Polymorphism screening of the neurotrophin receptor p75 gene and association analysis with schizophrenia

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Abstract

Based on both neurodevelopmental and neurodegenerative hypotheses in the etiology of schizophrenia, neurotrophic factors and their receptors may be involved in the pathogenesis of schizophrenia. In line with this, we previously reported a possible association between polymorphisms of the BDNF and NTF3 genes and the disorder. Here we searched for polymorphisms in the neurotrophin receptor p75 gene for genomic DNA from patients with schizophrenia. We detected one silent and one missense, nucleotide substitutions in the coding region. We performed an association analysis with respect to the missense polymorphism in a Japanese sample of 116 schizophrenics and 152 controls, matched for sex and age distributions. However, there was no significant difference in the genotype or allele frequency between the two groups, suggesting that the examined missense polymorphism is unlikely to play a major role in giving susceptibility to schizophrenia.

Introduction

Based on both neurodevelopmental and neurodegenerative hypotheses in the etiology of schizophrenia, neurotrophic factors and their receptors may be involved in the pathogenesis of schizophrenia. We previously reported a possible association between polymorphisms of the BDNF [1] and NTF3 [2,3] genes and the disorder. To further explore the possible role of the neurotrophins, we searched for polymorphisms in the gene encoding p75, a low affinity receptor for neurotrophin family. A detected missense polymorphism was examined for an association with schiziophrenia.

Methods

Polymorphism screening

Genomic DNA from 20 patients with schizophrenia was used. Six sets of primers were designed encompassing amino-acid coding region of the p75 gene. Polymorphisms were screened by direct sequencing (forward and reverse) of the PCR products.

Association analysis

Subjects for association analysis were 145 schizphrenics and 152 controls matched for age and sex distributions. Genotyping for a Ser/Leu missense polymorphism was done by PCR with primes 5'-gctaaaagggaggagtgggggaag-3' (p75E4F) and 5'-ttcaggtcaaggtcacagcaaagtct-3' (p75E4R) followed by digestion with a restriction enzyme BanII. To visualize polyacrylamide gel electrophoresis and etidium bromide staining was employed.

Resuls and Discussion

Two polymorphisms were found in the putative exon 4: one missense (Ser/Leu) and the other silent, nucleotide substitutions. In an association analysis for the missense (Ser/Leu) polymorphism (Table), there was no significant difference in the genotype or allele distribution between the patients and controls.

We performed polymorphism screening for the aminoacid coding region of the p75 gene. However, we obtained no evidence for the involvement of the p75 gene in the pathogenesis of schizphrenia.

References

1) Kunugi H, Hirasawa H, Kato N, Nabika T, Kobayashi S, Nanko S: Brain derived neurotrophic factor gene and schizophrenia: polymorphism screening and association analysis. Schizophr Res (in press)

2) Hattori M, Kunugi H, Akahane A, Tanaka H, Ishida S, Hirose T, Morita R, Yamakawa K, Nanko S: Novel polymorphisms in the promoter region of the neurotrophin-3 gene and their associations with schizophrenia. Am J Med Genet 114: 304-9, 2002.

3) Nanko S, Hattori M, Kuwata S, Sasaki T, Fukuda R, Dai XY, Yamaguchi K, Shibata Y, Kazamatsuri H. Neurotrophin-3 gene

polymorphism associated with
schizophrenia. Acta Psychiatr Scand 89:
390-2, 1994.

Table Genotype and allele frequencies for a missense polymorphism of the p75 gene among patients with schizophrenia and controls

	n	Genotype distribution S/S	S/L	L/L	Allele frequency S	L
Schizophr.	145	0.81	0.17	0.02	0.90	0.10
Controls	152	0.80	0.16	0.04	0.88	0.12
			p=0.64		p=0.56	

Ⅲ. 研究成果の刊行に関する一覧表　（主要なものを選択）

書　籍

著者氏名	論文タイトル名	書籍全体の編集者	書籍名	出版社名	出版地	出版年	ページ
Ujike H, Takaki M, Kodama M, Kurida S	Gene expression related to synaptogenesis, neuritogenesis, and MAP kinase in behavioral sensitization to psychostimulants.	Ali SF	Cellular and Molecular Mechanisms of Drugs of Abuse II, Cocaine, Substituted Amphetamines, GHB, and Opiates	Ann New York Acad Sci	New York	2002	55-67

雑　誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Matsumoto S, Sasaki T, Imamura A, Matsuo K, Kayashima T, Hashida A, Ono S, Tsujita T, Matsumto S, Nakane Y, Tokunaga K, Okazaki Y	HLA classI distribution in Japanese patients with schizophrenia.	Am J Med Genet	114	42-45	2002
Fujimaru K, Imamura A, Tsujita T, Uraguchi M, Hashida A, Mori T, Matsumoto S, Matsumoto S, Okazaki Y, Nakane Y	Minor Physical Anomalies in Japanese Patisents with Schizophrenia.	Acta Med Nagasaki	47	133-137	2002
Tsujita T, Arinami T, Yoshikawa T, Fukumaki Y, Tashiro N, Inada T, Someya T, Mineta M, Ujike H, Ozaki N, Ohara K, Ohmori O, Kojima T, Nanko S, Yoneda H, Kusumi I, Fukuzako H, Saito T, Kaneko S, Niwa S, Sora I, Sasaki T, Arai H, Nakamura M, Kato T, Yamamoto K, Kurachi M, Takei N, Harano M, Akiyoshi J, Hiramatsu K, Okazaki Y	A genome-wide linkage scan for schizophrenia susceptibility genes in 151 Japanese affected sibling pairs _ the initial screening of the Japanese Schizophrenia Sib-pair Linkage Group (JSSLG) study	Am J Med Genet	114	841-842	2002
Noda M, Yasuda S, Okada M, Higashida H, Shimada A, Iwata N, Ozaki N, Nishikawa K, Shirasawa S, Uchida M, Aoki S, Wada K	Recombinant human serotonin 5A receptors stably expressed in C6 glioma cells couple to multiple signal transduction pathways.	J Neurochem	84 (2)	222-232	2003
Iwase T, Kajimura N, Uchiyama M, Ebisawa T, Yoshimura K, Kamei Y, Shibui K, Kim K, Kudo Y, Katoh M, Watanabe T, Nakajima T, Ozeki Y, Sugishita M, Hori T, Ikeda M, Toyoshima R, Inoue Y,	Mutation screening of the human Clock gene in circadian rhythm sleep disorders.	Psychiatry Res	109 (2)	121-128	2002

Yamada N, Mishima K, Nomura M, Ozaki N, Okawa M, Takahashi K, Yamauchi T					
Ujike H	Stimulant-induced psychosis and schizophrenia: The role of sensitization	Current Psychiatry Reports	4	177-184	2002
Ujike H, Takaki M, Nakata K, Tanaka Y, Takeda T, Kodama M, Fujiwara Y, Sakai A, Kuroda S	CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia	Molecular Psychiatry	7	515-518	2002
Nakata K, Ujike H, Sakai A, Takaki M, Imamura T, Tanaka Y, Kuroda S	Association Study Between the Fibronectin Gene and Schizophrenia	Am J Med Genet	116	41-44	2003
Nakata K, Ujike H, Sakai A, Uchida N, Nomura A, Imamura T, Katsu T, Tanaka Y, Hamamura T, Kuroda S	Association study of the brain-derived neurotrophic factor (BDNF) gene with bipolar disorder.	Neurosci Lett	337	17-20	2003
Ujike H, Nakata K	Genetic study of schizophrenia: new targets for therapy	Exp Rev Neurotheraptics	3	41-50	2003
Obata T, Yamanaka Y, Inada T, et al.	In vivo generation of hydroxyl radicals and MPTP induced dopaminergic neurotoxicity in the striatum.	Biogenic Amines	17(1)	1-14	2002
Obata T, Aomine M, Inada T, Kinemuchi H	Nicotine suppresses 1-methyl-4-phenylpyridinium ion (MPP+) induced hydroxyl radical generation in rat striatum.	Neurosci Lett	330 (1)	122-124	2002
Kato T, Iwamoto K, Washizuka S, Mori K, Tajima O, Akiyama T, Nanko S, Kunugi H, Kato N	No association of mutations and mRNA expression of WFS1/wolframin with bipolar disorder in humans.	Neurosci Lett	338 (1)	21-24	2003
Akahane A, Kunugi H, Tanaka H, Nanko S	Association analysis of polymorphic CGG repeats in 5' UTR of the reelin and VLDLR genes with schizophrenia.	Schizophr Res	58 (1)	37-41	2002
Hata T, Kunugi H, Fukuda R, Kaminaga T, Nanko S	Possible effect of the APOE 4 allele on the hippocampal volume and asymmetry in schizophrenia.	Am J Med Genet	114	641-642	2002.
Kunugi H, Kato T, Fukuda R, Tatsumi M, Sakai T, Nanko S	Association study of C825T polymorphism of the G-protein β3 subunit gene with schizophrenia and mood disorders.	J Neural Transm	109	213-218	2002
尾崎紀夫	5-HT 系遺伝子を候補遺伝子とした精神分裂病の分子遺伝学的研究.	精神経誌	104 (6)	501-508	2002
池田匡志, 北島剛司, 岩田仲生, 尾崎紀夫	気分障害の分子遺伝学的研究.	日本神経精神薬理学雑誌	22	137-143	2002
氏家 寛	薬物依存におけるゲノム解析	分子精神医学	2	38-45	2002

滝本高広、氏家　寛、中村和彦、岩橋和彦	メタンフェタミン投与ラットにおける CYP2E1 mRNA の誘導	日本アルコール・薬物医学会雑誌	37	163-167	2002
氏家　寛	薬物依存の分子生物学	精神経誌	104	1055-1068	2002
飯嶋良味，北尾淑恵，稲田俊也	STR マーカーを用いた association study.	分子精神医学	2 (3)	51-53	2002
中村中，稲田俊也	Catechol-O-Methyltransferase (COMT) 遺伝子多型と精神科疾患.	分子精神医学	3 (1)	54-58	2003
藤丸浩輔、辻田高宏	一卵性双生児のゲノムの不一致について、分子精神医学	分子精神医学	2	260-261	2002