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ORIGINAL PAPER

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Association study of *interleukin 2* (*IL2*) and *IL4* with schizophrenia in a Japanese population

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Abstract Interleukin 2 (IL-2) and IL-4 are pleiotropic cytokines regulating Th1/Th2 balance and have a regulatory activity in brain function. Thus these cytokines have been implicated in the pathophysiology of schizophrenia. The latest studies provided controversial results regarding the genetic associations of these cytokines. The functional polymorphisms, *IL2*-330T/G and *IL4*-590C/T, were associated with schizophrenia in a German population, although contradictory findings were also reported in a Korean population. To ascertain whether *IL2* and *IL4* contribute to vulnerability to schizophrenia, we conducted a moderate-scale case-control (536 patients and 510 controls) association study for seven polymorphisms in Japanese subjects. There were no significant associations of these genes with schizophrenia using either single marker or haplotype analyses. The present study suggests that *IL2* and *IL4* do not contribute to vulnerability to schizophrenia in the Japanese population.

Key words case-control study · interleukin 2 · interleukin 4 · schizophrenia · single nucleotide polymorphism

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Introduction

Cytokines are implicated in the etiology or pathology of schizophrenia [33, 34]. T helper (Th) lymphocytes are classified into Th1 and Th2 according to their cytokine profile [31]. Schizophrenia has been associated with an imbalance in Th1/Th2 cytokines, with a shift toward the Th2 system [32]. Interleukin 2 (IL-2) and IL-4 are cytokines produced by Th1 and Th2, respectively. In brain, these cytokines also play important roles in inflammatory reactions, synaptic plasticity and glial differentiation [45]. For example, IL-2 prevents the induction of long-term potentiation in rat hippocampus [46], and IL-4 antagonizes inhibitory effects of amyloid-β on long-term potentiation, and modulates microglial cell activation [26, 27].

A decrease in IL-2 production is one of the most frequently confirmed immunological phenomena in schizophrenia [1, 5, 12, 13, 18, 22, 28, 42, 43, 48, 49], although contradictory findings have also been reported [6–8, 36, 51]. A recent meta-analysis including 20 studies with 1,149 subjects obtained evidence for a decrease in secretion of IL-2 by peripheral blood leukocytes from patients with schizophrenia (effect size = −0.420, 95% CI = −0.058 to −0.781) [37]. Also, several studies demonstrated increased blood and cerebrospinal fluid concentrations of IL-2 in patients with schizophrenia [17, 21, 22, 25, 29, 53–55]. However, these observations remain controversial [3, 14, 40, 47, 52]. Interestingly, administration of IL-2 has been associated with the development of clinically significant neuropsychiatric changes including delusions and hallucinations [10]. Similar to the findings on IL-2, some studies have shown abnormal blood and cerebrospinal fluid concentrations of IL-4 and impaired in vitro production of this cytokine in patients with schizophrenia [2, 23, 30], whereas other studies failed to replicate these changes [6, 7, 39, 51]. Antipsychotics have effects on human plasma levels and in vitro production of IL-4 [6, 23, 24]. Taken together, these findings suggest that disturbances in IL-2 and IL-4 may be related to the pathophysiology of schizophrenia.

John et al. [19] identified a T to G substitution at position −330 relative to the transcription start site of *IL2*. This single nucleotide polymorphism (SNP) in the promoter is associated with IL-2 protein production in anti-CD3/CD28-stimulated peripheral blood lymphocytes, suggesting that the *IL2* −330T/G polymorphism might be functional [16]. Rosenwasser et al. [41] described a C to T substitution at position −590 upstream from the open reading frame of *IL4*. The −590T allele was associated with increased gene expression of *IL4* [41]. These two functional polymorphisms, *IL2* −330T/G and *IL4* −590C/T, have been tested for their associations with schizophrenia. Jun et al. [20] found no significant association between the *IL4* −590C/T polymorphism and schizophrenia. Recently, Schwartz et al. [44] reported that both the *IL2* −330T/G polymorphism and the *IL4* −590C/T polymorphism were associated with schizophrenia. These studies examined a limited number of markers with relatively small sample sizes.

Replication at only the significant SNP from the previous studies runs a high risk of false-negative results [35]. To clarify the controversy, therefore, detailed studies, in which all common variations within a candidate gene are considered jointly, are required. Here, we tried to increase the power by testing more markers, taking into account linkage disequilibrium (LD) structure and increasing sample size. We conducted a moderate-scale case-control association study in Japanese subjects on *IL2* and *IL4*. We discuss differences in their genetic associations with schizophrenia across populations.

Methods

The present study was approved by the Ethics Committee on Genetics of the Niigata University School of Medicine, and written informed consent was obtained from all participants. All participants were unrelated Japanese subjects living in the Niigata Prefecture or Fukushima Prefecture.

Subjects

The study population consisted of 536 patients with schizophrenia (281 men and 255 women; mean age, 40.1 [SD 14.2] years) and 510 control subjects (275 men and 235 women: mean age, 37.4 [SD 10.2] years). No significant difference in the sex ratio was observed between the two groups ($\chi^2 = 0.235$, df = 1, $P = 0.628$). Although the mean age of the patients was significantly higher than that of the control subjects ($P = 0.025$, Mann–Whitney U test), the difference in mean age between the groups was relatively small (2.7 years). Patients meeting the diagnostic and statistical manual of mental disorders fourth edition (DSM-IV) criteria for schizophrenia were recruited from 14 hospitals. The diagnosis of schizophrenia had been assigned on the basis of all available sources of information, including unstructured interviews, clinical observations and medical records. The control subjects were mainly recruited from the staff of the participating hospitals. Although these subjects were not assessed by a structured psychiatric interview, they all showed good social and occupational skills and reported that they had no history of psychiatric disorders.

Genotyping

Genomic DNA was extracted from peripheral blood using standard phenol/chloroform methods. We examined three SNPs in *IL2* and four SNPs in *IL4*. Their order and physical locations are shown in Figs. 1a and 2a. We included the *IL2* −330T/G polymorphism (rs2069762) and the *IL4* −590C/T polymorphism (rs2243250), which have been reported to be associated with schizophrenia [44]. Next, we consulted the HapMap database (release#22, population: Japanese in Tokyo [JPT], minor allele frequency [MAF]: more than 0.05). For *IL2*, only one SNP (rs2069772) was listed in the HapMap database. For *IL4*, three 'tagging SNPs' (rs2227282, rs2243267 and rs2243283), which covered the *IL4* gene region but not the 5′ and 3′ flanking regions, were selected with the criterion of an r^2 threshold greater than 0.8 in 'aggressive tagging: use 2- and 3-marker haplotype' mode using the 'Tagger' program [9], an implement of Haploview v4.0 [4]. We also investigated one SNP in *IL2*, JST063967 (rs2069763), which was listed in the JSNP database [15]. All SNPs were genotyped using the TaqMan 5′-exonuclease assay, as described previously [50].

Statistical analysis

Deviation from the Hardy-Weinberg equilibrium (HWE) was tested by using the χ^2 test for goodness-of-fit. LD blocks defined in accordance with Gabriel's criteria [11] and haplotype frequencies were determined using Haploview v4.0 [4]. The allele, genotype and

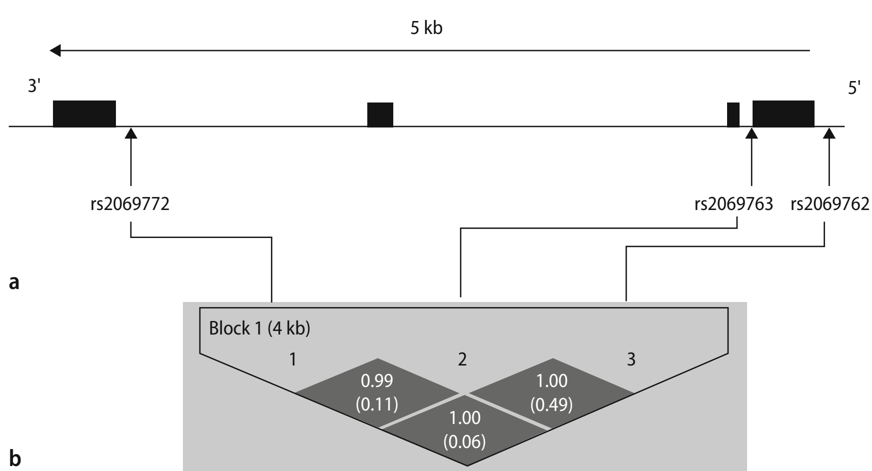

Fig. 1 Genomic structure and linkage disequilibrium (LD) of *IL2*. **a** Genomic structure of *IL2* and the locations of the single nucleotide polymorphisms (SNPs) analyzed in the present study. *IL2* has four exons (*rectangles*) and spans approximately 5 kb. *Horizontal arrow* and *vertical arrows* indicate the transcriptional orientation and locations of SNPs, respectively. **b** LD between markers of *IL2*. A block is defined in accordance with Gabriel's criteria using Haploview v4.0. Each *box* represents the D′ value and r^2 value (in parentheses) corresponding to each pair-wise SNP

Fig. 2 Genomic structure and linkage disequilibrium (LD) of *IL4*. (A) Genomic structure of *IL4* and the locations of the single nucleotide polymorphisms (SNPs) analyzed in the present study. *IL4* has three exons (rectangles) and spans approximately 9 kb. Horizontal arrow and vertical arrows indicate the transcriptional orientation and locations of SNPs, respectively. (B) LD between markers of *IL4*. A block is defined in accordance with Gabriel's criteria using Haploview v4.0. Each box represents the D' value and r^2 value (in parentheses) corresponding to each pair-wise SNP

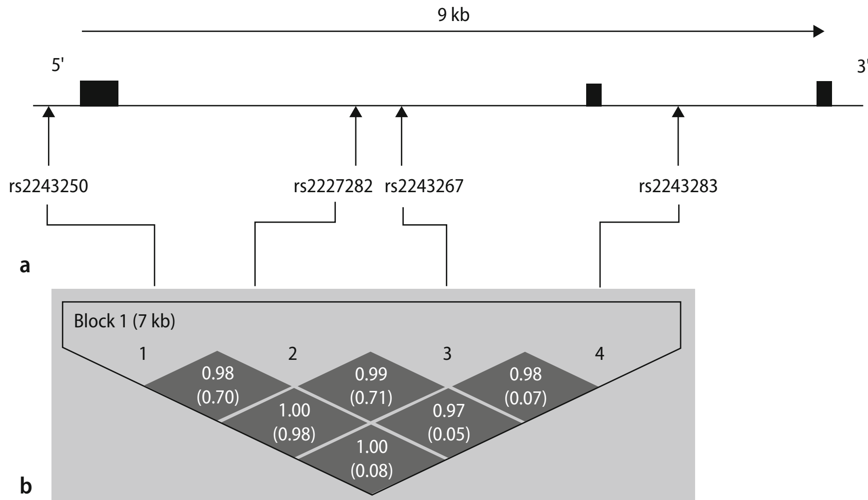

Table 1 Genotype and allele frequencies of *IL2* and *IL4* polymorphisms in patients with schizophrenia and control subjects

Gene symbol	SNP	Allele[a]	Patients						Controls						P	
			n	HWE	1/1[b]	1/2[b]	2/2[b]	MAF	*n*	HWE	1/1[b]	1/2[b]	2/2[b]	MAF	Genotype	Allele
IL2	rs2069772	T/C	536	0.029	432	93	11	0.107	510	0.684	415	91	4	0.097	0.225	0.441
	Rs2069763	G/T	536	0.869	140	266	130	0.491	510	0.425	125	264	121	0.496	0.766	0.805
	rs2069762	T/G	536	0.210	232	251	53	0.333	510	0.947	225	228	57	0.335	0.701	0.912
IL4	rs2243250	T/C	536	0.116	254	241	41	0.301	509	0.437	237	215	57	0.323	0.136	0.281
	rs2227282	G/C	536	0.270	299	209	28	0.247	510	0.182	294	179	37	0.248	0.227	0.965
	rs2243267	C/G	536	0.116	254	241	41	0.301	510	0.463	235	217	58	0.327	0.118	0.215
	rs2243283	G/C	534	0.747	398	125	11	0.138	510	0.910	369	130	11	0.149	0.725	0.458

SNP single nucleotide polymorphism, *HWE* Hardy–Weinberg equilibrium, *MAF* minor allele frequency
[a]Major/minor alleles
[b]Genotypes, major and minor alleles are denoted by 1 and 2, respectively

haplotype frequencies of the patients and control subjects were compared using the χ^2 test. A probability level of $P < 0.05$ was considered to be statistically significant.

Power calculation was performed using Genetic Power Calculator [38]. Power was estimated with an α of 0.05, assuming a disease prevalence of 0.01 and the risk allele frequencies to be the values observed in control samples.

Results

Table 1 shows the genotype and allele frequencies of three SNPs in *IL2* and four SNPs in *IL4* in the patients and control subjects. None of the genotype distributions of the SNPs examined deviated significantly from HWE in either group ($P > 0.05$), with the exception of rs2069772 in the patients ($P = 0.029$). None of the genotype or allele frequencies of the SNPs examined differed significantly between patients and control subjects ($P > 0.05$). We observed that either *IL2* or *IL4* were present in a single LD block (Figs. 1b and 2b, respectively). There were no associations between the common haplotypes of these LD blocks and schizophrenia ($P > 0.05$, Table 2).

Table 2 Haplotype analyses of *IL2* and *IL4* polymorphisms in patients with schizophrenia and control subjects

Gene symbol	Haplotype	Patients (frequency)	Controls (frequency)	*P*
IL2	TTT	0.383	0.401	0.421
	TGG	0.333	0.335	0.937
	TGT	0.176	0.168	0.629
	CTT	0.107	0.096	0.414
IL4	TGCG	0.558	0.529	0.175
	CCGG	0.244	0.243	0.966
	TGCC	0.138	0.146	0.589
	CGGG	0.057	0.078	0.056

Global *P* values of haplotypes of *IL2* and *IL4* were 0.755 and 0.211, respectively

Discussion

In the present study, we failed to find significant associations of three *IL2* polymorphisms and four *IL4* polymorphisms with schizophrenia in our Japanese subjects, using both single-marker and haplotype analyses. Schwartz et al. [44] found an association of the T/T genotype of the *IL2* −330T/G polymorphism (rs2069762) with schizophrenia in a German population. Interestingly, peripheral blood lymphocytes from individuals with the G/G genotype produce significantly more IL-2 than those from individuals with T/T and T/G genotypes [16]. Therefore, an association of the T/T genotype with schizophrenia could partly explain a reduced IL-2 production in schizophrenia, which is one of the most frequently confirmed immunological phenomena in schizophrenia [1, 5, 12, 13, 18, 22, 28, 37, 42, 43, 48, 49]. By contrast, we failed to replicate the previous finding for an association between the T/T genotype and schizophrenia ($P > 0.05$). In addition, there was no significant association between the G/G genotype and schizophrenia ($P > 0.05$). The genotype frequencies of the *IL2* −330T/G polymorphism did not differ significantly between patients and control subjects ($P > 0.05$). When we assessed HWE in control subjects of Schwartz et al. [44], the genotype distributions of the *IL2* −330T/G polymorphism significantly deviated from HWE ($\chi^2 = 4.890$, df = 1, $P = 0.027$), whereas they described that their control subjects followed HWE ($\chi^2 = 2.705$, df = 2, $P = 0.259$). The deviation from HWE can be caused by multiple factors such as typing error and population stratification, and can inflate the chance of a false-positive association. Thus, an association of the T/T genotype with schizophrenia reported by Schwartz et al. [44] should be interpreted with caution, although the deviation from HWE may not necessarily invalidate the results of an association study. In the present study, rs2069772 showed significant deviation from HWE only in the patient group. This kind of departure from HWE might be due to the fact that the case group is a nonrandom mating population, and not a result of typing errors.

Two previous association studies of schizophrenia and *IL4* focused on only the −590C/T polymorphism (rs2243250) [20, 44]. We conducted a moderate-scale case-control association study using four markers including −590C/T and three ‘tagging SNPs’. However, we failed to find significant associations of these *IL4* polymorphisms with schizophrenia in our Japanese subjects, using either single-marker or haplotype analyses. Our results are in line with previous negative findings for a Korean population [20]. By contrast, Schwartz et al. [44] showed evidence for an association between the −590C allele and schizophrenia in a German population. Thus, there is the possibility that the *IL4* −590C/T polymorphism could be implicated in vulnerability to schizophrenia in Caucasian but not in Asian populations. Our failure to replicate the previous positive finding for a German population may be due to ethnic differences. Indeed, there are differences in the allele frequencies of this polymorphism across populations. The frequencies of the −590C allele in Korean and Japanese control subjects (18.8 and 32.3%, respectively) are lower than that in German control subjects (83.3%).

We recognize several limitations of the study. No standardized structured interview was applied to verify the clinical diagnoses of included patients, but the diagnosis of schizophrenia had been assigned on the basis of all available sources of information. The control samples were not well characterized. We could not exclude the possibility that our control samples might contain some younger individuals who will be suffered with schizophrenia after getting on in years. To the best of our knowledge, however, there were no control subjects who were likely to develop schizophrenia at their stage of life. Thus, it is unlikely that our failure to find a significant association is attributable to misdiagnosis. The sample size of the present study ($n = 1046$) is more than twice as large as that of Jun et al. ($n = 387$) [20] and that of Schwartz et al. ($n = 481$) [44].

The power calculation showed that when genotypic relative risk was set at 1.69 for homozygous risk allele carriers under the multiplicative model of inheritance the power was more than 0.80 for four SNPs (rs2069763, rs2069762, rs2243250 and rs2243267). However, our sample size did not have sufficient statistical power for the other three SNPs (rs2069772, rs2227282 and rs2243283). Therefore, we could not exclude the possibility that our negative results for these SNPs were due to type II error.

In conclusion, the present study suggests that *IL2* and *IL4* do not contribute to vulnerability to schizophrenia in the Japanese population. To draw a definitive conclusion, however, further studies using larger sample sizes and sufficient markers will be needed in different ethnic populations.

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References

1. Arolt V, Rothermundt M, Wandinger K-P, Kirchner H (2000) Decreased in vitro production of interferon-gammma and interleukin-2 in whole blood of patients with schizophrenia during treatment. Mol Psychiatry 5:150–158
2. Avguštin B, Wraber B, Tavčar R (2005) Increased Th_1 and Th_2 immune reactivity with relative Th_2 dominance in patients with acute exacerbation of schizophrenia. Croat Med J 46:268–274
3. Barak V, Barak Y, Levine J, Nisman B, Roisman I (1995) Changes in interleukin-1β and soluble interleukin-2 receptor levels in CSF and serum of schizophrenic patients. J Basic Clin Physiol Pharmacol 6:61–69
4. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265
5. Bessler H, Levental Z, Karp L, Modai I, Djaldetti M, Weizman A (1995) Cytokine production in drug-free and neuroleptic-treated schizophrenic patients. Biol Psychiatry 38:297–302
6. Cazzullo CL, Sacchetti E, Galluzzo A, Panariello A, Adorni A, Pegoraro M, Bosis S, Colombo F, Trabattoni D, Zagliani A, Clerici M (2002) Cytokine profiles in schizophrenic patients

treated with risperidone: a 3- month follow-up study. Prog Neuropsychopharmacol Biol Psychiatry 26:33–39
7. Cazzullo CL, Sacchetti E, Galluzzo A, Panariello A, Colombo F, Zagliani A, Clerici M (2001) Cytokine profiles in drug-naive schizophrenic patients. Schizophr Res 47:293–298
8. Cazzullo C, Scarone S, Grassi B, Vismara C, Trabattoni D, Clerici M, Clerici M (1998) Cytokines production in chronic schizophrenia patients with or without paranoid behaviour. Prog Neuropsychopharmacol Biol Psychiatry 22:947–957
9. de Bakker PI, Yelensky R, Pe'er I, Gabriel SB, Daly MJ, Altshuler D (2005) Efficiency and power in genetic association studies. Nat Genet 37:1217–1223
10. Denicoff KD, Rubinow DR, Papa MZ, Simpson C, Seipp CA, Lotze MT, Chang AE, Rosenstein D, Rosenberg SA (1987) The neuropsychiatric effects of treatment with interleukin-2 and lymphokine-activated killer cells. Ann Intern Med 107: 293–300
11. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, Adeyemo A, Cooper R, Ward R, Lander ES, Daly MJ, Altshuler D (2002) The structure of haplotype blocks in the human genome. Science 296:2225–2229
12. Ganguli R, Brar JS, Chengappa KNR, DeLeo M, Yang ZW, Shurin G, Rabin BS (1995) Mitogen-stimulated interleukin-2 production in never-medicated, first-episode schizophrenic patients. Arch Gen Psychiatory 52:668–672
13. Ganguli R, Rabin BS, Bell SH (1989) Decreased interleukin-2 production in schizophrenic patients. Biol Psychiatry 26: 427–430
14. Gattaz WF, Dalgalarrondo P, Schröder HC (1992) Abnormalities in serum concentrations of interleukin-2, interferon-α and interferon-γ in schizophrenia not detected. Schizophr Res 6:237–241
15. Hirakawa M, Tanaka T, Hashimoto Y, Kuroda M, Takagi T, Nakamura Y (2002) JSNP: a database of common gene variations in the Japanese population. Nucleic Acids Res 30:158–162
16. Hoffmann SC, Stanley EM, Cox ED, Craighead N, DiMercurio BS, Koziol DE, Harlan DM, Kirk AD, Blair PJ (2001) Association of cytokine polymorphic inheritance and in vitro cytokine production in anti-CD3/CD28-stimulated peripheral blood lymphocytes. Transplantation 72:1444–1450
17. Hori H, Yoshimura R, Yamada Y, Ikenouchi A, Mitoma M, Ida Y, Nakamura J (2007) Effects of olanzapine on plasma levels of catecholamine metabolites, cytokines, and brain-derived neurotrophic factor in schizophrenic patients. Int Clin Psychopharmacol 22:21–27
18. Hornberg M, Arolt V, Wilke I, Kruse A, Kirchner H (1995) Production of interferones and lymphokines in leukocyte cultures of patients with schizophrenia. Schizophr Res 15:237–242
19. John S, Turner D, Donn R, Sinnott P, Worthington J, Ollier WER, Hutchinson V, Hajeer AH (1998) Two novel biallelic polymorphisms in the *IL-2* gene. Eur J Immunogenet 25: 419–420
20. Jun T-Y, Lee K-U, Pae C-U, Chae J-H, Bahk W-M, Kim K-S, Han H (2003) Polymorphisms of interleukin-4 promoter and receptor gene for schizophrenia in the Korean population. Psychiatry Clin Neurosci 57:283–288
21. Kim Y-K, Kim L, Lee M-S (2000) Relationships between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics. Schizophr Res 44:165–175
22. Kim YK, Lee MS, Suh KY (1998) Decreased interleukin-2 production in Korean schizophrenic patients. Biol Psychiatry 43:701–704
23. Kim Y-K, Myint A-M, Lee B-H, Han C-S, Lee H-J, Kim D-J, Leonard BE (2004) Th1, Th2 and Th3 cytokine alteration in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 28:1129–1134
24. Leykin I, Mayer R, Shinitzky M (1997) Short and long term immunosuppressive effects of clozapine and haloperidol. Immunopharmacology 37:75–86
25. Licinio J, Seibyl JP, Altemus M, Charney DS, Krystal JH (1993) Elevated CSF levels of interleukin-2 in neuroleptic-free schizophrenic patients. Am J Psychiatry 150:1408–1410
26. Lyons A, Downer EJ, Crotty S, Nolan YM, Mills KHG, Lynch MA (2007) CD200 ligand-receptor interaction modulates microglial activation in vivo and in vitro: a role for IL-4. J Neurosci 27:8309–8313
27. Lyons A, Griffin RJ, Costelloe CE, Clarke RM, Lynch MA (2007) IL-4 attenuates the neuroinflammation induced by amyloid-β in vivo and in vitro. J Neurochem 101:771–781
28. Mahendran R, Mahendran R, Chan YH (2004) Interleukin-2 levels in chronic schizophrenia patients. Ann Acad Med Singapore 33:320–323
29. McAllister CG, van Kammen DP, Rehn TJ, Miller AL, Gurklis J, Kelley ME, Yao J, Peters JL (1995) Increases in CSF levels of interleukin-2 in schizophrenia: effects of recurrence of psychosis and medication status. Am J Psychiatry 152:1291–1297
30. Mittleman BB, Castellanos FX, Jacobsen LK, Rapoport JL, Swedo SE, Shearer GM (1997) Cerebrospinal fluid cytokines in pediatric neuropsychiatiric disease. J Immunol 159:2994–2999
31. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL (1986) Two types of murine helper T cell clone. J Immunol 136:2348–2357
32. Müller N, Schwarz M (2006) Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. Neurotox Res 10:131–148
33. Nawa H, Takahashi M, Patterson PH (2000) Cytokine and growth factor involvement in schizophrenia–support for the developmental model. Mol Psychiatry 5:594–603
34. Nawa H, Takei N (2006) Recent progress in animal modeling of immune inflammatory processes in schizophrenia: implication of specific cytokines. Neurosci Res 56:2–13
35. Neale BM, Sham PC (2004) The future of association studies: gene-based analysis and replication. Am J Hum Genet 75:353–362
36. O'Donnell MC, Catts SV, Ward PB, Liebert B, Lloyd A, Wakefield D, McConaghy N (1996) Increased production of interleukin-2 (IL-2) but not soluble interleukin-2 receptors (sIL-2R) in unmedicated patients with schizophrenia and schizophreniform disorder. Psychiatry Res 65:171–178
37. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E (2007) Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry (in press)
38. Purcell S, Cherny SS, Sham PC (2003) Genetic power calculator: design of linkage and association genetic mapping studies of complex traits. Bioinformatics 19:149–150
39. Ramchand R, Wei J, Ramchand CN, Hemmings GP (1994) Increased serum IgE in schizophrenic patients who responded poorly to neuroleptic treatment. Life Sci 54:1579–1584
40. Rapaport MH, McAllister CG, Pickar D, Tamarkin L, Kirch DG, Paul SM (1997) CSF IL-1 and IL-2 in medicated schizophrenic patients and normal volunteers. Schizophr Res 25:123–129
41. Rosenwasser LJ, Klemm DJ, Dresback JK, Inamura H, Mascali JJ, Klinnert M, Borish L (1995) Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. Clin Exp Allergy 25:74–78
42. Rothermundt M, Arolt V, Weitzsch C, Eckhoff D, Kirchner H (1996) Production of cytokines in acute schizophrenic psychosis. Biol Psychiatry 40:1294–1297
43. Rothermundt M, Arolt V, Weitzsch C, Eckhoff D, Kirchner H (1998) Immunological dysfunction in schizophrenia: a systematic approach. Neuropsychobiology 37:186–193
44. Schwarz MJ, Krönig H, Riedel M, Dehning S, Douhet A, Spellmann I, Ackenheil M, Möller H-J, Müller N (2006) IL-2 and IL-4 polymorphisms as candidate genes in schizophrenia. Eur Arch Psychiatry Clin Neurosci 256:72–76
45. Sredni-Kenigsbuch D (2002) TH1/TH2 cytokines in the central nervous system. Int J Neurosci 112:665–703

46. Tancredi V, Zona C, Velotti F, Eusebi F, Santoni A (1990) Interleukin-2 suppresses established long-term potentiation and inhibits its induction in the rat hippocampus. Brain Res 525:149–151
47. Theodoropoulou S, Spanakos G, Baxevanis CN, Economou M, Gritzapis AD, Papamichail MP, Stefanis CN (2001) Cytokine serum levels, autologous mixed lymphocyte reaction and surface marker analysis in never medicated and chronically medicated schizophrenic patients. Schizophr Res 47:13–25
48. Villemain F, Chatenoud L, Galinowski A, Homo-Delarche F, Ginestet D, Loo H, Zarifian E, Bach J-F (1989) Aberrant T cell-mediated immunity in untreated schizophrenic patients: deficient interleukin-2 production. Am J Psychiatry 146:609–616
49. Villemain F, Chatenoud L, Guillibert E, Pelicier Y, Bach JF (1987) Decreased production of interleukin-2 in schizophrenia. Ann NY Acad Sci 496:666–675
50. Watanabe Y, Muratake T, Kaneko N, Nunokawa A, Someya T (2006) No association between the *brain-derived neurotrophic factor* gene and schizophrenia in a Japanese population. Schizophr Res 84:29–35
51. Wilke I, Arolt V, Rothermundt M, Weitzsch CH, Hornberg M, Kirchner H (1996) Investigations of cytokine production in whole blood cultures of paranoid and residual schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 246:279–284
52. Xu H-M, Wei J, Hemmings GP (1994) Changes of plasma concentrations of interleukin-1α and interleukin-6 with neuroleptic treatment for schizophrenia. Br J Psychiatry 164:251–253
53. Zhang XY, Zhou DF, Cao LY, Wu GY, Shen YC (2005) Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. Neuropsychopharmacology 30:1532–1538
54. Zhang XY, Zhou DF, Cao LY, Zhang PY, Wu GY, Shen YC (2004) Changes in serum interleukin-2, -6, and -8 levels before and during treatment with risperidone and haloperidol: relationship to outcome in schizophrenia. J Clin Psychiatry 65:940–947
55. Zhang XY, Zhou DF, Zhang PY, Wu GY, Cao LY, Shen YC (2002) Elevated interleukin-2, interleukin-6 and interleukin-8 serum levels in neuroleptic-free schizophrenia: association with psychopathology. Schizophr Res 57:247–2258