Val1483Ile polymorphism in the fatty acid synthase gene was associated with depressive symptoms under the influence of psychological stress

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</table>
Val1483Ile polymorphism in the fatty acid synthase gene was associated with depressive symptoms under the influence of psychological stress

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Abstract

Background: To study the association between lipid-metabolism and depressive symptoms, genetic polymorphisms in serotonin transporter linked promoter region (5-HTTLPR) and fatty acid synthase gene (FASN) were investigated.

Method: A cross-sectional study was conducted on 177 women (n = 166) and men (n = 15) recruited from workers in a hospital and nursing homes in Japan. Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression (CES-D) scale and perceived psychological stress was measured using visual analogue scale (VAS). The genotypes of 5-HTTLPR (insertion/deletion; L/S), and FASN (Val1483Ile) were determined by the PCR methods. Linear regression analysis was performed, in which CES-D scores served as a dependent variable, and VAS scores, gene polymorphism, and confounders as independent variables.

Results: Under the influence of perceived stress, S/S carriers of the 5-HTTLPR gene showed significantly higher CES-D scores in comparison with L/L+L/S carriers (F = 8.2, standardised \( \beta = 0.16, p < 0.05 \)). Regression analysis also confirmed that CES-D scores in participants with Val/Val + Val/Ile genotypes of the FASN gene were significantly higher than those with Ile/Ile genotype (F = 8.4, standardised \( \beta = 0.16, p < 0.05 \)). In relation to physical features, BMI among participants with S/S genotype of 5-HTTLPR was significantly lower compared with those with L/L+L/S genotype.

Conclusions: The Val1483Ile polymorphism in the FASN was associated with depressive symptoms under the influence of psychological stress. The S variant of 5-HTTLPR was related with less obese.

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1. Introduction

Literature suggested the association between depression and lipid metabolism: ex. lowered serum cholesterol levels were observed in depressive patients, particularly in those with suicidal behaviour (Fawcett et al., 1997), whereas the comorbidity between depression and hyperlipemia was also reported (Akbaraly et al., 2009). We are attempting to clarify this association from the point of view of different genotypes. Genetic variation in the 5' flanking transcriptional region of serotonin transporter gene (5-HTTLPR), which originates long (L) and short (S) alleles, plays a role in predisposition to major depression in interaction with stressful life events (Caspi et al., 2003). The serotonergic system was hypothesized to regulate behavioural and metabolic responses associated with the development of obesity through feeding and satiety (Barsch and Schwartz, 2002). Fatty acid (FA) metabolism may also

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explain one of the mechanisms to link the psychological and
somatic disorders. FA synthase (FAS), which is encoded by the
FAS gene (FASN), is the central enzyme in de novo lipogenesis,
catalysing the conversion of malonyl CoA into palmitate
(Semenovich, 1997). The Val1483Ile polymorphism in the
FASN is linked to central obesity and insulin sensitivity, and
putatively affects FAS action (Moreno-Navarrete et al., 2009).
Although the evidence of the relationships between lipid-
metabolism and affection remains controversial, it is relevant
to reason on the biological pathway. The aim of this study was
to investigate the common effects of the 5-HTTLPR and the
FASN genes.

2. Participants and methods

A cross-sectional study was carried out on 177 women
(n = 166) and men (n = 15) with a mean age of 42.4 (SD 13.17),
recruited from workers in a hospital and two nursing homes
located in Shizuoka Prefecture, Japan. The Ethics Committee of
University of Shizuoka approved the study protocol, and all
participants gave informed consent to participate in this study.
Self-administrated questionnaire was distributed to the par-
ticipants beforehand and answered one day before the exami-
nation day (working days). The questionnaire contains
the demographic measures (age, gender, medication, etc.), lifestyle
characteristics (smoking status: non-smoker or former/current),
current alcohol consumption: 0 vs ≥once per week, and leisure-
time physical activity: <once per month vs ≥once per week, and
psychological measures. Perceived stress was given using visual
analogue scales (10 cm) anchored with “not at all” and “quite
strong”. Depressive symptoms were assessed with the Center
for Epidemiologic Studies Depression Scale (CES-D) (Matthews
et al., 1985; Shima et al., 1985).

Fasting blood was sampled between 0830 and 1030 h from
the forearm vein of each participant with a heparinized and
serum-separator vacutainer tubes from which sera were
obtained by centrifugation. The sera samples were delivered
to a laboratory (FALCO Inc., Hamamatsu), and the heparinized
blood tubes were shipped to University of Shizuoka. Serum
triglycerides (TG) and total cholesterol (TC) were measured
enzymatically. High-density lipoprotein cholesterol (HDL-C)
and low-density lipoprotein cholesterol (LDL-C) were deter-
mined by the precipitation method using heparin-calcium. To
assess insulin resistance, the homeostasis model assessment of
insulin resistance (HOMA-IR) was used: fasting serum insulin
(μU/ml) × glucose (mg/dl) / 405 (Matthews et al., 1985). The
homeostasis model assessment of beta-cell function (HOMA-B)
was calculated as fasting serum insulin (μU/ml) × 360/[glucose
(mg/dl) − 63] (Matthews et al., 1985). Leukocytes were
isolated from the heparinized blood by density centrifugation
by the method of English and Andersen (1974), as described by
Albrechtsen et al. (1988). Genomic DNA was then extracted
from the leukocytes using the phenol-chloroform extraction
method (Sambrook et al., 2006). The genotype of 5-HTTLPR
(insertion/deletion; L/S) was determined by amplified the
fragments including the polymorphisms by PCR. The FASN
genotype (Val1483Ile, rs2228305) was determined by PCR–
restriction fragment length polymorphism analysis.

Data were analysed by the Japanese versions of SPSS (ver.
12.0.1) for Windows OS. For comparison of differences of
each genotype, analysis of covariance was utilised. Multiple
regression analysis was conducted to evaluate depressive
symptoms under the influence of perceived psychological
stress and covariates. A probability p value less than 0.05 was
considered significant.

3. Results

Prior to data analysis, one person taking steroid contained
medicine, one participant ingesting Graves disease remedy,

Table 1

<table>
<thead>
<tr>
<th>Characteristics of participants.</th>
<th>Female</th>
<th></th>
<th>Male</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>t.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t.1.4</td>
<td>Age</td>
<td>162</td>
<td>43.2 (13.00)</td>
<td>15</td>
</tr>
<tr>
<td>t.1.6</td>
<td>BMI (kg/m²)</td>
<td>162</td>
<td>22.4 (4.40)</td>
<td>15</td>
</tr>
<tr>
<td>t.1.7</td>
<td>Subjective stress (%)</td>
<td>162</td>
<td>57.9 (25.36)</td>
<td>15</td>
</tr>
<tr>
<td>t.1.8</td>
<td>Satisfation of life (%)</td>
<td>162</td>
<td>57.1 (23.21)</td>
<td>15</td>
</tr>
<tr>
<td>t.1.9</td>
<td>Subjective sleep quality (%)</td>
<td>162</td>
<td>65.8 (28.86)</td>
<td>15</td>
</tr>
<tr>
<td>t.1.10</td>
<td>CES-D scores</td>
<td>162</td>
<td>14.9 (6.95)</td>
<td>15</td>
</tr>
<tr>
<td>t.1.11</td>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t.1.12</td>
<td>No or ex-smoker</td>
<td>120</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>t.1.13</td>
<td>Present smoker</td>
<td>42</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>t.1.14</td>
<td>Current alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t.1.15</td>
<td>(almost) No</td>
<td>140</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>t.1.16</td>
<td>≥Once per week</td>
<td>21</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>t.1.17</td>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t.1.18</td>
<td>&lt;Once per month</td>
<td>102</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>t.1.19</td>
<td>≥Once per week</td>
<td>60</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>t.1.20</td>
<td>5-HTTLPR gene polymorphisms</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>t.21</td>
<td>L/L</td>
<td>8 (4.5%)</td>
<td>1</td>
<td>6.7%</td>
</tr>
<tr>
<td>t.22</td>
<td>L/S</td>
<td>53 (29.9%)</td>
<td>5</td>
<td>33.3%</td>
</tr>
<tr>
<td>t.23</td>
<td>S/S</td>
<td>114 (64.4%)</td>
<td>9</td>
<td>60.0%</td>
</tr>
<tr>
<td>t.24</td>
<td>FASN gene polymorphisms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t.25</td>
<td>Val/Val</td>
<td>159 (89.8%)</td>
<td>12</td>
<td>80.0%</td>
</tr>
<tr>
<td>t.26</td>
<td>Val/Ile</td>
<td>14 (7.8%)</td>
<td>3</td>
<td>20.0%</td>
</tr>
<tr>
<td>t.27</td>
<td>Ile/Ile</td>
<td>3 (1.7%)</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
and one who recently had a surgical operation were excluded; consequently, 162 female and 15 male participants were analysed. The characteristics of the sample are summarised in Table 1, together with the number of participants with data for each variable.

Table 2 exhibits the differences of variables concerning metabolic syndrome and psychological factors after controlling for gender, age and lifestyle factors. Since there were only nine subjects with L/L genotype of 5-HTTLPR, the L/L and L/S genotypes were pooled and compared with the S/S genotype in further analysis. In the same manner, FASN polymorphism was divided into Val/Val and Val/Val2+/Ile/Ile groups, and the dichotomized data were utilised for further analysis. As shown in Table 2, the subjects with S/S genotype of 5-HTTLPR exhibited significantly lower BMI in comparison with the L/L + L/S genotypes (p<0.05). In FASN, participants with Val/Val2+/Ile/Ile genotypes presented significantly higher CES-D scores (p<0.05) in comparison with those with Val/Val genotypes.

Depressive symptoms under the influence of psychological stress were analysed by the linear regression analysis: the CES-D scores as dependent variable, and subjective stress measured by VAS, gene polymorphism and covariates as independent variables (Table 3); consequently, the S/S genotype of 5-HTTLPR significantly contributed to depressive symptoms in comparison with S/S + L/L genotypes under the influence of psychological stress (Model 1: Standardised $\beta = 0.15$, p<0.05). Participants with the Val/Val2+/Ile/Ile genotype in the FASN revealed a significantly higher depressive symptoms in comparison with those with Val/Val under the psychological stress (Model 2: Standardised $\beta = 0.16$, p<0.05). Even though the 5-HTTLPR and FASN genotypes were put into the analysis model together, each of them showed significance (Model 3: Standardised $\beta = 0.15$, p<0.05; Standardised $\beta = 0.15$, p<0.05); i.e., the 5-HTTLPR and the FASN were independently related with depressive symptoms.

### Table 2

<table>
<thead>
<tr>
<th>Genotype</th>
<th>5-HTTLPR</th>
<th>FASN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S/S</td>
<td>L/L</td>
</tr>
<tr>
<td>n</td>
<td>114</td>
<td>61</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.0 (0.36)</td>
<td>23.6 (0.56)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Subjective stress (%)</td>
<td>58.2 (2.42)</td>
<td>58.9 (3.14)</td>
</tr>
<tr>
<td>CES-D scores</td>
<td>15.8 (0.71)</td>
<td>13.8 (0.81)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>80.8 (4.36)</td>
<td>998 (6.15)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>211.2 (3.67)</td>
<td>221.1 (5.82)</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>74.0 (1.67)</td>
<td>70.7 (2.38)</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>120.4 (2.99)</td>
<td>130.1 (4.83)</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>85.7 (1.17)</td>
<td>91.3 (3.75)</td>
</tr>
<tr>
<td>Insulin (mg/ml)</td>
<td>5.1 (0.04)</td>
<td>5.4 (0.14)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.03 (0.352)</td>
<td>7.35 (0.952)</td>
</tr>
<tr>
<td>HOMA-ß</td>
<td>115.5 (8.73)</td>
<td>93.6 (18.50)</td>
</tr>
</tbody>
</table>

Results are expressed as mean (SE). Comparisons are controlling for age, gender, BMI, smoking habit, alcohol consumption, and physical activities. BMI: body mass index. Subjective stress: perceived stress assessed using visual analogue scales anchored with “not at all” (0%) and “quite strong” (100%). 5-HTTLPR: Serotonin transporter gene linked polymorphism (L: long, S: short). FASN: Val(G)1483Ile(A) polymorphism in the fatty acid synthase gene. TC: Total cholesterol. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. HOMA-IR: homeostasis model assessment of insulin resistance. HOMA-ß: homeostasis model assessment of beta-cell function. Note that the subject number included in this analysis is slightly lower, owing to the lack of information for a few subjects.

### Table 3

<table>
<thead>
<tr>
<th>Gene polymorphism</th>
<th>5-HTTLPR (S/S: L/S + L/L)</th>
<th>FASN (Val/Val: Ile/Ile)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardised $\beta$</td>
<td>Standardised $\beta$</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.15&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>0.16&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Model 3 (Model 1 + Model 2)</td>
<td>0.15&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.15&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Each model was adjusted by gender, age, BMI, leisure time physical activities, smoking habit and alcohol consumption. All models of overall genotypes are significant (p<0.0005).

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HTTLPR S/S genotype exhibited higher depressive symptoms compared with those with L/S + L/L genotypes. In addition, in S/S participants, BMI was lower and serum TG levels appeared to be lower in comparison with L/S + L/L participants.

5-HTTLPR S variant has been thought to be associated with susceptibility for depression (Canli and Lesch, 2007) since a longitudinal study revealed the vulnerability of S variant to stressful life events (Caspi et al., 2003). The present study supports the result. In addition, our results indicated that 5-HTTLPR S variant could work to reduce obesity risks, though it is unsolved whether the 5-HTTLPR directly affect obesity-related index, or there were confounders between them.

Discrepant results concerning the 5-HTTLPR variants and obesity were obtained in previous studies. Sookoian et al. (2008) showed that S/S carriers had higher body weights in comparison with L/L carriers in obese (BMI ≥27 kg/m²) group of healthy male population. Lan et al. (2009) reported that S/S genotype was a determinant of increased BMI level in non-elderly stroke patients. On the other hand, Bah et al. (2010) presented that S allele tended to be more frequent in underweight persons among normal population. Discrepant results concerning 5-HTTLPR and BMI in previous studies might depend on participants’ characteristics such as healthy, having metabolic syndrome risks, etc. Since participants analysed in the current study were healthy volunteers, studies on normal population can support our results. Thus, it seems meaningless to discuss the relationships L allele and binge eating (Monteleone et al., 2006), or to think of the associations between S allele and anorexia nervosa (Hoffman et al., 2007) in relation to our results.

5-HTTLPR affects FAS gene, which encodes FAS, a key enzyme in de novo lipogenesis (Semenkovich, 1997). Moreno-Navarrete et al. (2009) recently showed that the adipose tissue FAS activity was significantly higher in subjects with the Val variant in comparison with carriers of the Ile variant. In addition, Val allele in the FASN is linked with impaired glucose tolerance, visceral obesity etc. (Kovacs et al., 2004; Moreno-Navarrete et al., 2009).

However, no differences were found between Val and Ile alleles in lipid and glucose-metabolism indices in this study. An interesting finding in the present study was that the FASN was related with depressive symptoms in the same degrees as the 5-HTTLPR under the influence of perceived stress, suggesting that Val1483Ile polymorphism in the FASN gene can affect the susceptibility to depression, and that the Ile variant may contribute to vulnerability to psychological stress. The pathway of the FASN effects on depressive symptoms is thought to differ from the one of 5-HTTLPR because each genotype was independently related with depressive symptoms as shown in model 3 of Table 3.

5. Limitations and conclusion

There are limitations in the current study. Serotonin levels in the central nervous system were unknown. The number of male participants was small, which unavoidably put the gender factor as an independent variable of linear statistical models. Sample size could not be enough large to compare FASN alleles. Our results may be considered as preliminary, and further research is needed to confirm these findings. However, we presented possible relationships between depressive symptoms and FASN gene, and between BMI and 5-HTTLPR.

6. Uncited reference

Sambrook et al., 1989

Role of funding source

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Conflicts of interest

None of the authors have any conflicts of interest.

Acknowledgement

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References


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