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Original Research Article

Genetic Association between Neurotrophin-3 Polymorphisms and Alzheimer's Disease in Japanese Patients

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Abstract

Background: Some polymorphisms of the neurotrophin family have previously been investigated as candidate genes for Alzheimer's disease (AD). In the present study, we examined whether neurotrophin-3 (NTF-3) polymorphisms are genetic risk factors in patients with AD. ***Methods:*** From a sample of 507 subjects, we recruited 248 age-matched subjects divided into 2 groups: AD patients (n = 143) and normal controls (NCs) (n = 105). We identified 3 representative *NTF-3* single nucleotide polymorphisms (SNPs): rs6332, rs6489630, and rs4930767. Next, we statistically compared the allele frequencies of each SNP between the AD and NC groups in the early-onset (<65 years) cases under a more limited age-matched condition. ***Results:*** We found a significant association between rs6332 and the total group of AD patients (p = 0.013) and significant associations between both rs6332 (p = 0.033) and rs6489630 (p = 0.035) and early-onset AD patients. ***Conclusion:*** These results suggest that *NTF-3* SNPs may not only be associated with AD itself, but also with early-onset AD in Japanese patients, assuming that the *NTF-3* gene may have age-related effects on neurodegenerative diseases.

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Introduction

Alzheimer's disease (AD) has a progressive neurodegenerative course characterized mainly by memory disorder, visuospatial impairment, and executive dysfunction as its core symptoms [1, 2]. The deposition of causative proteins, such as amyloid-beta (Aβ) and tau, in the pathogenesis of AD has previously been reported and has been focused on as a possible therapeutic target [4, 5]. *APOE* has been considered as a strong candidate gene for sporadic AD since the 1990s, and this speculation has recently been verified in a large-sample genome-wide association study [6, 7]. In Japan, a significant association between *APOE* and late-onset AD was replicated in a recent large-scale study [8]. On the other hand, various lifestyle-related diseases have been reported as risk factors, and sporadic AD itself is considered to be caused by a combination of several genetic and environmental factors [9, 10].

In postmortem analyses of the brain of patients with AD, regional quantitative alterations in neurotrophins, such as nerve growth factor, brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NTF-3), have been reported [11–13]. Similar results were obtained in AD mouse models, and these neurotrophins have been considered as practical therapeutic targets in AD patients or rodents [14–16]. Among such representative neurotrophins, NTF-3, in particular, protects cortical neurons against Aβ-dependent neural cell death by limiting caspase-8, caspase-9, and caspase-3 cleavage [17]. On the other hand, NTF-3 influences the development of mesolimbic dopaminergic neurons and the differentiation of noradrenergic neurons in the locus ceruleus [18, 19].

While some previous studies had reported BDNF polymorphisms to be risk factors for AD in Japanese populations, we observed that some single nucleotide polymorphisms (SNPs) of neurotrophins are associated with cognitive impairment in patients with AD [20–25]. Among the candidate genes in the neurotrophin family, Kunugi et al. [23] found that a missense mutation (Gly/–63/Glu) in the *NTF-3* gene was associated with a risk of AD; however, its mutant type (–63 Glu) was too rare in Caucasian populations to be investigated in subsequent studies in other countries [23, 26]. On the other hand, *NTF-3* has been reported to be a strong candidate gene for attention deficit/hyperactivity disorder (ADHD), in which social cognition is impaired as a core symptom in the neurodevelopmental course [27]. *NTF-3* SNPs (rs6332 and rs6489630) are functional polymorphisms located at chromosome 12p13 and are significantly associated with the severity of ADHD and intelligence (i.e. selective attentional tasks and performance execution) [28, 29]. A silent polymorphism, rs6332, is located within Pro-*NTF-3* gene exon 1 and influences the executive function in patients with limited mild-stage AD, but not mild cognitive impairment (MCI) [20]. The rs4930767 polymorphism in the promoter region of the same gene does not appear to be associated with any measure of ADHD [29]. Based on these studies, the neurodevelopmental or neurodegenerative associated gene, *NTF-3,* may influence the age-related effects during the course of the disease, and such confounding effects should be considered when comparing the disease group and the normal control (NC) group.

In the present study, we hypothesized that representative *NTF-3* SNPs (rs6332, rs6489630, and rs4930767) might be associated with a risk of AD in Japanese subjects, a topic that is of particular interest in view of Japan's aging society. Thus, to investigate the association between AD and *NTF-3* SNPs without age as a confounding factor, we statistically compared the allele frequencies of 3 SNPs between AD patients and age-matched NCs. Moreover, to compare these 2 groups under stricter or more limited age-matched conditions, we selected only the early-onset sample (<65 years) from the total sample (age range, 32–72 years) in the second stage of the analysis [9].

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Methods

Participants

Of the 507 Japanese subjects enrolled in the present genomic study, including patients with AD (n = 340; age range, 35–92 years; mean ± SD, 72.41 ± 10.71 years), patients with MCI (n = 47; age range, 63–83 years; mean ± SD, 75.26 ± 4.56 years), and NCs (n = 120; age range, 32–81 years; mean ± SD, 61.86 ± 8.41 years), we excluded 47 patients with MCI and 212 subjects (AD: n = 197; NCs: n = 15) who were older than 73 years. Thus, an age-matched sample (age range, 32–72 years; mean ± SD, 61.20 ± 7.24 years) of 248 subjects (AD: n = 143; NCs: n = 105) was recruited. All subjects were outpatients who had visited a memory clinic at the Jikei University Hospital (Tokyo), the Jikei University Kashiwa Hospital (Kashiwa city, Chiba prefecture), or the Juntendo University Hospital (Tokyo). They were all diagnosed with probable AD based on the National Institute of Neurology and Communicative Disorder and Stroke/Alzheimer Disease and Related Disorder Association (NINCDS/ADRDA) criteria or the diagnostic criteria for MCI [3, 30, 31]. This study was approved by the Ethics Committee of the Jikei University School of Medicine (Tokyo and Kashiwa) and Juntendo University School of Medicine (Tokyo). Written informed consent was obtained from both the patients and their caregivers.

Identification of NTF-3 SNP Genotypes

The method used to identify the *NTF-3* SNP (rs6332, rs6489630, rs4930767) genotypes, a SNaPshot analysis (Applied Biosystems, Foster City, Calif., USA), has been described in previous reports [20, 21, 32]. If the genotype of the SNP was unclear or ambiguous when determined using the SNaPshot method, we rechecked and confirmed the genotype using PCR products and direct nucleotide sequencing using an ABI 3730 DNA Analyzer [sequencing reactions were performed using BigDye Terminator v3.1 Cycle Sequencing Kits (Applied Biosystems)]. All sequence analyses were performed using DNA Sequencing Analysis software, version 5.3.1 (Applied Biosystems).

Comparing Allele Frequencies of rs6332, rs6489630, and rs4930767 between the Total and Early-Onset Group of Patients and the NCs

We statistically compared the allele frequencies of the *NTF-3* SNPs (rs6332, rs6489630, rs4930767) between all patients with AD (total) and the NCs. Next, to investigate the relation under a more limited age-matched condition, we analyzed 163 (AD: n = 86; NCs: n = 77) early-onset cases (<65 years); the frequencies of each allele were the same between the AD patients and the NCs.

Statistical Analysis

SPSS 19.0J for Windows (SPSS Japan Inc.) was used for all statistical analyses. To control for type I errors, we used a one-way ANOVA with a post hoc Tukey test for age. The sex ratio (female to male) and allele frequencies of the *NTF-3* SNPs were assessed using the Fisher exact probability test; the odds ratio (OR) was then calculated. A χ^2 test was used to compare the distributions among the 3 genotypic groups. To assess the deviation of SNPs from Hardy-Weinberg equilibrium (HWE), we used the HWE calculator Web program (http://www.oege.org/software/hwe-mr-calc.shtml). Moreover, we performed power calculations using the G*Power 3 (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/). A p value <0.05 was considered statistically significant.

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Table 1. Total subject characteristics (n = 248)

	Total AD (n = 143)	NC (n = 105)	χ^2 or F score	p value
Age, years	61.92±7.10	60.21±7.35	3.426	0.065
Sex ratio (M/F)	67/76	44/61	0.600[a]	0.518

Values represent number of patients or means ± SD.

[a] The χ^2 score. One-way ANOVA with post hoc tests (Tukey) for age: AD versus NC.

Results

Characteristics, Genotype Distributions, and Allele Frequencies of All Subjects
Among the 248 subjects that were selected, the age and sex ratios of the patients with AD (n = 143) were not significantly different from those of the NCs (n = 105) (tables 1, 2). The genotype distributions of rs6332 (G/G: n = 71, G/A: n = 130, A/A: n = 45), rs6489630 (C/C: n = 141, C/T: n = 93, T/T: n = 11), and rs4930767 (T/T: n = 94, C/T: n = 112, C/C: n = 40) among the total patient group did not deviate significantly from the HWE (p > 0.05) (tables 3, 4). The results of power analyses demonstrated that the power ranged from 50.8% (rs6332) to 78.9% (rs4930767). The genotypic distribution of rs6332 was significantly deviated ($\chi^2 = 6.979$, d.f. = 2, p = 0.031) and its allele frequency was significantly different between the patients with AD and the NCs ($\chi^2 = 6.496$, d.f. = 1, p = 0.013, OR = 1.602) (tables 3, 4). However, we could not find any significant differences in the genotypic allele frequencies of rs6489630 ($\chi^2 = 3.523$, d.f. = 1, p = 0.067, OR = 0.670) or rs4930767 ($\chi^2 = 0.133$, d.f. = 1, p = 0.779, OR = 1.071) between the patients with AD and the NCs (tables 3, 4).

Genotypic Distributions and Allele Frequencies in Subjects with an Age of Onset of Less than 65 Years
Next, 163 cases with early-onset AD (EAD: n = 86) and age-matched NCs (n = 77) were compared; the age and sex ratios were not significantly different between the EAD and NC groups (table 3). The genotype distributions of rs6332 (G/G: n = 51, G/A: n = 84, A/A: n = 27), rs6489630 (C/C: n = 94, C/T: n = 59, T/T: n = 8), and rs4930767 (T/T: n = 63, C/T: n = 74, C/C: n = 25) in the EAD group did not deviate significantly from the HWE (p > 0.05) (table 4). The results of power analyses demonstrated that the power ranged from 51.3% (rs6332) to 76.3% (rs4930767). While the 3 genotypic distributions were not significantly deviated, significant differences in the allele frequencies of rs6332 and rs6489630 were observed between the EAD group and the age-matched NCs (former: $\chi^2 = 4.687$, d.f. = 1, p = 0.033, OR = 1.631; latter: $\chi^2 = 4.605$, d.f. = 1, p = 0.035, OR = 0.566) (table 4).

Discussion

In the present study, we found significant differences in the allele frequencies of the *NTF-3* SNPs between patients with AD and the NCs and between the EAD group (<65 years) and age-matched NCs (tables 2, 4). While the A allele of rs6332 was associated with a risk of AD and EAD (former: OR = 1.602, 95% CI = 1.114–2.304; latter: OR = 1.631, 95% CI = 1.045–2.545), the T allele of rs6489630 was associated with a protective role only for EAD (OR = 0.566, 95% CI = 0.335–0.955). We could not find a significant association between rs4930767 and the manifestation of AD (tables 1–4).

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Table 2. Association between *NTF-3* and total AD patients

	AD (n = 141)[1]	NC (n = 105)
rs6332		
Genotype frequency		
G/G	33 (23.4%)	38 (36.2%)
G/A	76 (53.9%)	54 (51.4%)
A/A	32 (22.7%)	13 (12.4%)
χ^2 score	6.979	
p value	0.031*	
Allele frequency		
G	142 (50.4%)	130 (61.9%)
A	140 (49.6%)	80 (38.1%)
χ^2 score	6.496	
p value	0.013*	
OR (95% CI)	1.602 (1.114–2.304)	
rs6489630		
Genotype frequency		
C/C	87 (62.1%)	54 (51.4%)
C/T	49 (35.0%)	44 (41.9%)
T/T	4 (2.9%)	7 (6.7%)
χ^2 score	3.89	
p value	0.143	
Allele frequency		
C	223 (79.6%)	152 (72.4%)
T	57 (20.4%)	58 (27.6%)
χ^2 score	3.523	
p value	0.067	
OR (95% CI)	0.670 (0.440–1.019)	
rs4930767		
Genotype frequency		
T/T	51 (36.2%)	43 (41.0%)
C/T	68 (48.2%)	44 (41.9%)
C/C	22 (15.6%)	18 (17.1%)
χ^2 score	0.976	
p value	0.614	
Allele frequency		
T	170 (60.3%)	130 (61.9%)
C	112 (39.7%)	80 (38.1%)
χ^2 score	0.133	
p value	0.779	
OR (95% CI)	1.071 (0.742–1.545)	

* $p < 0.05$.
[1] For rs6489630, there were only 140 AD patients.

Table 3. Characteristics of subjects aged <65 years (n = 163)

	AD (n = 86)	NC (n = 77)	χ^2 or F score	p value
Age, years	57.38±5.28	57.23±6.21	0.028	0.868
Sex ratio (M/F)	43/43	36/41	0.171[a]	0.754

Values represent number of patients or means ± SD.
[a] The χ^2 score. One-way ANOVA with post hoc tests (Tukey) for age: AD versus NC.

Table 4. Association between *NTF-3* and EAD patients aged <65 years

	AD (n = 85)[1]	NC (n = 77)
rs6332		
Genotype frequency		
G/G	21 (24.7%)	30 (39.0%)
G/A	46 (54.1%)	38 (49.3%)
A/A	18 (21.2%)	9 (11.7%)
χ^2 score	4.967	
p value	0.083	
Allele frequency		
G	88 (51.8%)	98 (63.6%)
A	82 (48.2%)	56 (36.4%)
χ^2 score	4.687	
p value	0.033*	
OR (95% CI)	1.631 (1.045–2.545)	
rs6489630		
Genotype frequency		
C/C	56 (66.7%)	38 (49.4%)
C/T	25 (29.8%)	34 (44.2%)
T/T	3 (3.5%)	5 (6.4%)
χ^2 score	5.025	
p value	0.081	
Allele frequency		
C	137 (81.5%)	110 (71.4%)
T	31 (18.5%)	44 (28.6%)
χ^2 score	4.605	
p value	0.035*	
OR (95% CI)	0.566 (0.335–0.955)	
rs4930767		
Genotype frequency		
T/T	31 (36.5%)	32 (41.6%)
C/T	41 (48.2%)	33 (42.9%)
C/C	13 (15.3%)	12 (15.6%)
χ^2 score	0.527	
p value	0.768	
Allele frequency		
T	103 (60.6%)	97 (63%)
C	67 (39.4%)	57 (37%)
χ^2 score	0.197	
p value	0.731	
OR (95% CI)	1.107 (0.707–1.734)	

* p < 0.05.
[1] For rs6489630, there were only 84 AD patients.

In previous studies, rs6332 was reported to be a robust candidate gene polymorphism for ADHD and to influence intelligence [27, 29]. We found that the executive function of G allele carriers was significantly lower than that of A allele carriers among AD patients. However, carrying the A allele was associated with a risk of EAD in the present study [20]. The functional roles of rs6332 might influence executive dysfunction in comparatively older AD patients (approx. 74–76 years old) [20]. On the other hand, rs6332 might be associated with the manifestation of AD in patients with EAD.

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Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2013;3:272–280

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DOI: 10.1159/000354369

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Similarly, rs6489630 was reportedly associated with the intelligence of subjects with ADHD, and the intelligence scores of T allele carriers were significantly lower than those of C allele carriers [28]. In contrast, the present results indicate a predominantly protective role associated with the T allele, compared with C allele carriers, with regard to the manifestation of EAD. Thus, functional SNPs of neurotrophins might have age-related reversible influences clinically between the young and the elderly, similar to the *BDNF* gene Val66Met polymorphism [33]. Further investigations of age-dependent associations between the manifestation of AD and the *NTF-3* gene are needed.

A reduction in NTF-3 levels has been observed in septal regions containing neurotrophin-dependent cholinergic projections in APP mouse models [14]. Furthermore, NTF-3 protects cortical neurons against Aβ-dependent neural cell death through the regulation of the phosphorylation pathway [17]. The rs6332 SNP is a silent variation, and such synonymous polymorphisms have been implicated in the regulation of mRNA splicing or the translation of proteins [34]. Therefore, rs6332 might influence synonymous polymorphisms that in turn might impact the regional translational level of NTF-3, leading to the regulation of cholinergic neuron projections. The rs6489630 SNP is located in an intron on the 3′-side, but its functional roles (e.g. transcriptional regulation of the *NTF-3* gene) remain unclear and require further examination in the future.

The present study has some limitations. First, the sample size in this study was comparatively small. Therefore, the statistical values were also small, and some type II errors may have occurred, possibly resulting in the failure to detect a significant association between rs4930767 and the risk of AD. To match the age (age range, 32–72 years) between the AD patients and NCs, we selected only 248 of the 507 participants. Moreover, we could not compare the relation between late-onset AD patients (>65 years) and age-matched NCs because the sample size was too small (n = 85). Regarding the statistical values, a previous study investigating the association between AD and the *NTF-3* gene in the Japanese population reported the same p values (score range, 0.011–0.013) [23]. Secondly, we could not confirm whether the significant differences in the allele frequencies between the patients with AD and the NCs had been influenced by neuroprotective actions against degenerative progression or neurodevelopmental factors. Thirdly, other representative SNPs in the Japanese population, such as the missense mutation Gly/–63/Glu, were not examined; however, the mutant type (–63 Glu) is too rare in Caucasian populations to be investigated in subsequent studies in other countries [23, 26]. Therefore, a larger sampling should be added to the present study, and the data should be re-evaluated in the future.

In conclusion, despite some limitations, we found a significant association between AD and *NTF-3* as well as between EAD and *NTF-3*. These results may help to elucidate the neuroprotective or clinical age-related roles of not only the *NTF-3* gene, but also other neurotrophin gene polymorphisms in neurodegenerative diseases described in previous studies [20, 21, 28, 29, 33]. Furthermore, elucidating the detailed associations between *NTF-3* gene diversity and the manifestation of AD itself will be an important task in the future.

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Dement Geriatr Cogn Disord Extra 2013;3:272–280

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DOI: 10.1159/000354369

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