Association Study of the 5-HTTLPR Polymorphism and Depression in 75-Year-Old Nondemented Subjects From the Vienna Transdanube Aging (VITA) Study

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Background: The site of effect for the selective serotonin reuptake inhibitors (SSRIs) is the serotonin transporter (5-HTT), which is extensively investigated for its involvement in depressive symptoms. The 5-HTT gene exhibits a 5'-promoter-based length polymorphism (5-HTTLPR) that affects the transcription efficiency and activity, known as short (S) and long (L) alleles. We studied the association of this polymorphism in old age and depression in the Vienna Transdanube Aging (VITA) study, excluding subjects with dementia.

Method: We used retrospective data from the baseline of the VITA study, which is a cohort study of all inhabitants of a geographical area aged 75 years (N = 544). Depression was diagnosed and classified strictly according to the DSM-IV. To eliminate dementia effects, we excluded subjects with a Clinical Dementia Rating higher than or equal to 1 and/or a Mini-Mental State Examination score lower than 24. Genotyping for the 5-HTTLPR L/S allele was conducted using polymerase chain reaction methodology.

Results: We found significantly higher SS genotype frequency in all subjects with past/present depression compared to controls (trend test, p = .01). The SS genotype frequency was especially high in subjects with onset of depression before age 65. No correlations were found between genotypes/S allele carriers and actual Hamilton Rating Scale for Depression, Short-Geriatric Depression Scale, and anxiety scale scores.

Conclusions: These observations of higher frequency of the 5-HTTLPR S allele in subjects with past/present depression fit with previous findings and point to the important role of 5-HTT in depression.

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Although numerous studies attempt to find correlations between gene variations and emotionality phenotypes, in terms of both normal spectrum personality variation and mood-related psychopathology, there is no clear finding to this link. However, genes clearly can be risk factors for developing depression, increasing the likelihood that severe environmental stresses will precipitate the onset of this disease.[1] Many gene variations can be "silent," producing no signs of depression except after subjects find themselves in an unusual (e.g., stress) environment, described as a "trigger." One such candidate is the serotonin transporter (5-HTT), which is the target for a large group of clinically effective antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs).[2–4]

In humans, transcriptional activity of the 5-HTT gene (SLC6A4) is modulated by a polymorphic repetitive element (5-HTT gene-promoter-linked polymorphic region, 5-HTTLPR) located upstream of the transcription start site.[5–7] The 5-HTTLPR has the capacity to moderate both transcription efficiency[8] and basal activity in vitro. For example, the short allele (S, consisting of 14 repeat elements) is associated with decreased 5-HTT transcription relative to the long allele (L, 16 repeat elements). In vivo, this polymorphism was found to effect functional responsivity of the serotonergic system to pharmacologic challenge.[3,4]

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The use of genetic association methods for investigating the relationship between the 5-HTTLPR and human mood disorders, especially depression and anxiety, has been extensively studied.[6,7,9–13] In several studies, associations between the 5-HTTLPR S allele and depression were reported,[14–18] while others could not replicate these associations.[9,19]

Here, we investigated whether 5-HTTLPR S and/or L alleles were associated with all depressive subjects and/or with different depressive grades in the Vienna Transdanube Aging (VITA) study in which most subjects were not demented and at the beginning of the study were exactly 75 years of age. At baseline, all subjects were physically and neurologically examined and psychologically tested to define cognitive status as well as noncognitive behavioral changes and state of health (see previous publications[20,21]). In this present work, we investigated the occurrence of the 5-HTTLPR polymorphism in nondemented subjects of the VITA study at baseline.

METHOD

Subjects

Subjects of the present study were selected from the VITA study. Detailed information about the recruitment and character of the subjects has been given previously.[21,22] Briefly, the VITA project is a prospective community-based cohort study of all inhabitants aged 75 years in a geographical area of Vienna, Austria. There were no inclusion or exclusion criteria, but the VITA investigators contacted every inhabitant of the geographical area on the left shore of the river Danube born between May 1925 and June 1926 (N = 1505). Finally, 606 individuals participated completely in the VITA study at baseline and a further 91 participated without blood donation. The mean age of the 606 individuals was 75.8 years with a standard deviation of only 0.45 years, which minimized age-associated changes of variables within the cohort.

The standardized survey of causes of refusal to participate showed "lack of interest" in 52%, "somatic diseases" in 25%, "negativism" in 8%, "obvious affective problems" in 7%, and rare other causes. To obtain information about persons refusing participation, data on current medication of a consecutive series of refusers (N = 52) was compared with data of participants: we found no significant difference between rate of different types of medication, including antidepressants. This finding can be interpreted as indicating that depression was not more prevalent in nonparticipants.

In all, 606 volunteers consented to participate and went through the whole examination (9 hours per patient in 3 days), including general physical health check; questionnaires for education, psychosocial activities, memory complaints, etc.; psychological tests, including the Mini-Mental State Examination (MMSE), Fuld Object Memory Test (FULD), Clinical Dementia Rating (CDR), Hamilton Rating Scale for Depression (HAM-D), Short Geriatric Depression Scale (SGDS), Spielberger State-Trait Anxiety Inventory (STAI), and Unified Parkinson's Disease Rating Scale; and a cranial magnetic resonance imaging (all test and recruitment strategies have been described[20,22]).

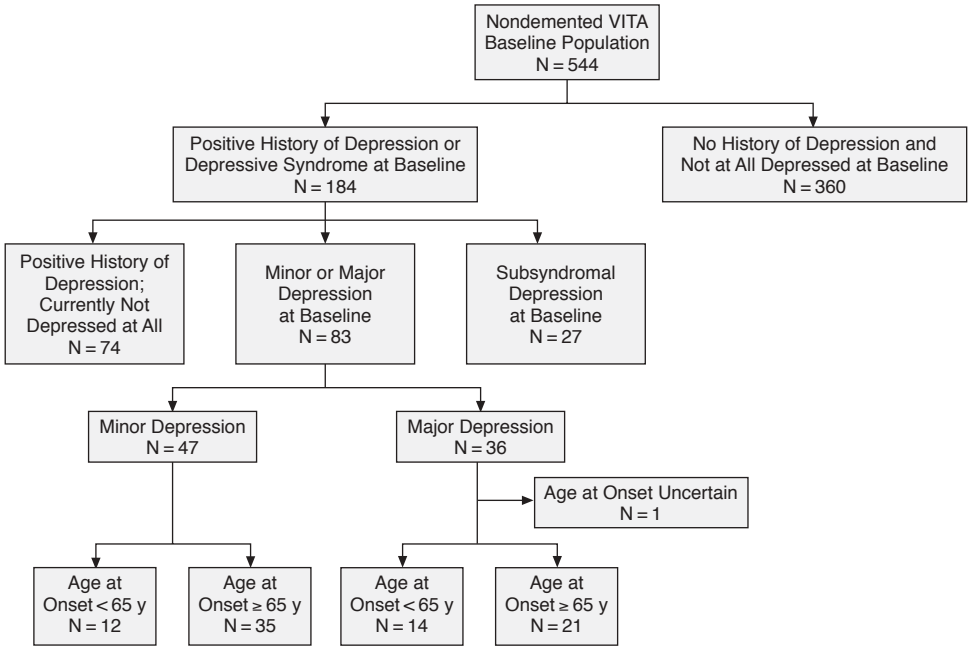
Depression was diagnosed and classified strictly according to the DSM-IV. Questions regarding history of depressive episodes and age at onset of depressive disorder were derived from the SKID interview,[23] the German translation of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I),[24,25] which has excellent reliability.[26] The existence of each of the 9 possible symptoms of a depressive episode (A1–A9) was evaluated by an experienced gerontopsychologist using an extended SKID interview without the so-called exclusion items. Thus, it was never judged whether the symptoms of depression could have been initiated or maintained by an organic factor. Every symptom A1 to A9 was judged after answers were given to questions structured according to the detailed description of the particular symptom by the DSM-IV. Those included 7 questions concerning A1 (depressed mood), 4 questions concerning A2 (diminished interest or pleasure), 3 questions concerning A3 (weight loss or gain, appetite), 4 questions concerning A4 (insomnia, hypersomnia), 9 questions concerning A5 (psychomotor agitation or retardation), 2 questions concerning A6 (loss of energy), 5 questions concerning A7 (feelings of worthlessness), 5 questions concerning A8 (thinking, concentration), and 4 questions concerning A9 (suicidal). The questions (in German language) can be obtained by request from coauthor S.J. The time frame for symptoms A1 to A9 was almost every day for the last 2 weeks. Major depression (5 to 9 symptoms) and minor depression (A1 and/or A2, 2 to 4 symptoms) were defined according to the DSM-IV. Subsyndromal depression was diagnosed in patients who fulfilled neither criterion A1 nor A2 but showed more than 1 of the other 7 items of depression (A3 to A9).[27]

Additionally, we excluded subjects with dementia using the criteria of CDR and MMSE. All 24 subjects with a CDR higher than or equal to 1 and/or an MMSE score lower than 24 were excluded. This approach tried to eliminate the possibility of associations as a consequence of dementia and rather looked only for the impact of depression.

Figure 1 shows the number of nondemented VITA subjects belonging to one of the depressive categories with regard to both the current depressive symptomatology and the history and onset of depressive disorder. In 1 patient suffering from major depressive episode at age 75, the age at onset of the first depressive episode could not be unequivocally ascertained.

For detailed information, the number of subjects; MMSE, FULD, CDR, HAM-D, SGDS, and STAI scores; and onset of depression can be viewed in Table 1. The

Figure 1. Nondemented VITA Population Subgrouped by Different Grades of Depression



Abbreviation: VITA = Vienna Transdanube Aging study.

VITA study was carried out with the permission of the Ethics Committee of the City of Vienna, Austria, and each participant gave informed consent.

Genomic DNA Isolation

DNA was prepared from 2 mL of EDTA-blood by using proteinase K as described previously.[21] The aliquot DNA is then saved in cryo-Vials (Nunk GmbH, Wiesbaden, Germany) and frozen at –70°C until processing.

Genotyping 5-HTTLPR

For genotyping, genomic DNA was extracted from patient's blood. The restriction analysis of the genotypes was conducted with primers flanking the gene for the promoter region of the 5-HTT (5-HTTLPR), gene accession number X76753, comprising a repetitive sequence with an insertion-deletion variation of 44-bp.[7] The polymerase chain reaction was conducted using the primer pair: 5'-GAG GGA CTG AGC TGG ACA AC-3' and 5'-GCA GCA GAC AAC TGT GTT CAT C-3'. The reaction mix consisted of 75 mM of Tris-Hcl (pH = 9), 20 mM of $(NH_4)_2SO_4$, 0.1% of Tween 20, 0.8 mM of $MgCl_2$, 400 μm of dNTP (each), 0.5 U of Taq-polymerase, 0.64 pmol/μL of primers (each), and DNA template. The reaction was as follows: denaturation at 95°C for 3 minutes, 30 cycles of 95°C for 45 seconds, 61.2°C for 45 seconds, and 72°C for 45 seconds, extension at 72°C for 3 minutes. The products were loaded on 2% agarose gel and stained with ethidium bromide. The analysis was conducted according to band lengths: Short allele (S) had 585 bp and long allele (L) had 673 bp.

Statistical Analysis

To investigate a difference in the scores between the 2 groups—patients with no history of depression and not at all depressed at baseline versus patients with past and/or present depressive symptoms—nonparametric Wilcoxon rank sum tests were performed (SAS 8.02; SAS Institute Inc., Cary, N.C.). In case of a significant result, further Wilcoxon tests were computed for the subgroups of past depressive symptoms and present depressive symptoms versus the control without any history of depression. For these 2 analyses, all p values < .025 were considered significant (Bonferroni correction for multiplicity); for all other tests, all p values < .05 were considered significant. A Kruskal-Wallis test and a Wilcoxon test were performed to find a difference in the HAM-D between the 5-HTT genotypes and between alleles. For the inference about the null hypothesis that the genotype frequency, respectively the allele frequency, is not associated with the disease, Cochran-Armitage trend tests were computed according to Sasieni.[28] In case of a significant result, the second group was again divided into the subgroups of past depressive symptoms and present depressive symptoms and again a Bonferroni correction for multiplicity was performed (p values < .025 were considered significant). Genotype frequencies were tested for conformity with Hardy-Weinberg equilibrium using the program at

Table 1. Study Variables in VITA Study Subjects by Different Depression Diagnoses in the First Recruitment Phase

Variable	All Subjects	No History of Depression and No Symptoms of Depression at Baseline (0)	Past and/or Present Symptoms of Depression	No Symptoms of Depression at Baseline but Positive History of Depression (1)	Subsyndromal Depression at Baseline (2)	Minor Depression at Baseline (2)	Major Depression at Baseline (2)	Minor or Major Depression at Baseline
No. of subjects	544	360	184	74	27	47	36	83
Male/female, N	228/316	167/193	61/123	23/51	11/16	14/33	13/23	27/56
Age, mean ± SD, y	75.8 ± 0.44	75.7 ± 0.44	75.8 ± 0.44	75.8 ± 0.44	75.8 ± 0.46	75.8 ± 0.38	75.8 ± 0.51	75.8 ± 0.44
Onset of depression before age 65 y/at age ≥ 65 y/unclear, N	…	...	95/86/3	48/24/2	21/6/0	12/35/0	14/21/1	26/56/1
MMSE score, mean ± SD[a]	28.0 ± 1.5	28.1 ± 1.4	27.7 ± 1.5	28.0 ± 1.3	27.4 ± 1.7	27.7 ± 1.6	27.5 ± 1.5	27.6 ± 1.6
FULD score, mean ± SD[b]	43.4 ± 4.2	44.0 ± 3.8	42.3 ± 4.8	43.6 ± 4.0	40.5 ± 4.9	42.1 ± 5.5	41.4 ± 4.6	41.8 ± 5.1
HAM-D score, mean ± SD[c]	3.2 ± 5.3	0.9 ± 1.6	7.8 ± 6.9	2.4 ± 2.9	5.7 ± 3.3	10.4 ± 5.4	16.8 ± 5.1	13.2 ± 6.2
SGDS score, mean ± SD[d]	2.3 ± 2.4	1.6 ± 1.6	3.6 ± 2.9	2.1 ± 1.7	3.0 ± 2.5	4.0 ± 2.6	6.6 ± 3.2	5.3 ± 3.1
STAI1 score, mean ± SD[e]	34.1 ± 9.1	31.6 ± 7.5	38.9 ± 10.1	34.4 ± 7.4	38.0 ± 9.2	40.1 ± 9.4	47.7 ± 11.0	43.4 ± 10.7
STAI2 score, mean ± SD[e]	35.3 ± 9.6	32.1 ± 7.1	41.9 ± 10.4	37.0 ± 7.8	39.5 ± 8.1	44.0 ± 9.1	51.6 ± 11.3	47.3 ± 10.7

[a]Wilcoxon test: (0) vs. (1) p = .39, vs. (2) p = .0008.
[b]Wilcoxon test: (0) vs. (1) p = .42, vs. (2) p < .0001.
[c]Wilcoxon test: (0) vs. (1) p < .0001, vs. (2) p < .0001.
[d]Wilcoxon test: (0) vs. (1) p = .008, vs. (2) p < .0001.
[e]Wilcoxon test analysis for the sum of STAI1 and STAI2: (0) vs. (1) p < .0001, vs. (2) p < .0001.
Abbreviations: FULD = Fuld Object Memory Test, HAM-D = Hamilton Rating Scale for Depression, MMSE = Mini-Mental State Examination, SGDS = Short Geriatric Depression Scale, STAI = Spielberger State-Trait Anxiety Inventory sum score of state (1) and trait (2) items, VITA = Vienna Transdanube Aging study.

http://kursus.kvl.dk/shares/vetgen/_Popgen/genetik/applets/kitest.htm.

RESULTS

Frequency analysis of the 5-HTT genotypes and alleles of subjects with or without depression classification are presented in Table 2. The distribution of genotypes within each of the study groups did not deviate significantly from the Hardy-Weinberg equilibrium. A significantly higher frequency in the SS genotype was observed in subjects who had past and/or present depressive symptoms compared to subjects who never had depressive symptoms (20.7% and 14.4%, respectively; trend test p = .01). Moreover, the frequency of the S allele in the depressive group was significantly higher than in the control group (45.4% and 37.2%, respectively; trend test p = .009). A significant increase in the frequency of the homozygote for the S allele was found in subjects with present symptoms of depression (24.6%, p = .013). This increase was observed in subjects experiencing symptom onset before age 65 (21.1%). Although the frequency of the SS genotype increased in subjects with major depression (16.7%), it did not show significance. When the frequency of the S allele was studied, a higher frequency was observed in subjects with minor depression (50%). A significant increase of the S allele was observed in subjects presently suffering from depression (46.8%, trend test p = .011). In addition, an increased S allele frequency was observed in subsyndromal depressive subjects (46.3%) but did not show significance.

Correlation study of different scale scores (Table 3) revealed no significant increase in HAM-D scores in subjects (present depression) with the SS genotype or in subjects carrying the S allele. We observed only a tendency to higher scores in subjects carrying the S allele (~112% vs. noncarriers). Similarly, no significant differences in SGDS scores were observed in the different 5-HTT genotypes or alleles. Studying the 2 State-Trait Anxiety Inventory scales, STAI1 and STAI2, we found no significant alterations in the sum of STAI1 or STAI2 scores in the different genotypes or in the carriers of the S allele.

DISCUSSION

This report presents a study of the association of 5-HTTLPR and depression in a unique elderly population. The use of elderly subjects aged 75 years without history of depression as controls eliminated the possibility of an admixture study related to possible-future cases of depression in the control group, which often happens with younger individuals. In this study of a unique elderly Viennese population, it was demonstrated that subjects who in the past and/or present experienced depressive symptoms bear the 5-HTTLPR S allele with statistically higher frequency than the healthy subjects. The same

Table 2. Genotype and Allele Frequency Distribution of the 5-HTT Polymorphism in Subjects With Different Degrees of Depression Compared to Healthy Subjects[a]

		Genotype			Allele	
Sample	N	LL (%)	LS (%)	SS (%)	L (%)	S (%)
No history of depression and no symptoms of depression at baseline (0)	360	144 (40.0)	164 (45.6)	52 (14.4)	(62.8)	(37.2)
Past and/or present symptoms of depression	184	55 (29.9)	91 (49.5)	38 (20.7)[b]	(54.6)	(45.4)[c]
No symptoms of depression at baseline but positive history of depression (1)	74	21 (28.4)	42 (56.8)	11 (14.8)[d]	(56.8)	(43.2)[e]
Subsyndromal depression at baseline (2)	27	9 (33.3)	11 (40.7)	7 (26.0)	(53.7)	(46.3)
Minor depression at baseline (2)	47	14 (29.8)	19 (40.4)	14 (29.8)	(50.0)	(50.0)
Major depression at baseline (2)	36	11 (30.6)	19 (52.8)	6 (16.7)	(56.9)	(43.1)
Present symptoms of depression (2)	110	34 (30.9)	49 (44.5)	27 (24.6)[f]	(53.2)	(46.8)[g]
Past and/or present symptoms of depression with onset before age 65 y	95	31 (32.6)	44 (46.3)	20 (21.1)[h]	(32.6)	(57.4)[i]
Past and/or present symptoms of depression with onset at age ≥ 65 y	89	24 (27.0)	47 (52.8)	18 (20.2)	(27.9)	(73.0)

[a]Hardy-Weinberg equilibrium conformity: $\chi^2 = 0.3$, $p > .05$ (does not statistically deviate from Hardy-Weinberg).
[b]SS genotype: past and/or present symptoms of depression vs. controls, Cochran-Armitage trend test, p = .01.
[c]S allele: past and/or present symptoms of depression vs. controls, Cochran-Armitage trend test, p = .009.
[d]Group 0 vs. group 1: Cochran-Armitage trend test, p = .17.
[e]Group 0 vs. group 1: Cochran-Armitage trend test, p = .17.
[f]SS genotype: group 0 vs. group 2: Cochran-Armitage trend test, p = .013.
[g]S allele: group 0 vs. group 2, Cochran-Armitage trend test, p = .011.
[h]Cochran-Armitage trend test: p = .64.
[i]Cochran-Armitage trend test: p = .64.

Table 3. Depression and Anxiety Scale Scores (mean ± SD) in the Different 5-HTT Genotypes and Alleles in Subjects With Present Symptoms of Depression

	Genotype			Allele	
Scale	LL (N = 34)	LS (N = 49)	SS (N = 27)	Carrier S (N = 76)	Noncarrier S (N = 34)
HAM-D	10.5 ± 6.3	12.1 ± 6.4	11.1 ± 6.8	11.8 ± 6.5	10.5 ± 6.3
SGDS	5.0 ± 2.6	5.3 ± 3.5	2.9 ± 2.2	4.5 ± 3.3	5.0 ± 2.6
STAI1	44.3 ± 8.1	42.3 ± 12.3	38.7 ± 9.4	41.1 ± 11.5	44.3 ± 8.1
STAI2	45.7 ± 9.9	46.6 ± 11.4	42.4 ± 9.8	45.2 ± 11.0	45.7 ± 9.9

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SGDS = Short Geriatric Depression Scale, STAI = Spielberger State-Trait Anxiety Inventory sum score of state (1) and trait (2) items.

finding was established in subjects suffering from minor depression, and a trend toward higher frequency was found in subjects with depressive onset before age 65, defined as having the first symptoms of depression before 65 years of age. These findings confirm many other previous investigations in which the 5-HTTLPR S allele was associated with depression.[1,10,14,17,18,29,30] On the other hand, we could find no correlation of 5-HTTLPR genotypes or allele carriers with depression and anxiety scales, such as the HAM-D for depression or STAI1 for anxiety. This conflict of result has often been discussed in the literature where investigations did not manage to replicate the association between this polymorphism and depression.[9,19,31,32] These inconsistencies between the positive association study concerning grouping for depression in the past or present according to DSM-IV and the lack of correlations with depression ratings may arise from the fact that depression is a chronic recurrent disorder, not present in the diseased subject at every time of investigation. In addition, although we have no measurements of life stress or early life stress available, stress may also influence our results as found by Caspi and colleagues.[1] Other support for our results comes from association studies for the 5-HTTLPR variations and behavioral phenotypes, such as suicide or depression in other neurodegenerative diseases.[11,14,29,33,34] In the first, association between the S allele and suicide attempts was demonstrated. Association study for depression occurrence in Parkinson's disease patients demonstrated similar results.[29]

The risk of developing depressive symptoms in carriers of the 5-HTTLPR S allele can be explained via the decrease in transcriptional activity of the 5-HTT gene promoter in this variant.[7] Lower 5-HTT mRNA expression was observed in cell lines transfected with at least 1 copy of the S variant. Moreover, the rate of specific 5-HT uptake was more than 2-fold higher in cells homozygous for the L form of the 5-HTTLPR than in cells carrying 1 or 2 copies of the S variant of the promoter. Further evidence from studies of 5-HTT promoter activity in other cell lines,[35] mRNA concentrations in the raphe complex of human postmortem brain,[36] platelet 5-HT uptake and content,[37] levels of 5-hydroxyindoleacetic acid (5-HIAA) in human cerebrospinal fluid,[38,39] and in vivo imaging of human midbrain 5-HTT[40] confirmed that the S form is associated with lower 5-HTT expression, whereas this association was not found in prefrontal cortex.[41] Susceptibility to developing depressive symptoms can then be an outcome of the lower activity of 5-HTT, which under a "trigger" will cause this result.

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