Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research 153 (2007) 1 – 6
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

No association between the tumor necrosis factor-alpha gene promoter polymorphisms and schizophrenia in a Japanese population

Yuichiro Watanabe [a], Tatsuyuki Muratake [a,b,*], Naoshi Kaneko [a], Naoki Fukui [a], Yasushi Nara [a], Toshiyuki Someya [a]

[a] *Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan*
[b] *CREST, Japan Science and Technology Agency, Kawaguchi, Japan*

Received 15 November 2005; received in revised form 31 January 2006; accepted 1 March 2006

Abstract

Tumor necrosis factor-alpha (TNF-α) is a pleiotrophic cytokine and exerts neuroprotective and neurodegenerative effects in brain. Several studies have indicated that TNF-α is likely related to the pathogenesis of schizophrenia. Recent genetic investigations have revealed that a TNF-α gene promoter polymorphism (–G308A) is associated with schizophrenia, although negative findings have also been reported. To assess whether the TNF-α gene promoter variants including –G308A could be implicated in vulnerability to schizophrenia, we conducted a case-control association analysis (265 cases and 424 controls) and the transmission disequilibrium test (TDT) analysis (83 trios) for four polymorphisms (–G238A, –G308A, –C857T and –T1031C) in Japanese subjects. In a case-control analysis, there was no significant association between the promoter polymorphisms or haplotypes in the TNF-α gene and schizophrenia. In the TDT analysis, we also did not observe transmission distortion. Our results suggest that the above four polymorphisms in the promoter region of the TNF-α gene appear not to confer increased susceptibility for schizophrenia in a Japanese population.

Keywords: Tumor necrosis factor-alpha; Schizophrenia; Case-control study; Transmission disequilibrium test; Cytokine

1. Introduction

Schizophrenia is a complex genetic disorder and affects approximately 1% of the population worldwide. The pathogenesis of schizophrenia is still unclear; however, cytokines might be implicated in the etiology or pathology of schizophrenia (for review, Nawa et al., 2000). Tumor necrosis factor-alpha (TNF-α), a pleiotrophic cytokine, exerts neuroprotective and neurodegenerative effects in brain (for review, Venters et al., 2001). Several studies have shown that blood concentrations and in vitro production of TNF-α were significantly higher in patients with schizophrenia than in healthy controls (Monteleone et al., 1997; Kowalski et al., 2001; Theodoropoulou et al., 2001), whereas some studies failed to find this increase (Haack et al., 1999; Erbağci et al., 2001). Buka et al. (2001) have reported that elevated TNF-α levels of maternal serum at the time

* Corresponding author. Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan. Tel.: +81 25 227 2213; fax: +81 25 227 0777.
E-mail address: mura@med.niigata-u.ac.jp (T. Muratake).

0165-1781/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2006.03.009

Table 1
Primers and probes used in genotyping

SNP	Primers	Probes
–G238A	5′-CAGTCAGTGGCCCAGAAGAC-3′	5′-VIC-CTCGGAATCGGAGCAG-NFQ-3′
	5′-CCCTCACACTCCCCATCCT-3′	5′-FAM-CTCGGAATCAGAGCAG-NFQ-3′
–G308A	5′-CCAAAAGAAATGGAGGCAATAGGTT-3′	5′-VIC-CCCGTCCCCATGCC-NFQ-3′
	5′-GGACCCTGGAGGCTGAAC-3′	5′-FAM-CCCGTCCTCATGCC-NFQ-3′
–C857T	5′-GGGCTATGGAAGTCGAGTATGG-3′	5′-VIC-CCCTGTCTTCGTTAAGG-NFQ-3′
	5′-GTCCTGGAGGCTCTTTCACT-3′	5′-FAM-CCTGTCTTCATTAAGG-NFQ-3′
–T1031C	5′-GTGAGGCCGCCAGACT-3′	5′-VIC-CTTTTCCTTCGTCTTCTC-NFQ-3′
	5′-GCCCCTCCAGACCCTGA-3′	5′-FAM-TTTTCCTTCATCTTCTC-NFQ-3′

of birth were associated with schizophrenia and related psychotic disorders in offspring, although Brown et al. (2004) found a significant association between maternal interleukin-8 but not TNF-α levels during the second trimester and the risk of schizophrenia spectrum disorders in offspring. Interestingly, Skurkovich et al. (2003) reported a case of schizophrenia whose negative symptoms improved with antibodies to TNF-α and to interferon-γ. Thus, these findings suggest that cytokines, including TNF-α, are likely related to the pathogenesis of schizophrenia.

Wilson et al. (1997) demonstrated that the minor A-allele of a polymorphism at the −308 position in the promoter region of the TNF-α gene, located on chromosome 6p21.1–21.3, is a much more powerful transcriptional activator than the major G-allele. Recently, several studies have shown that the –G308A polymorphism of the TNF-α gene is associated with schizophrenia (Boin et al., 2001; Meira-Lima et al., 2003; Schwab et al., 2003; Tan et al., 2003). However, other studies have failed to confirm this association (Riedel et al., 2002; Handoko et al., 2003; Pae et al., 2003; Tsai et al., 2003; Duan et al., 2004; Hashimoto et al., 2004; Hänninen et al., 2005; Kampman et al., 2005; Pae et al., 2006). This inconsistency requires further investigations. Therefore, we performed a case-control association study and the transmission disequilibrium test (TDT) analysis in Japanese subjects to assess whether

Table 2
Genotype and allele frequencies of the TNF-α gene promoter region polymorphisms in cases and controls

SNP	Genotype (%)			P[a]	Allele (%)		P[a]
–G238A	G/G	G/A	A/A		G	A	
Cases	259 (97.7)	6 (2.3)	0 (0.0)	1.00	524 (98.9)	6 (1.1)	0.64
With family history	110 (99.1)	1 (0.9)	0 (0.0)	0.58	221 (99.5)	1 (0.5)	0.32
Without family history	149 (96.8)	5 (3.2)	0 (0.0)	0.83	303 (98.4)	5 (1.6)	1.00
Controls	412 (97.2)	11 (2.6)	1 (0.2)		835 (98.5)	13 (1.5)	
–G308A	G/G	G/A	A/A		G	A	
Cases	258 (97.4)	7 (2.6)	0 (0.0)	0.66	523 (98.7)	7 (1.3)	0.66
With family history	107 (96.4)	4 (3.6)	0 (0.0)	1.00	218 (98.2)	4 (1.8)	1.00
Without family history	151 (98.0)	3 (2.0)	0 (0.0)	0.42	305 (99.0)	3 (1.0)	0.43
Controls	409 (96.5)	15 (3.5)	0 (0.0)		833 (98.2)	15 (1.8)	
–C857T	C/C	C/T	T/T		C	T	
Cases	184 (69.4)	73 (27.6)	8 (3.0)	0.20	441 (83.2)	89 (16.8)	0.08
With family history	78 (70.3)	28 (25.2)	5 (4.5)	0.50	184 (82.9)	38 (17.1)	0.26
Without family history	106 (68.8)	45 (29.2)	3 (2.0)	0.17	257 (83.4)	51 (16.6)	0.13
Controls	271 (63.9)	130 (30.7)	23 (5.4)		672 (79.2)	176 (20.8)	
–T1031C	T/T	T/C	C/C		T	C	
Cases	188 (71.0)	74 (27.9)	3 (1.1)	0.43	450 (84.9)	80 (15.1)	1.00
With family history	79 (71.2)	31 (27.9)	1 (0.9)	0.67	189 (85.1)	33 (14.9)	1.00
Without family history	109 (70.8)	43 (27.9)	2 (2.3)	0.67	261 (84.7)	47 (15.3)	0.93
Controls	306 (72.2)	108 (25.5)	10 (2.3)		720 (84.9)	128 (15.1)	

[a] Compared with control group.