Tyrosine Hydroxylase Gene Microsatellite Polymorphism Associated With Insulin Resistance in Depressive Disorder

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A high association between type 2 diabetes mellitus and depressive illness has been reported. Insulin resistance during depressive illness might contribute to the linkage between depression and type 2 diabetes. To determine whether the genetic polymorphisms of the tyrosine hydroxylase ([TH] HUMTH01) and insulin (INS-VNTR) genes contribute to insulin resistance in depressive illness, we analyzed the association between the polymorphisms and insulin resistance in 41 Japanese patients with depressive disorder, 204 normal control subjects, 161 cohort subjects with normal glucose tolerance (NGT) and without depressive symptomatology, and 59 NGT subjects with depressive symptomatology. The depressive patients had a significantly lower insulin sensitivity index (SI) than the control subjects ($P = .016$). Depressive NGT subjects had a significantly higher homeostasis model assessment (HOMA) insulin resistance index [HOMA(R)] than the nondepressive NGT subjects ($P < .0001$). The depressive patients and NGT subjects had more HUMTH01 allele 7 (TH7) than the controls and nondepressive NGT subjects. SI was significantly lower in patients with the TH7/7 homozygote versus patients with the other genotypes and the controls. TH7 was associated with higher HOMA(R) as compared with the other alleles in the NGT subjects. Insulin resistance was associated with depressive disorders. The HUMTH01 and INS-VNTR were associated with insulin resistance and depressive symptoms.

AN ASSOCIATION between diabetes mellitus and depressive disorder has been previously reported.[1,2] An episode of depression increases the risk for the onset of type 2 diabetes.[3,4] Two reports demonstrated that depressive patients tend to show an impaired glucose pattern with a higher cumulative insulin response.[5,6] These findings suggested the presence of insulin resistance and hyperinsulinemia during depressive illness.

Tyrosine hydroxylase (TH) is a rate-limiting enzyme in the synthesis of noradrenaline and dopamine, and is speculated to be involved in the pathophysiology of psychiatric disorders.[7,8] The (TCAT)n tetranucleotide repeat microsatellite (HUMTH01) in the TH gene is suggested to regulate the alternative splicing process of the human TH mRNA and the turnover of catecholamine.[9,10] A dysfunction of the catecholamine system has been reported to be involved in depressive disorder.[7,8,11] It has been reported that HUMTH01 is positively associated with manic-depressive illness[12-14] and negatively associated with depressive symptoms in mood disorders.[15] However, some reports demonstrated no association between HUMTH01 and affective disorder[16] or manic-depressive illness.[17]

The human insulin gene is located adjacent to the TH gene. Recent evidence has suggested that the human insulin gene VNTR (variable number of tandem repeats) minisatellite (INS-VNTR) regulates the transcriptional process of the insulin gene and contributes to some insulin-related disorders, including type 1 diabetes.[18-20] We speculated that a genetic polymorphism of HUMTH01 and INS-VNTR might contribute to insulin resistance in depressive illness, and we discuss a potential role of TH in the pathogenesis of insulin resistance in depressive disorder.

SUBJECTS AND METHODS

Subjects

Forty-one unrelated patients with depressive disorder (depression group) were recruited from among inpatients and outpatients of the Third Department of Internal Medicine and the Department of Psychosomatic Medicine, Tohoku University Hospital. All patients had a diagnosis of depressive disorder according to DSM-IV criteria,[21] including major depressive disorders (n = 25) and depressive disorders not otherwise specified (n = 16), but not manic-depressive disorder. Depressive symptoms were scored using the Hamilton Rating Scale for Depression.[22] Clinical and laboratory tests were normal, with the exception of mild hypertension in 11 patients and mild hyperlipidemia in 11 patients. None of the subjects had a previous history of diabetes. All depressive patients were shown to have normal fasting plasma glucose according to the new diagnostic criteria of the American Diabetes Association.[23]

The control subjects (control group) were selected from individuals who visited Sendai Kosei Hospital (Sendai, Japan) for a general health examination. They had no personal or family history of psychiatric disorders, hypertension, hyperlipidemia, coronary vascular disease, or diabetes. All control subjects were shown not to have a depressive disorder according to DSM-IV criteria[21] and had normal clinical and laboratory examinations and normal glucose tolerance (NGT) by an oral glucose tolerance test (OGTT) after a 75-g load.[23]

The other cohort subjects with NGT were selected from individuals who also visited the 7 local private hospitals in Miyagi and Totigi Prefecture for a general health examination. They also had no personal or family history of psychiatric disorders, hypertension, hyperlipidemia, coronary vascular disease, or diabetes. All subjects stayed at the hospital for 2 days for their general health examination. The cohort subjects (NGT group) were selected from the subjects who also had NGT on an OGTT and normal clinical and laboratory tests. The level of depressive symptoms in NGT subjects was classified on the basis of the Zung Self-Rating Depression Scale (ZSDS) as normal (20 to 39), mild (40 to 47), and moderate or severe (>48).[4,24-26] The original English scale was translated into Japanese, and the Japanese version has been well

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Table 1. Clinical Characteristics of the Subjects

Variable	Control Group	Depression Group	NGT Groups	
			A	B
No. of subjects	167	41	161	59
Male/female ratio	102/65	28/13	99/62	39/20
Age (yr)	46 ± 12	47 ± 13	49 ± 7	48 ± 12
BMI (kg/m^2)	22.6 ± 2.9	23.1 ± 2.3	23.6 ± 2.6	23.1 ± 2.1
Hamilton Depression Rating Scale	—	15.8 ± 7.1	—	—
Fasting plasma glucose (mg/dL)	91.6 ± 6.2	88.1 ± 6.1	92.4 ± 8.8	90.7 ± 7.7

validated.[27] One hundred sixty-one NGT subjects had normal symptoms, 56 subjects had mild depressive symptoms, and 3 subjects had moderate or severe symptoms. NGT subjects were divided into 2 subgroups, with NGT subjects with normal symptoms denoted as NGT group A, and NGT subjects with depressive symptoms (ZSDS > 40) as NGT group B. There were no significant differences in clinical characteristics between the control group and the depression group or between NGT groups A and B (Table 1).

Assessment of Insulin Sensitivity

Insulin sensitivity in the depressive group and the controls was assessed by minimal model analysis.[28] SI was assessed by the modified Bergman minimal model method[29] with an additional administration of regular human insulin (0.02 U/kg) 20 minutes after the glucose bolus (0.3 g/kg) as described previously.[30,31] Minimal model analysis was performed in the fasting condition. Insulin sensitivity in the NGT cohort was measured by homeostasis model assessment (HOMA) model analysis.[32] The HOMA model was validated against the hyperinsulinemic-euglycemic clamp for insulin resistance. Plasma insulin was analyzed using radioimmunoassay kits. Plasma glucose was determined using the glucose oxidase method. The clinical characteristics of the subjects are shown in Table 1. After the study protocol was approved by the Tohoku University Institutional Review Board, the study was performed according to the Declaration of Helsinki. All participants provided informed consent.

DNA Analysis

HUMTH01 and INS-VNTR class 1 alleles were identified by polymerase chain reaction followed by agarose electrophoresis and class 2 and 3 alleles were identified by Southern blot analysis as described previously.[33] The HUMTH01 was a (TCAT)n tetranucleotide repeat microsatellite and is denoted as repeat numbers of tetranucleotide, for example, allele 6 was 6 repeats of TCAT.[34]

Statistical Analysis

Differences between groups were tested by 1-way ANOVA, chi-square test for independence, and Fisher's exact probability test with Yates' correction. Wilcoxon's test was used for paired comparison and the Mann-Whitney *U* test for unpaired comparison. All *P* values are based on 2-sided comparisons and were taken to be significant at less than .05.

RESULTS

Five different alleles of HUMTH01 (alleles 6, 7, 8, 9, and 10) described by Puers et al,[34] were observed. Alleles 5 and 11 were not observed in the subjects, and the variant allele 10-1 was not distinguished from allele 10. Alleles 6, 7, 8, 9, and 10 correspond to HUMTH01 alleles Z-16, Z-12, Z-8, Z-4, and Z, respectively, in the report by Bennett and Todd.[20]

The distribution of HUMTH01 genotypes ($\chi^2 = 34.2$, $P < .0001$) or alleles ($\chi^2 = 14.0$, $P = .007$) was significantly different in the depression group versus the control group. The genotype frequency of TH7/7 was significantly higher in the depression group versus the control group ($P = .0004$) (Table 2). In contrast, the depression group had a lower frequency of TH6/9 than the control group ($P = .017$). The allele frequency of TH7 was also significantly higher in the depression group versus the control group ($P = .0043$). We investigated the genetic distribution of HUMTH01 in the NGT cohort. There was a significant difference in the allele frequencies of

Table 2. Frequency of TH Microsatellite Genotypes and Alleles

Parameter	Control Group	Depression Group	*P*	NGT Groups		
				A	B	*P*
Genotype	167 (100)	41 (100)		161 (100)	59 (100)	
6/6	12 (7.2)	1 (2.4)	NS	14 (8.7)	1 (1.7)	NS
6/7	22 (13.2)	11 (26.8)	NS	14 (8.7)	14 (23.7)	NS
6/9	32 (19.2)	1 (2.4)	.017	39 (24.2)	2 (3.4)	.0009
7/7	5 (3.0)	8 (19.5)	.0004	4 (2.5)	11 (18.6)	.0001
7/9	39 (23.4)	7 (17.1)	NS	40 (24.8)	11 (18.6)	NS
9/9	27 (16.2)	12 (29.3)	NS	19 (11.8)	15 (25.4)	.023
Others	30 (18.0)	1 (2.4)	.024	31 (19.3)	5 (8.5)	NS
Allele	334 (100)	82 (100)		322 (100)	118 (100)	
6	82 (24.6)	14 (17.1)	NS	91 (28.3)	18 (15.3)	.0075
7	83 (24.9)	34 (41.5)	.0043	64 (19.8)	50 (42.4)	<.00001
8	21 (6.3)	0 (0)	.04	16 (5.0)	4 (3.5)	NS
9	138 (41.3)	33 (40.2)	NS	137 (42.5)	43 (36.4)	NS
10	10 (3.0)	1 (1.2)	NS	14 (4.3)	3 (2.5)	NS

P values were calculated by Fisher's exact probability test with Yates' correction. Data are presented as the no. (%).

Table 3. Frequency of INS-VNTR Genotypes and Alleles

Parameter	Control Group	Depression Group	*P*	NGT Groups A	NGT Groups B	*P*
VNTR genotype	167 (100)	41 (100)		161 (100)	59 (100)	
1S/1S	33 (19.8)	11 (26.8)	NS	30 (18.6)	13 (22.0)	NS
1S/1M	65 (38.9)	12 (29.3)	NS	67 (41.6)	17 (28.8)	NS
1S/1L	17 (10.2)	3 (7.3)	NS	20 (12.4)	4 (6.8)	NS
1M/1M	18 (10.8)	9 (22.0)	NS	9 (5.6)	15 (25.4)	<.0001
1M/1L	21 (12.6)	5 (12.2)	NS	21 (13.0)	6 (10.2)	NS
1L/1L	3 (1.8)	0 (0)	NS	3 (1.9)	2 (3.4)	NS
Others	10 (6.0)	1 (2.4)	NS	11 (6.8)	2 (3.4)	NS
VNTR allele	334 (100)	82 (100)		322 (100)	118 (100)	
1S	153 (45.8)	38 (46.3)	NS	151 (46.9)	47 (39.8)	NS
1M	127 (38.0)	35 (42.7)	NS	110 (34.2)	54 (45.8)	NS
1L	44 (13.2)	8 (9.8)	NS	49 (15.2)	15 (12.7)	NS
III	10 (3.0)	1 (1.2)	NS	12 (3.7)	2 (1.7)	NS

NOTE. *P* values were calculated by Fisher's exact probability test with Yates' correction. Data are the no. (%).
Abbreviations: 1S, VINS-NTR class 1S with repeats 25-38; 1M, repeat numbers 39-41; 1L, repeat numbers 42-44.

HUMTH01 between groups A and B ($\chi^2 = 24.8$, $P < .0001$). Every group was within the Hardy-Weinberg proportion. The genotype frequency of TH7/7 was significantly higher in group B compared with group A ($P = .0001$). In contrast, group B had a lower frequency of TH6/9 than group A ($P = .0009$). Group B had a higher frequency of TH7 than group A ($P < .00001$).

There was no difference in the genetic distribution of INS-VNTR between the depression group and the control group. The genotype frequency of INS-VNTR was different in group A versus group B ($\chi^2 = 20.5$, $P < .005$). Group B had a higher frequency of INS-VNTR 1M/1M than group A ($P = .00008$) (Table 3).

The depression group had significantly lower SI than the control group (4.25 ± 3.20 *v* $8.31 \pm 5.12 \times 10^{-4}$ mL · μU · min^{-1}, $P = .001$). The SI was significantly lower for patients with the TH7/7 homozygote compared with the control group ($P = .004$) and patients with the other genotypes (TH7/9, $P = .004$; TH9/9, $P = .005$; Fig 1). Patients with the TH6/7 heterozygote had significantly lower SI than the control group ($P = .006$) and patients with the TH9/9 homozygote ($P = .024$). Insulin sensitivity in the depression group improved after successful antidepressive treatment (A. Tashiro, unpublished observation, 2000).

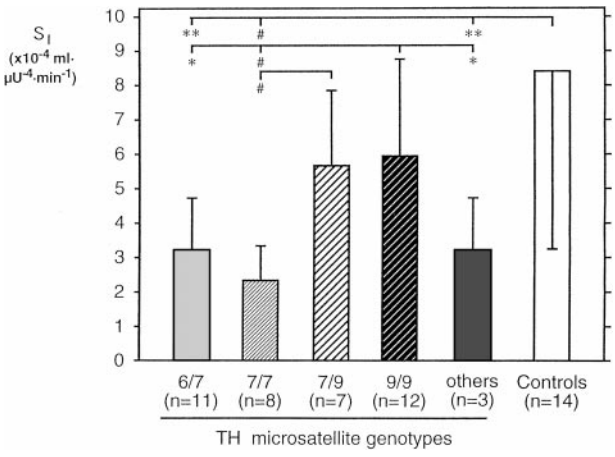

Fig 1. SI in the depression group and the control group. Results are the mean ± SD. *$P < .05$, **$P < .01$, #$P < .001$.

Group B had a significantly higher HOMA insulin resistance index (HOMA(R) 2.31 ± 1.34) than group A (1.09 ± 0.95, $P < .0001$) and the control group (0.99 ± 0.67, $P < .0001$). Subjects in group B with TH6 ($P < .0001$) or TH7 ($P < .0001$) had a higher HOMA(R) than subjects in group A with the same allele, respectively (Table 4). Subjects in group B with TH7 had a significantly higher HOMA(R) than group B with TH8 ($P = .036$), TH9 ($P < .0001$), and TH10 ($P = .042$).

Table 4. TH Microsatellite Genotypes, Alleles, and HOMA(R) in NGT Subjects (mean ± SD)

Parameter	Group A	Group B
TH Genotype		
6/6	1.15 ± 1.00 (14)	1.79 (1)
6/7	1.17 ± 1.23 (14)	3.21 ± 2.23 (14)*††
6/9	1.32 ± 0.98 (39)	2.00 (2)
7/7	2.45 ± 1.33 (4)††	4.51 ± 2.02 (11)§††
7/9	0.88 ± 0.97 (40)	1.77 ± 0.87 (11)†#
9/9	0.94 ± 0.91 (19)	1.24 ± 0.75 (15)‡**
Others	0.92 ± 0.72 (31)	1.32 ± 0.91 (5)
TH Allele		
6	1.14 ± 1.33 (91)§§	2.92 ± 1.73 (18)
7	1.25 ± 1.08 (64)‡‡	3.48 ± 1.81 (50)
8	1.18 ± 1.02 (16)	1.49 ± 1.02 (4)‖
9	0.98 ± 0.95 (137)	1.41 ± 0.75 (43)‡‡
10	0.94 ± 1.09 (14)	1.27 ± 0.98 (3)¶
Control	0.99 ± 0.67 (120)	

NOTE. Number of subjects is shown in parentheses.
**P* = .006 *v* group A TH6/7.
†*P* = .008 *v* group A TH7/9.
‡*P* = .03 *v* group B TH6/7.
§*P* = .0005 *v* group B TH7/9.
‖*P* = .036 *v* group B TH7.
¶*P* = .042 *v* group B TH7.
#*P* = .0005 *v* control.
***P* < .0001 *v* group B TH7/7.
††*P* < .0001 *v* control.
‡‡*P* < .0001 *v* group B TH7.
§§*P* < .0001 *v* group B TH6.

TH9 was associated with INS-VNTR IS, TH7 with 1M, TH6 with 1L, and TH10 with class III, suggesting a tight linkage disequilibrium between HUMTH01 and INS-VNTR.[19,28] The NGT subjects with the haplotype of TH7 and 1M had higher fasting plasma insulin than NGT subjects with haplotype TH9 and 1S (12.3 ± 6.7 *v* 8.6 ± 5.6 μU/mL, $P < .0001$). There was no significant difference in the body mass index (BMI), total cholesterol, triglyceride, and blood pressure among the genetic variations of HUMTH01 and INS-VNTR.

DISCUSSION

Both insulin resistance and decreased insulin secretion have been shown to be antecedents of type 2 diabetes. Previous prospective studies have consistently shown that insulin resistance and hyperinsulinemia are strong predictors of type 2 diabetes.[35] An episode of depression increases the risk for the onset of type 2 diabetes.[3,4] One report demonstrated that depressive patients tend to show an impaired glucose pattern with a higher cumulative insulin response.[5] We previously reported an insulin hyperresponse in a patient with depressive disorder.[6] The present study demonstrated insulin resistance in the depression group and in NGT subjects with depressive symptoms. The presence of insulin resistance in depressive illness suggests that depressive disorder may be related to the onset and course of type 2 diabetes.

Several studies have mapped the candidate genes for depressive illness to the TH locus in 11p15.[7] The 4 isoforms of TH have different functional characteristics, which are produced through an alternative splicing process of the human TH mRNA in the brain and adrenal medulla.[8] HUMTH01 has been suggested to regulate the alternative splicing process of human TH mRNA[10] and the catecholamine turnover.[9,36] Some reports have shown that HUMTH01 was positively associated with manic-depressive illness[12-14] and negatively associated with depressive symptoms in mood disorders.[15] However, some conflicting results have been reported concerning the association between HUMTH01 and affective disorder[16] or manic-depressive illness.[17] Bellivier et al[37] suggested the presence of methodologic problems in the association studies resulting from the wrong selection of control subjects. In this study, we selected control subjects and the NGT cohort without a personal and familial history of psychiatric disorders and diabetes, and confirmed an association between TH7 and depressive symptoms in the selected subjects.

HUMTH01 is in tight linkage disequilibrium with the INS-VNTR class.[20,33] HUMTH01 allele 9 is linked with INS-VNTR IS, allele 7 with 1M, allele 6 with 1L, and allele 10 with INS-VNTR class III.[20,31] INS-VNTR class III is associated with central obesity and hyperinsulinemia.[18] Sten-Linder et al[19] reported a significant association between TH genotypes and the early insulin response to glucose infusion in healthy subjects. However, they did not find a significant difference in TH genotype frequencies between type 2 diabetic and healthy subjects. Most Japanese are homozygous for the class 1 allele.[31] NGT subjects with the haplotype of TH allele 7 and INS-VNTR class 1M (7/1M) had higher fasting plasma concentrations of insulin than the subjects with haplotype TH allele 9 and INS-VNTR class 1S (9/1S) (12.3 ± 6.7 *v* 8.6 ± 5.6 μU/mL, $P < .0001$). Thus, the haplotype of TH7/1M is associated with increased insulin secretion and insulin resistance in the Japanese.

The present study demonstrates the presence of insulin resistance in patients with depression. Nine depressive patients had mild hypertension, 9 had mild hyperlipidemia, and 2 had both. There was no significant association between insulin resistance and hypertension or hyperlipidemia in the patients with depression. However, there was a significant association between insulin resistance and depressive symptoms in NGT subjects, who did not have hypertension or hyperlipidemia. Thus, depressive symptoms were associated with insulin resistance.

The precise mechanism of insulin resistance observed in depressive disorder remains unclear. Depression may be related to confounding factors such as obesity and exercise. Depressed individuals sometimes suffer from too much appetite and too little exercise. However, there was no change in the BMI or exercise after antidepressant treatment. Neuroendocrine abnormalities in depressive disorder have been reported.[38] Since antidepressant therapy with selective serotonin reuptake was reported to ameliorate insulin sensitivity in type 2 diabetic patients,[39,40] dysregulation of the central nervous system may play a role in the pathogenesis of insulin resistance. On the other hand, it is well known that the hypothalamic-pituitary-adrenal axis is activated in depressive disorder.[38] Both the relative insulin insensitivity and enhanced secretion of cortisol in depressive illness improve after successful antidepressive treatment.[41] These lines of evidence suggest that glucocorticoid hypersecretion may also be partly responsible for insulin resistance. TH7, a genetic marker for a low turnover of noradrenaline, might play a role in insulin resistance through regulation of the hypothalamic-pituitary-adrenal axis.

From this study, we conclude that genetic variations of the TH locus contribute to insulin resistance in depressive illness. TH7-associated insulin resistance might be an important mechanism in the link between type 2 diabetes and depression. Further investigations are required to clarity the precise role of TH7 in the pathogenesis of insulin resistance in depressive disorder.

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