSS and scores on the BDI-II in an allele dose-dependent manner, and to have a predictive impact on depressive symptoms via a negative-self schema. The results suggest the involvement of a genetic factor regulating oligodendrocyte function in generating a negative-self schema as a trait factor underlying susceptibility to depression.

Keywords: depressive symptoms, negative self-schema, single nucleotide polymorphism, *OLIG2*, oligodendrocyte

INTRODUCTION

Major depressive disorder (MDD) is a common disease with a 12-month and lifetime prevalence of 6.6 and 16.2%, respectively (1). Depressive disorders, including MDD and dysthymia, are also a leading cause of the global disease burden (2). Although effective treatments (e.g., antidepressants and cognitive behavioral therapy) are available for MDD, remission rates for antidepressants are not currently optimally achieved (3). Therefore, the development of new and more effective drugs is required in the future and elucidating the pathology of MDD could help us develop these novel medicines. Depressive disorders are multifactorial diseases that are thought to develop through interactions between genetic and psychosocial factors. Although the neurobiological mechanism underlying MDD has been extensively investigated, the definitive biological mechanism remains unclear.

Prior studies based on post-mortem brain, neuroimaging, and animal studies have indicated the involvement of disrupted oligodendrocytes in the pathology of MDD. Histological examination of the post-mortem brain revealed that patients with MDD have a substantially reduced density and number of oligodendrocytes in their prefrontal cortex (4, 5). Oligodendrocyte-related genes were also found to be reduced in the temporal frontal cortex and in the white matter of the ventral prefrontal cortex in patients with MDD (6, 7). More recent studies have reported that psychological stress results in the downregulation of oligodendrocyte-related genes and reduced myelination fiber length and density in the brains of mice (8, 9). Cathomas et al. (8) revealed that after psychological stress, emotion, and microglial activity were altered in mice that were heterozygous for the cyclic nucleotide phosphodiesterase (Cnp1) oligodendrocyte gene compared to wild-type mice; this suggests that oligodendrocyte gene expression affects behavioral changes after psychosocial stress. Several diffusion tensor imaging studies have documented decreased white matter integrity in the corpus callosum and several frontal, temporal, and parietal regions in patients with MDD (10–13). In addition, other studies have found microstructural abnormalities in some fiber tracts, such as anterior callosal fibers, in patients with MDD (14, 15). Patients with MDD also show a reduced magnetic transfer ratio, which reflects demyelination in brain regions, such as the frontal and striatal regions, limbic areas, occipital white matter, and the genu and splenium of the corpus callosum (16–18). Evidence found in post-mortem brains, neuroimaging, and animal studies suggests that disrupted oligodendrocyte function may be involved in impaired mood regulation in MDD.

The *OLIG2* gene is a basic helix-loop-helix transcription factor that is expressed exclusively in oligodendrocytes and oligodendrocyte precursors and is involved in oligodendrocyte differentiation (19, 20). One post-mortem brain study found that *OLIG2* gene expression was downregulated in the temporal cortex of patients with MDD (6). The *OLIG2* gene single nucleotide polymorphism (SNP) rs1059004 is a functional SNP that influences *OLIG2* gene expression and influences white matter integrity in Caucasian populations (21–23). A more recent study revealed that SNP rs1059004 affects resting-state cerebral blood flow in a broad region of the brain as well as white matter integrity in the Japanese population (23). Genetic association studies have shown that *the OLIG2* SNP rs1059004 is associated with several psychiatric disorders such as schizophrenia and obsessive-compulsive disorder in a certain population (24–28). However, no previous studies have investigated the genetic association between this SNP and MDD.

Beck proposed the cognitive model of depression, in which negative self-schema individuals are vulnerable to developing depression in the future (29). Previous studies have shown a marked association between the schemata concerning the self and others, and the severity of depressive symptoms (30, 31). Evans et al. revealed that a negative self-schema was a risk factor for the development of depression in women (32). The results of these studies support the cognitive model of depression hypothesized by Beck (29).

Based on prior evidence indicating the involvement of oligodendrocyte abnormalities in the pathology of MDD, the present study hypothesized the association between *OLIG2* SNP rs1059007 and the negative-self core schema, as it plays a major role in constructing trait factors underlying susceptibility to MDD by influencing the function of oligodendrocytes. To verify this hypothesis, we investigated whether *the OLIG2* SNP rs1059007 was associated with self-negative core schema in healthy subjects.

MATERIALS AND METHODS

Subjects

A total of 777 healthy, right-handed individuals were recruited, and their genotyping data, mood states, core beliefs, brain imaging data, cognitive function, aging, genetics, and daily habits were examined as detailed below and elsewhere (33–36). Of the 777 participants, all gene polymorphism data, scores on the Beck Depression Inventory-II (BDI-II), and scores on the Brief Core Schema Scale (BCSS) were successfully obtained from 546 subjects (313 men and 233 women; 20.5 ± 1.8 years of age). All subjects had normal vision and were university, college or postgraduate students, or subjects who had graduated from these institutions within 1 year prior to the experiment. None of the participants had a history of neurological or psychiatric illness. Handedness was evaluated using the Edinburgh Handedness Inventory (37). High-molecular-weight DNA was isolated from saliva specimens using Oragene containers (DNA Genotek Inc., Ottawa, Canada), according to the manufacturer's instructions. After the study procedures were fully explained, written informed consent was obtained from all participants in accordance with the Declaration of Helsinki (1991). This study was approved by the Ethics Committee of Tohoku University.

Psychological Assessments

Participants were administered the Japanese version of the Brief Core Schema Scale (BCSS) to assess core schemas about the self and others. The BCSS is a 24-item self-report scale developed by Fowler et al. to measure core schemata with regard to the self and others (30). The BCSS includes four dimensions of self- and other-assessment: negative self, positive self, negative others, and

positive others. Each dimension comprised six items that were evaluated on a five-point rating scale (0–4), and respondents were asked to indicate "yes" or "no" for whether they held each belief. If they held the belief, they were then asked to indicate the degree of their conviction on a 4-point scale ranging from 1 to 4 (1: believe slightly, 2: believe it moderately, 3: believe it very much, 4: believe it totally).

Participants were also tested using the Japanese version of the BDI-II to evaluate the degree of depressive symptoms. BDI-II, developed by Beck et al. (38), is a 21-item self-report questionnaire used to evaluate the severity of depression in normal and psychiatric subjects (39). Each item consisted of a 4-point scale from 0 (symptoms absent) to 3 (severe symptoms). The minimum and maximum BDI-II scores were 0 and 63, respectively with higher scores indicating greater severity of depressive symptoms. In normal subjects, scores above 20 have been reported to indicate depression (40).

SNP Genotyping

Genotyping of *OLIG2* SNP rs1059004 was carried out using TaqMan assays (Applied Biosystems, Foster City, CA, USA). Polymerase chain reactions (PCRs) were performed using 20 ng of genomic DNA, 40 × TaqMan Probe Assay Mix (Probe ID: C_2442961_10) (Applied Biosystems, Waltham, MA, USA), 2 × Universal PCR Master Mix (Applied Biosystems), and nuclease-free water in a 10 µL total reaction volume; allele-specific fluorescence was measured using the CFX96 Real-Time System (Bio-Rad, Hercules, CA, USA). Information about the TaqMan Probe sequence can be obtained from https://www.thermofisher.com/order/genome-database/details/genotyping/C___2442961_20?CID=&ICID=&subtype=. The PCR cycle conditions consisted of an initial denaturation at 95°C for 10 min, followed by 50 cycles at 92°C for 15 s and at 57°C for 1 min. Then, PCR products spanning the SNP were amplified with primers (forward: gagcgctgtctggctttaac, reverse: gaggaacggccacagttcta) from two representative subjects for each of the three genotypes of this SNP and were subjected to direct sequencing to validate the TaqMan assay-based genotyping.

Statistical Analysis

Statistical evaluations were performed using SPSS statistics 24 and Amos 23 (Japan IBM, Tokyo, Japan) software packages. Demographic variables among groups were compared using χ^2-tests, analysis of variance, *t*-tests, or Kruskal-Wallis test, where appropriate. Deviations in genotype distribution from the Hardy-Weinberg equilibrium (HWE) were assessed using the χ^2-test for goodness of fit. Spearman's bivariate correlation analysis was performed to examine the correlations between BDI-II scores and the four BCSS subscales. The Jonckheere-Terpstra test was performed to investigate whether *the OLIG2* SNP rs1059004 was associated with the scores on the four BCSS subscales or those of BDI-II in an allele dose-dependent manner. After the Jonckheere-Terpstra test, the *post-hoc* test was used to compare the differences between each genotype using the Bonferroni corrections.

The associations between *the OLIG2* SNP rs1059004, self-schema, and depressive symptoms were assessed using path analysis. Structural equation modeling was performed to evaluate the association between the above-mentioned three variables using SPSS and Amos 23, and model fits were estimated using the maximum likelihood method. The two initial hypothetical models shown in **Figure 1** were constructed based on the results of the trend test, bivariate correlation analysis, and a previous study (32). In the two initial models shown in **Figure 1**, the self-schema affects depressive symptoms, and *OLIG2* SNP rs1059004 impacts schema and depressive symptoms in one direction. In contrast, a negative schema influences or is affected by a positive schema about the self. We removed paths scoring $p > 0.05$ from the initial models and examined whether the model fit improved. The best-fitting path model was ultimately adopted in the path analysis. Chi-square statistics were used to test the goodness-of-fit model, and the following fit indices were calculated: goodness-of-fit index (GFI), adjusted GFI (AGFI), comparative fit index (CFI), Akaike information criterion (AIC), and root mean square error of approximation (RMSEA).

To investigate whether *the OLIG2* SNP rs1059004 influenced the severity of depressive symptoms and core schema about the self and others in a gender-dependent manner, two-way analysis of covariance (ANCOVA) controlling for age, with genotype and gender as independent variables, was used to assess differences in scores on the BDI-II and on the four BCSS subscales between A-allele carriers (AA genotype + AC genotype) and non-A-allele carriers (CC genotype). As few individuals carried the AA genotype, subjects carrying the AA genotype were combined with those carrying the AC genotype, and the differences in scores on the BDI-II and BCSS subscales were compared between carriers and non-carriers of the A allele. *Post-hoc* analyses were performed using Bonferroni corrections. Statistical significance was defined as a two-tailed $p < 0.05$.
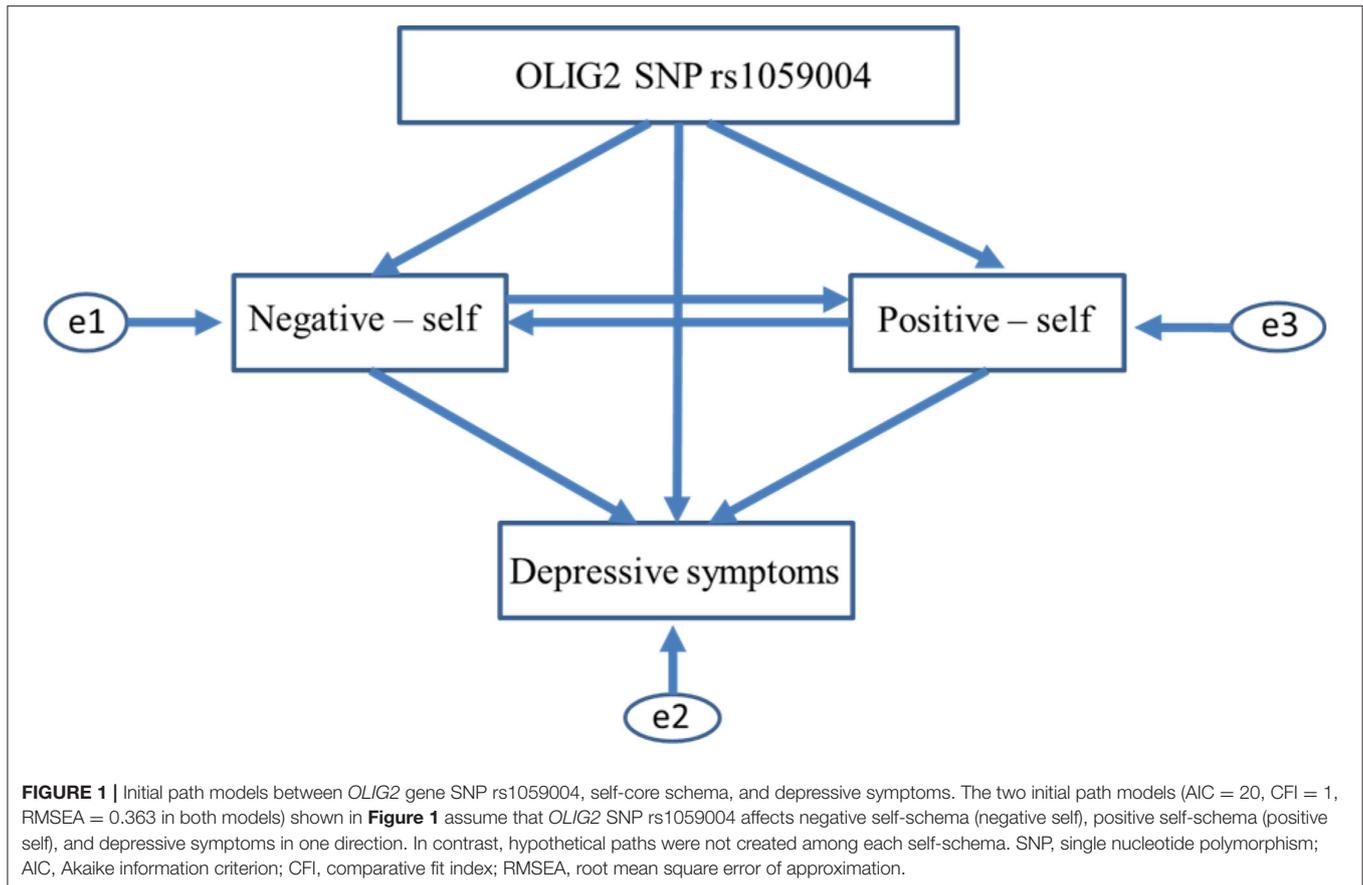
RESULTS

There were significant differences in age and in positive, negative, and other subscale scores between men and women (**Table 1**).

The genotype distribution of the subjects was as follows: homozygous A allele ($n = 14$, 2.5%), heterozygous A/C ($n = 155$, 28.3%), and homozygous C allele ($n = 377$, 69%), which did not deviate from the HWE ($\chi^2 = 0.33$, $p > 0.05$). There were no significant differences in age or sex among the three *OLIG2* genotypic groups (**Table 2**).

Meanwhile, the Kruskal-Wallis test showed significant differences in BDI-II and the negative and positive self subscales of the BCSS among *OLIG2* genotypes ($p = 0.03$, $p = 0.042$, $p = 0.015$, respectively, **Table 2**). The Cronbach's α values for the BDI-II total score, the negative and positive self subscale scores, and the negative and positive other subscale scores were 0.82, 0.80, 0.82, 0.78, and 0.86, respectively.

Bivariate Associations Between BDI-II and Four BCSS Subscale Scores

Spearman's bivariate correlation analysis revealed a positive association between BDI-II score and the negative self

FIGURE 1 | Initial path models between *OLIG2* gene SNP rs1059004, self-core schema, and depressive symptoms. The two initial path models (AIC = 20, CFI = 1, RMSEA = 0.363 in both models) shown in **Figure 1** assume that *OLIG2* SNP rs1059004 affects negative self-schema (negative self), positive self-schema (positive self), and depressive symptoms in one direction. In contrast, hypothetical paths were not created among each self-schema. SNP, single nucleotide polymorphism; AIC, Akaike information criterion; CFI, comparative fit index; RMSEA, root mean square error of approximation.

TABLE 1 | Demographics of all variables in the healthy subjects.

	Men (N = 313)	Women (N = 233)	t-value	p-value[a]	All subjects (N = 546)
Age (mean ± sd, range)	20.7 ± 1.9, 18–27	20.3 ± 1.5, 18–26	2.622	**0.009**	20.5 ± 1.8, 18–27
BDI-II score (mean ± sd, range)	8.0 ± 6.2, 0–31	8.4 ± 6.3, 0–31	−0.78	0.436	8.2 ± 6.2, 0–31
BCSS subscale scores					
Negative self score (mean ± sd, range)	5.2 ± 4.4, 0–23	4.8 ± 4.3, 0–20	0.887	0.461	5.0 ± 4.3, 0–23
Positive self score (mean ± sd, range)	6.0 ± 4.3, 0–23	5.2 ± 3.8, 0–23	2.219	**0.04**	5.6 ± 4.1, 0–23
Negative other score (mean ± sd, range)	2.3 ± 3.1, 0–19	1.6 ± 2.5, 0–15	2.755	**0.003**	2.0 ± 2.9, 0–19
Positive other score (mean ± sd, range)	8.0 ± 4.4, 0–20	8.9 ± 5.0, 0–24	−2.236	**0.024**	8.4 ± 4.7, 0–24

The table represents the mean ± sd of age and BDI-II and the BCSS scores among males and females, in addition to all other variables for all participants. The p-values and t-values from t-tests are also shown.
BDI-II, Beck Depression Inventory-II; BCSS, Brief Core Schema Scale; sd, standard deviation.
[a]t-test between men and women.

and negative other subscales of the BCSS ($r = 0.636$ and $r = 0.296$, respectively, $p < 0.001$, **Table 3**). There was a significant negative association between BDI-II score and the positive self and positive other subscales of the BCSS ($r = −0.459$ and $r = −0.306$, respectively, $p < 0.001$, **Table 3**).

Association Between OLIG2 SNP rs1059004 and the Severity of Depressive Symptoms

The present study found a significant association between *the OLIG2* SNP rs1059004 and BDI-II score in an allele dose-dependent manner (Jonckheere-Terpstra test, $p = 0.022$,

TABLE 2 | The demographics of subjects subdivided according to *OLIG2* genotype.

	Genotype			
	C/C	**C/A**	**A/A**	***p*-value**
N	377 (69.0%)	155 (28.3%)	14 (2.5%)	
Age (mean ± sd, range)	20.5 ± 1.8, 18–27	20.6 ± 1.8, 18–27	20.3 ± 1.6, 18–24	0.864
Gender (male/female)	221/156	87/68	5/9	0.221
BDI-II (mean ± sd, range)	11 ± 5.6, 0–31	8.9 ± 6.6, 0–31	7.9 ± 6.1, 1–20	0.03
Scores on BCSS subscales				
Negative self score (mean ± sd, range)	4.8 ± 4.3, 0–23	5.7 ± 4.5, 0–20	5.8 ± 4.3, 0–13	0.042
Positive self score (mean ± sd, range)	5.9 ± 4.1, 0–23	5.4 ± 4.2, 0–18	3.1 ± 3.6, 0–11	0.015
Negative other score (mean ± sd, range)	2.1 ± 3.0, 0–19	2.0 ± 2.8, 0–15	1.5 ± 2.2, 0–8	0.847
Positive other score (mean ± sd, range)	8.3 ± 4.7, 0–24	10.5 ± 4.9, 0–21	10.4 ± 4.5, 3–17	0.17

The table shows mean ± sd for age and gender for each OLIG2 SNP rs1059004 genotype. P-values for the analysis of variance (ANOVA) are used to compare the differences in age among OLIG2 genotypes, and the chi-square tests between gender and OLIG2 genotype were represented in the table. The table shows p-values for the Kruskal-Wallis test to compare the difference in BDI-II and BCSS subscales among OLIG2 genotypes.
sd, standard deviation.

TABLE 3 | Spearman's bivariate correlation analysis of age, BDI-II score, and BCSS scores.

	Age	**BDI-II**	**Negative self**	**Positive self**	**Negative other**	**Positive other**
Age	–					
BDI-II	−0.057	–				
Negative self	−0.062	0.636**	–			
Positive self	0.096	−0.459**	−0.404**	–		
Negative other	−0.033	0.296**	0.357**	0.009	–	
Positive other	−0.050	−0.306**	−0.202**	0.296**	−0.349**	–

The table exhibits Spearman's correlation coefficients between age and scores on the BDI-II and the four BCSS subscales.
BDI-II, Beck Depression Inventory-II; BCSS, Brief Core Schema Scale.
***Bonferroni-corrected p < 0.001.*

Figure 2A). *Post-hoc* analysis showed that AA genotype carriers had a significantly higher BDI-II score than the CC genotype carriers (Bonferroni-corrected $p = 0.041$, **Figure 2A**). Two-way ANCOVA adjusted for age, with genotype and gender as the fixed factors showed that there was a significant main effect of genotype on BDI-II score (**Table 4**). However, the genotype-gender interaction was not significant for the BDI-II score (**Table 4**).

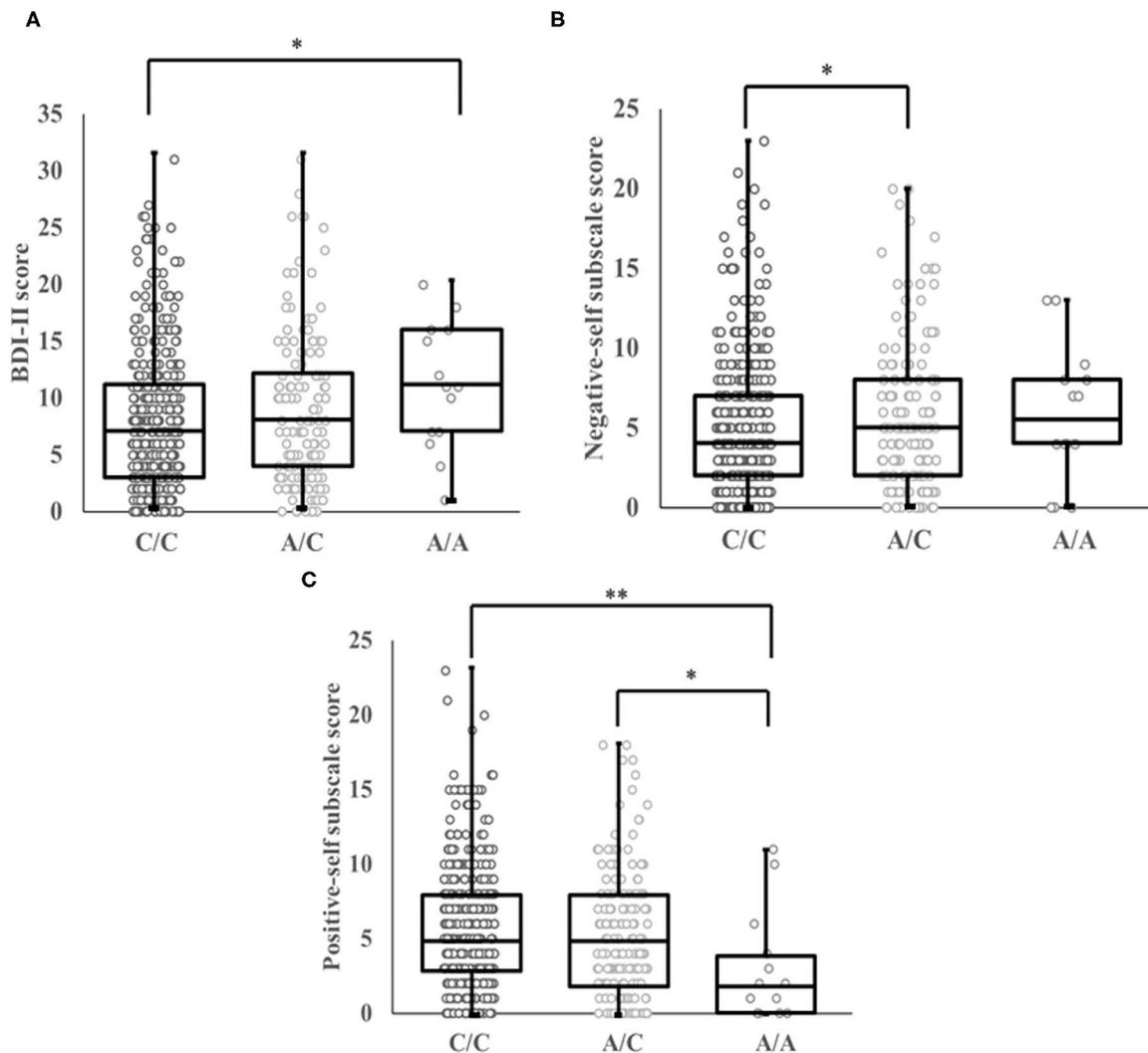## Association Between OLIG2 SNP rs1059004 and Core Schema About the Self and Others

The Jonckheere-Terpstra test showed that *the OLIG2* SNP rs1059004 was associated with both negative and positive self-schema in an allele dose-dependent manner (Jonckheere-Terpstra test, $p = 0.012$, $p = 0.037$; **Figures 2B,C**). Subjects with the AC genotype had a significantly higher negative-self subscale score than those with the CC genotype (Bonferroni-corrected $p = 0.026$, **Figure 2B**). Individuals carrying the AA

genotype had a significantly lower positive-self subscale score than those with the CC genotype and AC genotype, respectively (Bonferroni-corrected $p = 0.009$, $p = 0.049$, **Figure 2C**).

Two-way ANCOVA controlling for age and with genotype and gender as the fixed factors showed that there was a significant main effect of genotype on negative-self subscale score (**Table 4**). However, no significant genotype-gender interactions were observed for scores on the four BCSS subscales (**Table 4**).

Path Analysis of the Relationship Between OLIG2 rs1059004, the Self-Core Schema, and Depressive Symptoms

We removed paths scoring $p > 0.05$ from the initial models (AIC = 20, CFI = 1, RMSEA = 0.363 in both models) and examined whether the model fit improved. Ultimately, the path model shown in **Figure 3** produced the best results in the model fit evaluations (Chi-square = 2.669, df = 2, P = 0.263; GFI = 0.998; AGFI = 0.988; CFI = 0.998; AIC = 18.669; RMSEA = 0.025). The number of C alleles of the *OLIG2* gene SNP rs1059004

FIGURE 2 | (A) Association between genotype at SNP rs1059004 in the *OLIG2* gene and BDI-II scores. There were significant correlations between A allele dosage and BDI-II scores among the three genotype groups. BDI-II scores decreased in a C-allele dose-dependent manner ($p = 0.022$, Jonckheere-Terpstra test). AA genotype carriers had a significantly higher BDI-II score than the CC genotype carriers (Bonferroni-corrected $p = 0.041$). **(B)** Association between genotype at SNP rs1059004 in the *OLIG2* gene and negative-self subscale scores. Significant gene-dose associations between the SNP rs1089004 and negative-self subscale scores were observed among the three genotype groups. Negative-self subscale scores decreased in a C-allele dose-dependent manner ($p = 0.012$, Jonckheere-Terpstra test). Subjects with AC genotype had a significantly higher negative-self subscale score compared to those with CC genotype ($p = 0.026$). **(C)** Association between genotype at SNP rs1059004 and positive-self subscale scores. The Jonckheere-Terpstra test also showed significant associations between A allele dosage and positive-self subscale scores among the three genotype groups. Positive-self subscale scores increased in a C-allele dose-dependent manner ($p = 0.037$, Jonckheere-Terpstra test). People carrying the AA genotype had a significantly lower positive-self subscale score than those with the CC genotype and AC genotype, respectively (Bonferroni-corrected $p = 0.009$, $p = 0.049$). The bars of the box plot show the range from minimum scores to maximum scores. SNP, single nucleotide polymorphism. *$p < 0.05$, **$p < 0.01$ compared to the CC genotype.

was negatively associated with the negative self-schema, and the schema was assumed to affect the positive self-schema and lead to a higher severity of depressive symptoms (**Figure 3**).

DISCUSSION

Based on prior evidence that the disruption of oligodendrocytes may be implicated in the pathology of MDD, the present

study hypothesized an association between the *OLIG2* SNP rs1059004 and the negative self-schema, constructing trait factors underlying susceptibility to MDD. To verify this hypothesis, the associations between *the OLIG2* SNP rs1059004, BCSS and BDI-II scores were examined in 546 healthy subjects. Consistent with the above hypothesis, the number of C alleles in *the OLIG2* gene SNP rs1059004 was associated with decreased BDI-II scores and the negative BCSS self-schema subscale in an allele

TABLE 4 | The results of two-way ANCOVA controlling for age, with genotype and gender as independent variables.

	Men		Women		Genotype		Gender		Genotype× Gender	
	Non-A-allele carriers (CC genotype)	A-allele carriers (AA genotype +AC genotype)	Non-A-allele carriers (CC genotype)	A-allele carriers (AA genotype +AC genotype)	F	p	F	p	F	p
N	221	92	156	77						
BDI-II (mean ± sd)	7.88 ± 6.03	8.48 ± 6.63	7.86 ± 6.30	9.74 ± 6.28	4.569	**0.033**	0.889	0.346	1.219	0.27
Scores on subscales of BCSS										
Negative self schema score (mean ± sd)	4.98 ± 4.33	5.79 ± 4.61	4.51 ± 4.29	5.62 ± 4.41	5.626	**0.018**	0.81	0.368	0.131	0.718
Positive self schema score (mean ± sd)	6.18 ± 4.28	5.59 ± 4.52	5.40 ± 3.78	4.82 ± 3.81	2.449	0.118	2.988	0.084	0	0.998
Negative other schema score (mean ± sd)	2.41 ± 3.20	2.09 ± 2.99	1.56 ± 2.56	1.75 ± 2.42	0.055	0.815	5.444	**0.02**	0.911	0.34
Positive other schema score (mean ± sd)	7.79 ± 4.39	8.73 ± 4.69	8.92 ± 5.05	9.13 ± 5.18	1.722	0.19	2.492	0.115	0.664	0.416

The table displays differences in the scores on the BDI-II and the BCSS by gender between A-allele carriers and non-A allele carriers. F-values and p-values for the main effect of genotype, gender and their interaction effect are also represented in the table.
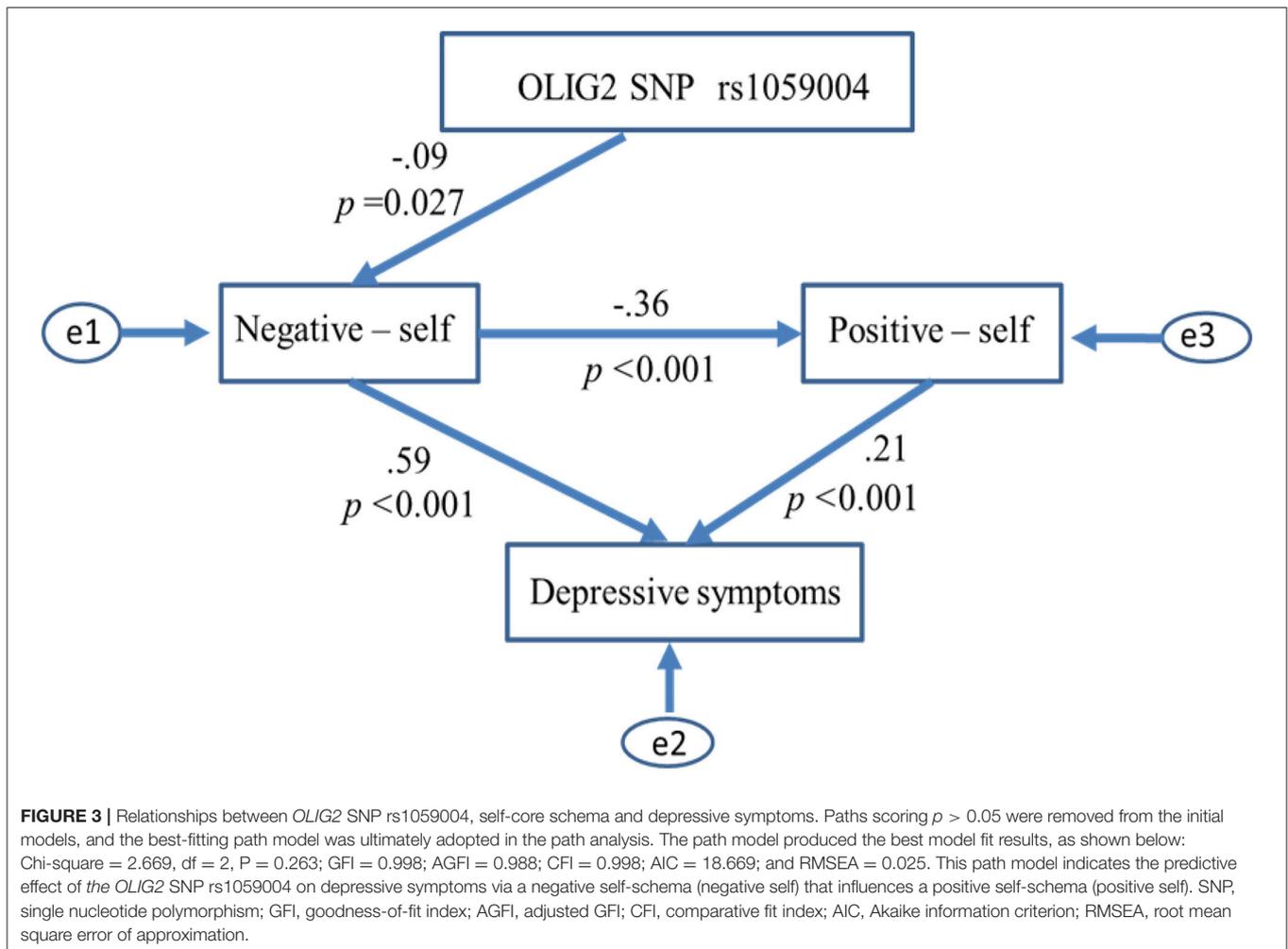*BDI-II, Beck Depression Inventory-II; BCSS, Brief Core Schema Scale; sd, standard deviation.*

dose-dependent manner. Path analysis revealed that a negative self-schema mediated the association between *the OLIG2* SNP rs1059004 and the severity of depressive symptoms. The results of the present study indicate that *the OLIG2* SNP rs1059004 has a predictive impact on depressive symptoms via a negative schema of the self. In addition, the results suggest the involvement of a genetic factor regulating oligodendrocyte function in generating a negative-self schema that plays a major role in constructing factors underlying susceptibility to depression.

Although previous studies have not found significant differences in scores for any BCSS subscale between men and women (30, 31), the current study found that gender created significant differences in positive, negative, and "other" BCSS subscale scores. This discrepancy in the results may be due to differences in the ethnicities, number, and/or ages of the participants. The findings of the present study indicate that the positive self-schema may be affected by a variety of experiences during young adulthood in the Japanese population. In contrast, four of the BCSS subscales were significantly correlated with the severity of depressive symptoms, consistent with previous reports (30, 31).

Previous genetic association studies have exclusively focused on genes related to monoamines, the hypothalamic-pituitary-adrenal axis, and glutamatergic neurotransmitters. For example, polymorphisms of the glucocorticoid receptor gene, monoamine oxidase A gene, and group-2 metabotropic glutamate receptor gene have been previously reported to be associated with MDD (41–44). Although polymorphisms of oligodendrocyte-related genes have been shown to be associated with schizophrenia (24), no previous studies have investigated the genetic association between the polymorphisms of oligodendrocyte-related

genes and MDD. This is the first study to reveal that *the OLIG2* SNP rs1059004 was associated with the severity of depressive symptoms and with negative self-schema. Whether oligodendrocyte disruption is a causative factor in mood dysregulation remains unclear, but several studies have suggested that changes in oligodendrocyte function and structure can influence neural circuits that mediate mood regulation in mice (8, 45–47). For example, mice exposed to cuprizone, a mouse model of demyelination, showed deceased anxiety-like behavior. Moreover, mice lacking the Cnp1 oligodendrocyte-related gene were found to show depressive-like behaviors (45). Therefore, *the OLIG2* SNP rs1059004 may be associated with the severity of depressive symptoms and negative self-schema by influencing the function of oligodendrocytes. One functional magnetic resonance imaging-based study indicated that the activities of the anterior cingulate cortex and the inferior frontal cortex are involved in negative self-reflection (48), and prior investigations have found that the *OLIG2* polymorphism rs1059004 affects not only white matter integrity but also resting-state cerebral blood flow in widespread brain regions, including the anterior cingulate and inferior frontal regions (23). Therefore, the effect of SNP rs1059004 on brain perfusion may be a biological mechanism underlying the association between the variant and negative self-schema. Further studies are needed to reveal the biological basis of the association between *the OLIG2* SNP rs1059004 and negative self-schema.

Beck proposed the cognitive model of depression, in which individuals who hold negative self-schemas are vulnerable to developing depression in the future (29). Evans et al. revealed that a negative self-schema was a risk factor for the onset of depression in women in a longitudinal study (32). This finding may support

FIGURE 3 | Relationships between *OLIG2* SNP rs1059004, self-core schema and depressive symptoms. Paths scoring *p* > 0.05 were removed from the initial models, and the best-fitting path model was ultimately adopted in the path analysis. The path model produced the best model fit results, as shown below: Chi-square = 2.669, df = 2, P = 0.263; GFI = 0.998; AGFI = 0.988; CFI = 0.998; AIC = 18.669; and RMSEA = 0.025. This path model indicates the predictive effect of *the OLIG2* SNP rs1059004 on depressive symptoms via a negative self-schema (negative self) that influences a positive self-schema (positive self). SNP, single nucleotide polymorphism; GFI, goodness-of-fit index; AGFI, adjusted GFI; CFI, comparative fit index; AIC, Akaike information criterion; RMSEA, root mean square error of approximation.

the cognitive model of depression proposed by Beck. Therefore, negative self-schema could play a major role in constructing trait factors underlying susceptibility to MDD. The results of the present study indicate a significant association between *the OLIG2* SNP rs1059004 and a negative self-schema, constructing trait factors concerning susceptibility to MDD. Considering the significant association between the *OLIG2* SNP rs1059004 and a negative self-schema as the trait factor underlying the development of depression, it would be worthwhile to conduct a longitudinal study investigating whether SNP rs1059004 affects the risk of the onset of MDD by influencing negative self-schema.

The present study has several limitations. First, the participants were limited in terms of age and education history; that is, only young adults and university, college, or postgraduate students were examined; therefore, the results of the present study may not apply to the general population. The second limitation is the cross-sectional nature, which cannot disentangle the direction of effects between variables. The third limitation is that some problems have recently arisen regarding single-gene studies of multifactorial phenotypes, such as depression, and many studies have failed to be replicable.

For example, Culverhouse et al. found no proof that the thousands of studies on the relationship between 5-HTTLPR and depression provided evidence of a genuine genetic difference (49). More recently, Border et al. found no evidence for "any candidate gene polymorphism associations with depression phenotypes or any polymorphism-by-environment moderator effects (50)." Although a negative self-schema can relatively reflect trait factors compared with depression, the phenotype is also highly polygenic, and the genetic effect expected from a single gene can be small. However, in the present study, the number of participants was small, the AA genotype was relatively low compared to other genotypes, the power was insufficient, and cross-validation was not performed. Therefore, it will be necessary to replicate these results with a much larger sample size in the future. The fourth limitation is that it is not clear whether the genetic association in the present study is applied to ethnicities other than Japanese. The fifth limitation is that although prior studies indicated that SNP rs1059004 predicted OLIG2 gene expression in Caucasian subjects, it is unclear whether a significant association exists between the SNP rs1059004 and OLIG2 gene expression in Japanese

subjects. This study is the first to indicate a significant genetic association between the *OLIG2* SNP rs1059004 and negative self-schema as a trait factor in susceptibility to MDD in Japanese subjects. The results of the present study suggest an association between *the OLIG2* SNP rs1059004 and negative self-schema by influencing the function of oligodendrocytes. These results may support the involvement of a genetic factor regulating oligodendrocyte function in generating a negative self-schema as a trait factor underlying susceptibility to depression in the pathology of MDD.

DATA AVAILABILITY STATEMENT

The SNP data presented in the study are publicly available. This data can be found in dbSNP (https://www.ncbi.nlm.nih.gov/SNP/snp_viewTable.cgi?handle=TOHOKUPSY).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of Tohoku University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HK, HTa, YKi, CO, ZY, and HTo contributed to the acquisition of data or the analysis and interpretation of data. HK and HTa were involved in drafting the manuscript. HTa, YKa, SF, TO, and HTo critically revised the manuscript for important scientific content. HTa, RK, YT, and HTo made substantial contributions to the conception and design of the study. All authors read and approved the final version of the manuscript and agreed on the order in which their names would be listed in the manuscript.

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