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ORIGINAL PAPER

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IL-2 and IL-4 polymorphisms as candidate genes in schizophrenia

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Abstract An immune process, characterized by a relative predominance of the T helper-2 (Th2) system and possibly induced by a viral infection, may be involved in the pathophysiology of schizophrenia. In this context, functional polymorphisms in the Interleukin-2 (IL-2) and Interleukin-4 (IL-4) genes appear to be principal candidates for genetic schizophrenia research. Further evidence for these candidate genes comes from several linkage analyses, pointing to susceptibility gene loci on chromosomes 4q and 5q, where the genes coding for IL-2 and IL-4 are located. We carried out a case-control study including 230 schizophrenic patients and 251 healthy persons, investigating the IL-2 –330 T/G single nucleotide polymorphism (SNP) and the IL-4 –590 C/T SNP. A significant association of the IL-2 –330 TT genotype and of the IL-4 –590 CC genotype with schizophrenia could be identified. Our findings may partly account for the relative predominance of the Th2 system in schizophrenia, although they cannot directly explain this immunological imbalance, but may be related to an altered antiviral immune response in patients with schizophrenia.

Key words schizophrenia · single nucleotide polymorphism · IL-2 · IL-4 · Th2 · immune system

Introduction

Schizophrenia is a genetically complex disorder with an incidence rate in the range of 0.16 to 0.42 per 1000 in the general population (Jablensky 2000). The most probable genetic basis of schizophrenia involves a mode of transmission with several to multiple susceptibility genes (Sullivan et al. 2003). In addition to the hereditary component, there is major evidence supporting pre- or perinatal exposure to viral infection as a risk factor for developing schizophrenia, with main focal points on the influenza, rubella, measles, and herpes simplex viruses (Pearce 2001). Moreover, viral infections during childhood (Koponen et al. 2004) and even preceding the onset of the illness (Leweke et al. 2004) have been associated with schizophrenia.

Given the hereditary component of schizophrenia and the possible causative role of a viral infection, immunologically relevant genes may shape up as susceptibility genes for schizophrenia, altering the immune defence of viral infections. Accordingly, the immunological phenotype of schizophrenic patients is altered: a large body of evidence indicates a reduced activation of the T-helper lymphocytes type 1 (Th1, inducing a cell-mediated immune response) and a relative predominance of Th2 cells (which induce an antibody-mediated immune response) (Schwarz et al. 2001). The key molecules in the regulation of anti-viral immune response and in the regulation of the Th1/Th2 balance are cytokines. In this study, we focused on the two cytokines Interleukin(IL)-2 and IL-4. Potent antiviral activity is mediated by IL-2, while IL-4, in sharp contrast, may increase virus virulence, due to a downregulation of host type 1 immune responses (Ramshaw et al. 1997).

IL-2 acts as a growth factor for T cells, NK cells and B cells (Cohen and Cohen 1996; Feghali and Wright 1997). A significantly decreased production of IL-2 by peripheral lymphocytes is one of the best replicated immunological findings in schizophrenia (Ganguli et al. 1992, 1995; Yang et al. 1994; Kim et al. 1998; Arolt et al. 2000).

The gene coding for IL-2 is located on chromosome 4q26-q27 (Degrave et al. 1983); some linkage studies point to a susceptibility gene for schizophrenia in this chromosomal region, e. g. 4q22–23, or 4q31 (Kennedy et al. 1999; Mowry et al. 2000), although there are conflicting data (Paunio et al. 2001). The binding domains

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for transcription factors like the nuclear factor of activated T-cells (NFAT) that are responsible for the T cell-specific transcription of the IL-2 gene are located in the promotor region, approximately 300 base pairs 5' proximal of the coding sequence of the IL-2 gene (Crabtree and Clipstone 1994). This region contains a functional T→G single nucleotide polymorphism (SNP) at position –330 (John et al. 1998). In vitro studies using anti-CD3/CD28 stimulated peripheral blood lymphocytes demonstrated that homozygosity for the G allele is associated with an early and sustained enhancement of IL-2 production (Hoffmann et al. 2001).

IL-4 plays a major role as a Th2-type response mediator. It induces T-helper cells to differentiate into Th2 cells while suppressing the development of Th1 cells (Kubo et al. 1999). This major Th2 cytokine activates B cell proliferation, antibody production, and immunoglobulin class-switching from IgG to IgE (Spellberg and Edwards Jr. 2001).

The IL-4 coding gene is located within the cytokine gene cluster on chromosome 5q31.1 (Kelso 1998), which is a chromosomal region again identified by linkage analyses as containing a susceptibility gene for schizophrenia (Schwab et al. 2000; Paunio et al. 2001). Rosenwasser and colleagues described a C→T SNP at position –590 upstream from the open reading frame of the IL-4 gene, corresponding to the nomenclature –523 counted from the start codon (Rosenwasser et al. 1995; Walley and Cookson 1996). The –590 T-allele is associated with an increased IL-4 gene expression in vitro and with increased total serum IgE in vivo (Rosenwasser et al. 1995). Besides the IL-4 –590 promotor polymorphism, two additional polymorphisms, the –34 C→T SNP (Takabayashi et al. 1999) and a Variable-Number Tandem-Repeats sequence in the third intron (Buchs et al. 2000), have been described. However, the corresponding haplotypes are characterized by the T- or C-allele of the –590 SNP (Johnson et al. 2001; Vandenbroeck and Goris 2003). The SNPs that allow the largest number of haplotypes to be captured by the minimum number of SNPs are called haplotype tagging SNPs (Johnson et al. 2001). Thus, the –590 SNP serves as the haplotype tagging SNP of the IL-4 gene. We, therefore, selected this –590 SNP to investigate the IL-4 gene.

In view of the potential role of IL-2 and IL-4 in the pathogenesis of schizophrenia and the linkage studies pointing to the chromosomal regions containing the IL-2 and IL-4 genes, the present study was designed to examine the afore-described polymorphisms with schizophrenia. According to the proposed Th1/Th2 imbalance in schizophrenia, we hypothesized an association of the IL-2 –330 T-allele and of the IL-4 –590 T-allele with schizophrenia.

Methods

Patients and control persons

A total of 230 unrelated Caucasian patients suffering from schizophrenia (100 female, 130 male; mean age 33.7 ± 12.4 years, ranging from 17 to 78 years) were recruited at the Psychiatric Hospital of the University of Munich. Diagnoses were established according to the criteria of the DSM-IV (Diagnostic and Statistical Manual) by two independent experienced psychiatrists. Paranoid schizophrenia was diagnosed (DSM-IV: 295.3x) in 71 % of the patients, 13 % carried a diagnosis of disorganized schizophrenia (DSM-IV: 295.1x), 2 % had a diagnosis of residual schizophrenia (DSM-IV: 295.6x), 3 % of catatonic schizophrenia (DSM-IV: 295.2x), 6 % of undifferentiated schizophrenia (DSM-IV: 295.9x), 3.5 % had a schizophreniform disorder (DSM-IV: 295.4x) and 1.5 % were suffering from a schizoaffective (DSM-IV: 295.7x) disorder. The mean age of onset was 27.5 ± 9.8 years. Sixty-four (38 %) of the patients were suffering from first-episode schizophrenia.

From the general population of Munich and surrounding areas, 251 healthy Caucasians (119 female, 132 male; mean age 40.2 ± 14.0 years, ranging from 19 to 76 years), representing various social groups, were recruited as the control group. All controls were screened for past or present psychiatric illness by interview and by use of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2). Medical examinations including standard laboratory tests were performed. History of a psychosis in a first-degree relative was ascertained by interviewing the control persons and was considered an exclusion criterion.

The study was approved by the local Ethics Committee and all patients and controls gave their written informed consent after the aim of the study had been fully explained.

Genotyping

Genomic DNA was isolated from whole blood according to standard procedures. The genotyping was performed by the fluorescence resonance energy transfer method (FRET) using the Light Cycler System (Roche Diagnostics). A detailed description of the theoretical background and methodology is given by Toyota et al. (2000).

The genotyping of IL-2 and IL-4 were carried out by means of the fluorescence resonance energy transfer method (FRET) using the Light Cycler System (Roche Diagnostics). For the single base polymorphism at position T330G in the IL-2 promotor region the following conditions were applied: forward primer: 5'- ATg CAA TTA gCT CTT TgT gTg g – 3'; reverse primer: 5' - TTC TTT AAA CCC CCA AAg ACT g – 3'; donor hybridization probe: 5'- TTT CTT TgT CAT AAA ACT ACA C - fluorescein-3'; acceptor hybridization probe: 5'- LCRed640 - ACA TgT gAA TAg CAT ATT gTg gTg gAC Aag - 3'. The PCR was performed with 50 ng DNA in a total volume of 10 µl containing 1 µl reaction mix, 0.4 µl $MgCl_2$, 0.25 µl of each primer and 0.1 µl of each hybridization probe according to the manufacturer's instructions for 45 cycles of denaturation (95 °C, 0 s, ramp rate 20 °C/s), annealing (58 °C, 10 s, ramp rate 20 °C/s) and extension (72 °C, 10 s, ramp rate 20 °C/s). After amplification a melting curve was generated by holding the reaction at 40 °C for 30 s and then heating slowly to 95 °C with a ramp rate of 0.1 °C/s. The fluorescence signal was plotted against temperature to give melting curves for each sample. Peaks were obtained at 54 °C for the T-allele and at 51 °C for the G-allele.

For the C→T SNP at position 589 of the IL-4 promotor we chose the following conditions: forward primer: 5'- ATC AAA CAT TgC ATT TCA gCC -3'; reverse primer: 5'- gTT gTA Atg Cag TCC TCC Tgg - 3'; donor hybridization probe: 5'- ggA gAA CAT TgT CCC CCA gTg CT - fluorescein-3'; acceptor hybridization probe: 5'- LCRed640 - ggT Agg AgA gTC TgC CTg TTA TTC TgC C - 3'. The PCR was performed with 50 ng DNA in a total volume of 10 µl containing 1 µl reaction mix, 0.8 µl $MgCl_2$, 0.25 µl of each primer and 0.1 µl of each hybridization probe according to the manufacturer's instructions for 45 cycles of denaturation (95 °C, 0 s, ramp rate 20 °C/s), annealing (58 °C, 10 s, ramp rate 20 °C/s) and extension (72 °C, 10 s, ramp rate 20 °C/s). After amplification, a melting curve was generated by holding the reaction

at 45 °C for 30 s and then heating slowly to 95 °C with a ramp rate of 0.2 °C/s. The fluorescence signal was plotted against temperature to give melting curves for each sample. Peaks were obtained at 67 °C for the C-allele and at 63 °C for the T-allele.

Statistics

Statistical analyses were performed using SPSS for Windows. Results are reported as the mean ± SD. We used the t-test for independent samples and the Chi² test. The age difference between the two groups was compared by two-tailed Student's t-test.

Results

The two study groups did not differ concerning their gender ($\chi^2 = 0.844$, df = 1, $p = 0.358$), but the control group was markedly older than the patients' group ($t = 5.395$, df = 479, $p < 0.001$).

The genotype distribution of the IL-2 –330 T→G promotor polymorphism was different between the two groups ($\chi^2 = 7.418$, df = 2, $p = 0.024$; see Table 1). Both groups followed the Hardy-Weinberg equilibrium (schizophrenic patients: $\chi^2 = 0.780$; df = 2; $p = 0.677$; controls: $\chi^2 = 2.705$; df = 2; $p = 0.259$). Since homozygosity for the T allele was overrepresented in schizophrenia, whereas the heterozygous genotype was less frequent, the two populations did not differ regarding the allele frequencies ($\chi^2 = 0.844$; df = 1; $p = 0.358$).

As for the IL-2 –330 SNP, there was also a marked difference between the two investigated groups regarding the IL-4 –590 C→T genotypes ($\chi^2 = 7.323$, df = 2, $p = 0.026$, see Table 2). Again, the two groups lay in the Hardy-Weinberg equilibrium (schizophrenic patients: $\chi^2 = 0.189$; df = 2; $p = 0.910$; controls: $\chi^2 = 1.091$; df = 2; $p = 0.580$). Since in this case homozygosity for the polymorphic T-allele was extremely rare, we combined the TT and CT genotypes for comparison with the homozygous CC genotype: schizophrenic patients showed a significantly higher frequency of the CC genotype ($\chi^2 = 6.830$, df = 1, $p = 0.009$).

Further, we compared the subgroup of paranoid patients with the non-paranoid subtypes regarding their genotype distribution. The two groups did not differ, regarding both the IL-2 –330 SNP ($\chi^2 = 0.083$, df = 1, $p = 0.773$), and the IL-4 –590 SNP ($\chi^2 = 0.006$, df = 1, $p = 0.939$).

Table 1 Genotype distribution and allele frequency of the IL-2 –330 T→G polymorphism in schizophrenic patients (SCH) and healthy controls (CON) with the TT genotype being associated with schizophrenia ($\chi^2 = 7.418$, $p = 0.024$)

	IL-2 –330			Allele frequency	
	GG	GT	TT	T	G
SCH	24 (10%)	88 (38%)	118 (51%)	29.6%	70.4%
CON	20 (8%)	127 (51%)	104 (41%)	33.3%	66.7%

Table 2 Genotype distribution and allele frequency of the IL-4 –590 C→T polymorphism in schizophrenic patients (SCH) and healthy controls (CON). The CC genotype showed association with schizophrenia ($\chi^2 = 7.323$, $p = 0.026$)

	IL-4 –590			Allele frequency	
	TT	CT	CC	CC	CT/TT
SCH	4 (2%)	45 (20%)	181 (79%)	11.5%	88.5%
CON	4 (2%)	76 (30%)	171 (68%)	16.7%	83.3%

Discussion

Based on the proposed involvement of an imbalanced immune reaction in the etiology of schizophrenia and considering the important hereditary component, we examined two well-established polymorphisms in the genes coding for IL-2 and IL-4. We report a significant association of the IL-2 –330 TT genotype and of the IL-4 –590 CC genotype with schizophrenia.

T helper (Th) cells can be subdivided into two groups based on the cytokine profiles they produce. Upon antigen encounter in the presence of IL-12 and IFN-γ, naive Th cells can differentiate into Th1 cells that are characterized by the production of IFN-γ and IL-2, for example. Alternatively, antigen signalling in the presence of IL-4 induces the naive Th cell population to develop into Th2 effectors secreting IL-4, IL-5 and IL-13 (Abbas et al. 1996). Both an increased production of Th2 cytokines like IL-4 (Spellberg and Edwards Jr. 2001), and a blunted signal of Th1 cytokines like IL-2 (Suzuki et al. 1995) activate B cell proliferation, antibody production, and immunoglobulin class-switching to IgE. Several studies indicate an increased activation of B cells accompanied by elevated antibody titers against several antigens in schizophrenia; there are even data on increased IgE levels in schizophrenic patients. Altogether, a relative predominance of the Th2-like immune response can be proposed as an immunologic characteristic of schizophrenia (Schwarz et al. 2001).

However, the genetic findings reported here can only partly account for the Th2 dominated phenotype in schizophrenia.

In vitro data show that the IL-2 –330 polymorphism is functionally linked with an altered IL-2 production (Hoffmann et al. 2001): the GG genotype is associated with high levels of IL-2, while TT, but also GT, genotypes are linked with a reduced in vitro production of the cytokine. Since in our study the TT genotype was significantly associated with schizophrenia, but the GT genotype was markedly less frequent in schizophrenia, our data can only partly explain the repeatedly reported findings of a reduced IL-2 in vitro production in schizophrenia (Ganguli et al. 1992, 1995; Yang et al. 1994; Kim et al. 1998; Arolt et al. 2000).

Regarding the IL-4 SNP, Rosenwasser and colleagues reported an increased promotor activity for IL-4 transcription and elevated levels of serum IgE in asthmatic families, associated with the T-allele (Rosenwasser et al.

1995). The rare T-allele is additionally associated with pulmonary dysfunction in asthma patients (Burchard et al. 1999) and with asthma severity (Sandford et al. 2000). On the other hand, the common C-allele is associated with a more progressive and more destructive form of rheumatoid arthritis (Buchs et al. 2000; Genevay et al. 2002), as well as an earlier age of onset and a higher severity of Multiple Sclerosis (Vandenbroeck et al. 1997; Kantarci et al. 2003). In this context, the herein-reported association of the CC genotype with schizophrenia is contradictory, as it would point to a more pronounced Th1-like activation.

The –590 SNP has already been investigated as a candidate gene for schizophrenia in a Korean population (Jun et al. 2003). Jun et al. reported a tendential, albeit not significant, association of the C-allele with schizophrenia ($\chi^2 = 3.65$; df = 1; p = 0.056), which is in accordance with our results. However, the two populations may not be comparable due to ethnical differences in the IL-4 genotype distribution. As demonstrated by a recent study on the IL-4 –590 SNP in healthy Korean blood donors, the C-allele is markedly less frequent in the Korean population than in Caucasian populations (Burchard et al. 1999; Choi et al. 2002). Thus, our study represents the first association study of this IL-4 polymorphism with schizophrenia in a Caucasian population.

Although the significant associations of the IL-2 and the IL-4 genes with schizophrenia coincide with recent linkage analyses (Kennedy et al. 1999; Mowry et al. 2000), these results should be replicated by a large independent cohort.

The Th2-dominated immunological phenotype of schizophrenic patients, however, appears to be caused not only by these genetic factors. Environmental factors like viral infections may account for this phenomenon. Viral infections can specifically affect immune regulation and lead to inappropriate levels of Th1 or Th2 cells in later life (Openshaw et al. 2004). Neuron-glia interactions during persistent viral infections, accompanied by a Th2 predominance in the chronic phase of the disease, are discussed to play a key role in the pathogenesis of schizophrenia (Hatalski et al. 1998; Sawa et al. 2004). At least for the IL-4 –590 SNP, a modulating effect during the antiviral immune response has been described (Nakayama et al. 2002; Vasilescu et al. 2003). The investigated cytokine gene polymorphisms may, therefore, be involved in the susceptibility to certain viral infections.

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References

1. Abbas AK, Murphy KM, Sher A (1996) Functional Diversity of Helper T Lymphocytes. Nature 383:787–793
2. Arolt V, Rothermundt M, Wandinger KP, Kirchner H (2000) Decreased in Vitro Production of Interferon-Gamma and Interleukin-2 in Whole Blood of Patients With Schizophrenia During Treatment. Mol Psychiatry 5:150–158
3. Buchs N, Silvestri T, di Giovine FS, Chabaud M, Vannier E, Duff GW, Miossec P (2000) IL-4 VNTR Gene Polymorphism in Chronic Polyarthritis. The Rare Allele Is Associated With Protection Against Destruction. Rheumatology (Oxford) 39:1126–1131
4. Burchard EG, Silverman EK, Rosenwasser LJ, Borish L, Yandava C, Pillari A, Weiss ST, Hasday J, Lilly CM, Ford JG, Drazen JM (1999) Association Between a Sequence Variant in the IL-4 Gene Promoter and FEV(1) in Asthma. Am J Respir Crit Care Med 160:919–922
5. Choi EH, Lee HJ, Yoo T, Chanock SJ (2002) A Common Haplotype of Interleukin-4 Gene IL-4 Is Associated With Severe Respiratory Syncytial Virus Disease in Korean Children. J Infect Dis 186: 1207–1211
6. Cohen MC, Cohen S (1996) Cytokine Function: a Study in Biologic Diversity. Am J Clin Pathol 105:589–598
7. Crabtree GR, Clipstone NA (1994) Signal Transmission Between the Plasma Membrane and Nucleus of T Lymphocytes. Annu Rev Biochem 63:1045–1083
8. Degrave W, Tavernier J, Duerinck F, Plaetinck G, Devos R, Fiers W (1983) Cloning and Structure of the Human Interleukin 2 Chromosomal Gene. EMBO J 2:2349–2353
9. Feghali CA, Wright TM (1997) Cytokines in Acute and Chronic Inflammation. Front Biosci 2:12–26
10. Ganguli R, Brar JS, Chengappa KR, DeLeo M, Yang ZW, Shurin G, Rabin BS (1995) Mitogen-Stimulated Interleukin-2 Production in Never-Medicated, First-Episode Schizophrenic Patients. The Influence of Age at Onset and Negative Symptoms (See Comments). Arch Gen Psychiatry 52:668–672
11. Ganguli R, Brar JS, Solomon W, Chengappa KN, Rabin BS (1992) Altered Interleukin-2 Production in Schizophrenia: Association Between Clinical State and Autoantibody Production. Psychiatry Res 44:113–123
12. Genevay S, di Giovine FS, Perneger TV, Silvestri T, Stingelin S, Duff G, Guerne PA (2002) Association of Interleukin-4 and Interleukin-1B Gene Variants With Larsen Score Progression in Rheumatoid Arthritis. Arthritis Rheum 47:303–309
13. Hatalski CG, Hickey WF, Lipkin WI (1998) Evolution of the Immune Response in the Central Nervous System Following Infection With Borna Disease Virus. J Neuroimmunol 90:137–142
14. Hoffmann SC, Stanley EM, Darrin CE, 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
15. Jablensky A (2000) Epidemiology of Schizophrenia: the Global Burden of Disease and Disability. Eur Arch Psychiatry Clin Neurosci 250:274–285
16. John S, Turner D, Donn R, Sinnott P, Worthington J, Ollier WE, Hutchinson IV, Hajeer AH (1998) Two Novel Biallelic Polymorphisms in the IL-2 Gene. Eur J Immunogenet 25:419–420
17. Johnson GC, Esposito L, Barratt BJ, Smith AN, Heward J, Di Genova G, Ueda H, Cordell HJ, Eaves IA, Dudbridge F, Twells RC, Payne F, Hughes W, Nutland S, Stevens H, Carr P, Tuomilehto-Wolf E, Tuomilehto J, Gough SC, Clayton DG, Todd JA (2001) Haplotype Tagging for the Identification of Common Disease Genes. Nat Genet 29:233–237
18. Jun TY, Lee KU, Pae CU, Chae JH, Bahk WM, Kim KS, Han H (2003) Polymorphisms of Interleukin-4 Promoter and Receptor Gene for Schizophrenia in the Korean Population. Psychiatry Clin Neurosci 57:283–288
19. Kantarci OH, Schaefer-Klein JL, Hebrink DD, Achenbach SJ, Atkinson EJ, McMurray CT, Weinshenker BG (2003) A Population-Based Study of IL-4 Polymorphisms in Multiple Sclerosis. J Neuroimmunol 137:134–139
20. Kelso A (1998) Cytokines: Principles and Prospects. Immunol Cell Biol 76:300–317

21. Kennedy JL, Basile VS, Macciardi FM (1999) Chromosome 4 Workshop Summary: Sixth World Congress on Psychiatric Genetics, Bonn, Germany, October 6–10:1998. Am J Med Genet 88: 224–228
22. Kim YK, Lee MS, Suh KY (1998) Decreased Interleukin-2 Production in Korean Schizophrenic Patients. Biol Psychiatry 43: 701–704
23. Koponen H, Rantakallio P, Veijola J, Jones P, Jokelainen J, Isohanni M (2004) Childhood Central Nervous System Infections and Risk for Schizophrenia. Eur Arch Psychiatry Clin Neurosci 254:9–13
24. Kubo M, Yamashita M, Abe R, Tada T, Okumura K, Ransom JT, Nakayama T (1999) CD28 Costimulation Accelerates IL-4 Receptor Sensitivity and IL-4-Mediated Th2 Differentiation. J Immunol 163:2432–2442
25. Leweke FM, Gerth CW, Koethe D, Klosterkotter J, Ruslanova I, Krivogorsky B, Torrey EF, Yolken RH (2004) Antibodies to Infectious Agents in Individuals With Recent Onset Schizophrenia. Eur Arch Psychiatry Clin Neurosci 254:4–8
26. Mowry BJ, Ewen KR, Nancarrow DJ, Lennon DP, Nertney DA, Jones HL, O'Brien MS, Thornley CE, Walters MK, Crowe RR, Silverman JM, Endicott J, Sharpe L, Hayward NK, Gladis MM, Foote SJ, Levinson DF (2000) Second Stage of a Genome Scan of Schizophrenia: Study of Five Positive Regions in an Expanded Sample. Am J Med Genet 96:864–869
27. Nakayama EE, Meyer L, Iwamoto A, Persoz A, Nagai Y, Rouzioux C, Delfraissy JF, Debre P, McIlroy D, Theodorou I, Shioda T (2002) Protective Effect of Interleukin-4 –589T Polymorphism on Human Immunodeficiency Virus Type 1 Disease Progression: Relationship With Virus Load. J Infect Dis 185:1183–1186
28. Openshaw PJ, Yamaguchi Y, Tregoning JS (2004) Childhood Infections, the Developing Immune System, and the Origins of Asthma. J Allergy Clin Immunol 114:1275–1277
29. Paunio T, Ekelund J, Varilo T, Parker A, Hovatta I, Turunen JA, Rinard K, Foti A, Terwilliger JD, Juvonen H, Suvisaari J, Arajarvi R, Suokas J, Partonen T, Lonnqvist J, Meyer J, Peltonen L (2001) Genome-Wide Scan in a Nationwide Study Sample of Schizophrenia Families in Finland Reveals Susceptibility Loci on Chromosomes 2q and 5q. Hum Mol Genet 10:3037–3048
30. Pearce BD (2001) Schizophrenia and Viral Infection During Neurodevelopment: a Focus on Mechanisms. Mol Psychiatry 6:634–646
31. Ramshaw IA, Ramsay AJ, Karupiah G, Rolph MS, Mahalingam S, Ruby JC (1997) Cytokines and Immunity to Viral Infections. Immunol Rev 159:119–135
32. 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(Suppl 2):74–78
33. Sandford AJ, Chagani T, Zhu S, Weir TD, Bai TR, Spinelli JJ, Fitzgerald JM, Behbehani NA, Tan WC, Pare PD (2000) Polymorphisms in the IL4, IL4RA, and FCERIB Genes and Asthma Severity. J Allergy Clin Immunol 106:135–140
34. Sawa A, Pletnikov MV, Kamiya A (2004) Neuron-Glia Interactions Clarify Genetic-Environmental Links in Mental Illness. Trends Neurosci 27:294–297
35. Schwab SG, Hallmayer J, Albus M, Lerer B, Eckstein GN, Borrmann M, Segman RH, Hanses C, Freymann J, Yakir A, Trixler M, Falkai P, Rietschel M, Maier W, Wildenauer DB (2000) A Genome-Wide Autosomal Screen for Schizophrenia Susceptibility Loci in 71 Families With Affected Siblings: Support for Loci on Chromosome 10p and 6. Mol Psychiatry 5:638–649
36. Schwarz MJ, Chiang S, Müller N, Ackenheil M (2001) T-Helper-1 and T-Helper-2 Responses in Psychiatric Disorders. Brain Behav Immun 15:340–370
37. Spellberg B, Edwards JE Jr. (2001) Type 1/Type 2 Immunity in Infectious Diseases. Clin Infect Dis 32:76–102
38. Sullivan PF, Kendler KS, Neale MC (2003) Schizophrenia As a Complex Trait: Evidence From a Meta-Analysis of Twin Studies. Arch Gen Psychiatry 60:1187–1192
39. Suzuki H, Kundig TM, Furlonger C, Wakeham A, Timms E, Matsuyama T, Schmits R, Simard JJ, Ohashi PS, Griesser H (1995) Deregulated T Cell Activation and Autoimmunity in Mice Lacking Interleukin-2 Receptor Beta. Science 268:1472–1476
40. Takabayashi A, Ihara K, Sasaki Y, Kusuhara K, Nishima S, Hara T (1999) Novel Polymorphism in the 5'-Untranslated Region of the Interleukin-4 Gene. J Hum Genet 44:352–353
41. Vandenbroeck K, Goris A (2003) Cytokine Gene Polymorphisms in Multifactorial Diseases: Gateways to Novel Targets for Immunotherapy? Trends Pharmacol Sci 24:284–289
42. Vandenbroeck K, Martino G, Marrosu M, Consiglio A, Zaffaroni M, Vaccargiu S, Franciotta D, Ruggeri M, Comi G, Grimaldi LM (1997) Occurrence and Clinical Relevance of an Interleukin-4 Gene Polymorphism in Patients With Multiple Sclerosis. J Neuroimmunol 76:189–192
43. Vasilescu A, Heath SC, Ivanova R, Hendel H, Do H, Mazoyer A, Khadivpour E, Goutalier FX, Khalili K, Rappaport J, Lathrop GM, Matsuda F, Zagury JF (2003) Genomic Analysis of Th1-Th2 Cytokine Genes in an AIDS Cohort: Identification of IL4 and IL10 Haplotypes Associated With the Disease Progression. Genes Immun 4:441–449
44. Walley AJ, Cookson WO (1996) Investigation of an Interleukin-4 Promoter Polymorphism for Associations With Asthma and Atopy. J Med Genet 33:689–692
45. Yang ZW, Chengappa KN, Shurin G, Brar JS, Rabin BS, Gubbi AV, Ganguli R (1994) An Association Between Anti-Hippocampal Antibody Concentration and Lymphocyte Production of IL-2 in Patients With Schizophrenia. Psychol Med 24:449–455