informa
healthcare

Interleukin (IL)-12, IL-2, interferon-γ gene polymorphisms in subacute sclerosing panencephalitis patients

Vuslat Yılmaz,[1] Veysi Demirbilek,[2] Candan Gürses,[3] Sibel P Yentür,[1] Serap Uysal,[4] Zuhal Yapıcı,[3] Gülden Yılmaz,[5] Aaron Muncey,[1] Özlem Çokar,[6] Emel Önal,[7] Ayşen Gökyiğit,[3] and Güher Saruhan-Direskeneli[1]

Departments of [1]Physiology, [3]Neurology, [5]Microbiology, and [7]Public Health, Istanbul Medical Faculty, Istanbul, Turkey
Departments of [2]Neurology and [4]Pediatrics, Cerrahpasa Medical Faculty, Istanbul University, Istanbul Turkey
[6]Department of Neurology, Haseki Hospital, Istanbul, Turkey

Mutated measles virus variants have been claimed as the causing agent for subacute sclerosing panencephalitis (SSPE) developing several years after the recovery from measles infection. However, immune dysfunction may be considered related to a genetic susceptibility to this rare disease. Interleukin (IL)-2 −330 (rs2069762) and +160 (rs2069763), IL-12 p40 3′ UTR (rs3213113), and interferon (IFN)-γ+874 (rs2430561) polymorphisms are screened by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) and PCR–sequence-specific priming (SSP) methods in 87 SSPE patients and 106 healthy controls (HCs) as candidate genes of susceptibility. The distribution of the *IL12B* genotypes (rs3213113) showed a trend for a significant difference ($P = .053$). The frequency of *IL12B* C allele ($P = .04$, OR: 1.6) and CC genotype ($P = .03$, OR: 3.2) were both higher in SSPE patients than in HC. The *IL2* −330 genotypes revealed lower frequencies of GG genotype ($P = .03$, OR: 0.4) as well as G allele ($P = .02$, OR: 0.6) in SSPE. *IL2* −330+160 TG haplotype was more frequent in patients ($P = .005$, OR: 1.8), whereas GG haplotype was less frequent, compared to controls ($P = .02$, OR: 0.6). *IFNG* +874 polymorphism revealed no difference. These findings implicate possible effects of genetic polymorphisms in the susceptibility to SSPE, which need to be confirmed in other populations. *Journal of NeuroVirology* (2007) **13**, 410–415.

Keywords: subacute sclerosing panencephalitis; IL-12; IL-2; IFN-γ

Introduction

Subacute sclerosing panencephalitis (SSPE) is a fatal progressive disease of the central nervous system (CNS) caused by a persistent measles virus (MV). The cause of persistence, the late reactivation of MV, and the pathogenesis of SSPE are still not resolved; however, both viral and host factors seem to be involved (Dyken, 2001; Graves, 1984). Transcriptional defects

of MV (Ayata *et al*, 1998) or variants that had undergone hypermutation events (Baczko *et al*, 1993; Breschkin *et al*, 1979) have been reported in the etiology of SSPE. However, recently the development of SSPE is shown to be associated with the previous measles resurgence in the United States (Bellini *et al*, 2005), not supporting the viral changes in SSPE. Ill-defined defects in host cell–mediated immune responses has been considered as playing a role in SSPE as well (Schneider-Schaulies *et al*, 2003).

Immune reactions towards MV are unique, as the infection induces both antiviral effector mechanisms as well as significant immunosuppression (Schneider-Schaulies *et al*, 2001; van Els and Nanan, 2002). The suppression of delayed type hypersensitivity reactions with predominant humoral immune

IL-12, IL-2, IFN-γ gene polymorphisms in SSPE
V. Yılmaz *et al*
411

response is attributed to the generalized dominance of type 2 pattern of cytokines in measles (Karp, 1999). Impairment of MV-specific cell-mediated immunity has also been observed in SSPE (Dhib-Jalbut *et al*, 1988). No significant difference was observed in interferon (IFN)-γ and interleukin (IL)-10 production in peripheral blood mononuclear cells (PBMCs) stimulated with live measles virus vaccine (MVV) *in vitro* between controls and patients, and minimal IL-12 and IL-4 production to MV was observed in both groups (Hara *et al*, 2000). IL-12 production in response to myelin basic protein (MBP) and to MVV was lower in SSPE patients than controls. Proliferation, as well as IFN-γ IL-12, and IL-10 production, in response to purified protein derivate was impaired in SSPE patients (Yentur *et al*, 2005). However, anti-MV antibodies are present in serum and cerebrospinal fluid (CSF). Thus, it is likely that Th1 is generally down-regulated and Th2 function is well preserved, resembling a persistence of a relative dominance of Th2 response at the initial measles infection (Hara *et al*, 2000). When cytokines were measured in patients with SSPE, IL-12 p70+p40 was found to be elevated in CSF and sera of SSPE patients when compared to other noninflammatory neurological disease groups. However, no increase of IL-12 p70 levels in CSF indicated the increase of p40 (Saruhan-Direskeneli *et al*, 2005).

On the other hand, genetic susceptibility to SSPE has been implicated in Japan by the recent reports of associations with IL-4, interferon regulatory factor-1 as well as *MxA* gene polymorphisms (Inoue *et al*, 2002; Torisu *et al*, 2004).

In the present study, single nucleotide polymorphisms (SNPs) of IL-12, IL-2, and IFN-γ genes have been screened in a SSPE patient group and compared with healthy controls (HCs) to provide possible susceptibility markers for the Turkish population.

Results

The distributions of all SNPs in the control group were in Hardy-Weinberg equilibrium, which confirmed that the observed genotyping results were not different from the expected frequency in the population studied.

The polymorphism at 3′UTR (A/C) (rs3213113) of the gene encoding IL-12 p40 subunit (*IL12B*) was screened in all 87 SSPE patients and 106 HC. The distribution of the *IL12B* genotypes showed a trend towards a significant difference (χ^2 for trend, $P = .053$). The frequencies of *IL12B* C allele ($P = .04$) and CC genotype ($P = .03$) were both higher in SSPE patients than in HCs (Table 1), conferring a higher risk for susceptibility to SSPE (odds ratio [OR]: 1.6, confidence interval [CI]: 1.0–2.5 and OR: 3.2, CI: 1.2–8.7, respectively). As the CC genotype of this polymorphism has been reported to be associated with higher IL-12 production, we have compared the serum lev-

Table 1 Allele and genotype frequencies of *IL12, IL2, and IFNG* and haplotype distribution of *IL2* polymorphisms in subacute sclerosing panencephalitis (SSPE) patients and healthy controls (HC)

	SSPE (N = 87)			HC (N = 106)					
	N	f	%	N	f	%	P	OR	95% CI
IL12: 1188 (rs3213113)									
Allele									
A	112	0.64		157	0.74				
C	**62**	**0.36**		**55**	**0.26**		**0.04**	**1.6**	**1.0–2.5**
Genotype									
AA	39		44.8	57		53.8			
CA	34		39.1	43		40.6			
CC	**14**		**16.1**	**6**		**5.7**	**0.03**	**3.2**	**1.2–8.7**
IL2: −330 (rs2069762)									
Allele									
G	**64**	**0.37**		**104**	**0.49**		**0.02**	**0.6**	**0.4–0.9**
T	110	0.63		108	0.51				
Genotype									
GG	**10**		**11.5**	**24**		**22.6**	**0.06**	**0.4**	**0.2–1.0**
GT	44		50.6	56		52.8			
TT	33		37.9	26		24.5			
IL2: +160 (rs2069763)									
Allele									
G	143	0.82		171	0.81				
T	31	0.18		41	0.19				
Genotype									
GG	59		67.8	71		67.0			
GT	25		28.7	29		27.4			
TT	3		3.4	6		5.7			
IL2: −330+160									
Haplotype									
TG	**80**	**0.46**		**67**	**0.32**		**0.005**	**1.8**	**1.2–2.8**
GG	**64**	**0.37**		**104**	**0.49**		**0.02**	**0.6**	**0.4–0.9**
TT	30	0.17		41	0.19				
IFNG: +874 (rs2430561)									
Allele									
A	96	0.55		102	0.48				
T	78	0.45		110	0.52				
Genotype									
AA	27		31.0	21		19.8			
AT	42		48.3	60		56.6			
TT	18		20.7	25		23.6			

Note. f = frequency; OR = odds ratio.

els of IL-12 in three genotype groups of 51 SSPE patients, which overlapped with our previous study group (Saruhan-Direskeneli *et al*, 2006). The median IL-12 levels in the sera of the SSPE patients with CC genotype (139.5 pg/ml) were slightly higher than AC (113.4 pg/ml) and AA (106.3 pg/ml) genotypes. But no significant difference was detected.

The allele and genotype frequencies of the *IL2* −330 promoter (rs2069762) and *IL2* +160 intron (rs2069763) polymorphisms and the haplotype distribution in SSPE patients and in the HC group are shown in Table 1. The distribution of the *IL2* −330 genotypes revealed a significant difference (χ^2 for trend, $P = .042$). A decrease of G allele frequency ($P = .02$, OR: 0.6, CI: 0.4–0.9) was detected at the promoter polymorphism of *IL2* −330 in SSPE. Homozygote GG genotype at *IL2* −330 promoter was also less frequent in SSPE ($P = .06$, OR: 0.4, CI: 0.2–1.0). The distribution of allele and genotype frequencies

of the *IL2* +160 G/T polymorphism did not differ significantly between groups (Table 1). Only three haplotypes of the two polymorphisms of *IL2* (−330 and +160) were detected in both groups. The distribution of these true *IL2* haplotypes revealed a significant difference (χ^2 for trend, $P = .013$). As *IL2* −330 G allele was only present in GG haplotype, *IL2* −330+160 GG haplotype showed the same lower frequency in SSPE compared to controls ($P = .02$, OR: 0.6, CI: 0.4–0.9), reflecting the same protective/allelic association *IL2* −330 with the disease (Table 1). On the other hand, *IL2* −330+160 TG haplotype was more frequent in SSPE patients ($P = .005$, OR: 1.8, CI: 1.2–2.8, $P_c = .015$).

The distribution of *IFNG* +874 (rs2430561) polymorphism revealed that both *IFNG* +874 alleles were homogenously detected in SSPE patients and HC group (Table 1). *IFNG* +874 TT genotype was detected in 21% of the patients and in 24% of the HC, whereas AA genotype was slightly more frequent in SSPE patients than HCs (32% versus 20%).

When the patients were subgrouped according to measles infection and measles vaccination history and age of disease onset, no association could be detected between the genotypes and these groups.

Discussion

The expression of many cytokines is thought to be influenced by functional polymorphisms in their gene loci that may contribute to susceptibility to diseases. Despite the possible role played by cytokines, the role of altered cytokine production in disease development has been addressed scarcely in SSPE.

Based on the data of altered IL-12 production with measles infection (Atabani *et al*, 2001; Karp *et al*, 1996; Schnorr *et al*, 1997) and increased IL-12 p40 levels in the CSF and serum of SSPE patients (Saruhan-Direskeneli *et al*, 2005), we hypothesized that production of this cytokine may be related to a genetic polymorphism in the diseased individuals leading to susceptibility to disease. IL-12 plays a key role in cell-mediated immunity by regulating the differentiation of naïve T cells into helper T cells and production of interferon-γ by T and natural killer (NK) cells. Various studies on disease associations with this SNP of *IL12B* gene have reported conflicting results in type 1 diabetes and tuberculosis (Hall *et al*, 2000; Tso *et al*, 2004). The substitution of A to C at *IL12B* 3′UTR has been associated with decreased expression levels in cell lines; however, increased production of IL-12 p70 in *in vitro* experiments (Seegers *et al*, 2002; Yilmaz *et al*, 2005). The increased frequency of *IL12B* 1188 C allele and CC genotype in the present study is in accordance with the reported higher IL-12 levels in the serum and CSF of the patients (Saruhan-Direskeneli *et al*,

2005) and may cause the increased release of regulatory component (p40) of the cytokine in SSPE patients, not inducing a Th1 response. However, this association is weak and not significant after correction so that it needs to be confirmed by other studies.

Being a cell growth factor for both T-cell groups, IL-2 may be effective in the development of SSPE as well. Screening two different polymorphisms in the study group, decreased frequencies of GG genotype and G allele at *IL2* −330 SNP were detected in SSPE. Functional data on this SNP is rather divergent; *IL2* promoter-construct in a cell line showed higher levels of gene expression with the G allele, whereas the transcriptional effect in lymphocytes showed that the G allele was related to lower expression of IL-2 (Matesanz *et al*, 2004). The *IL2* −330 gene promoter polymorphism has been associated with multiple sclerosis and an increased IL-2 expression among GT and TT genotypes associated with susceptibility to disease. Accumulated data revealed no detectable levels of IL-2 in the CSF and serum (Ichiyama *et al*, 2006; Tekgul *et al*, 1999) and no expression in the brain tissue (Nagano *et al*, 1991, 1994) of SSPE patients. Moreover *in vitro* stimulated cells of the patients secreted decreased levels IL-2 in SSPE patients compared to controls (Brajczewska-Fischer *et al*, 1989). When *IL2* −330 G allele is associated with higher IL-2 activity, the decrease of G allele in patients may result in lower levels of IL-2 in SSPE patients. Considering the complex interactions of the genetic polymorphisms in the gene locus, haplotype structure of genes may determine transcription actions in respective cells. Association of SSPE with *IL2* haplotype (TG) in the present study may also point to a functional relevance of *IL2* haplotypes, which needs further evaluation.

IFNG polymorphism, which has been reported to be associated with several diseases, was not differently distributed in the present study, which confirmed the previous data from Japan (Inoue *et al*, 2002). Findings on IFN-γ in SSPE are not indicative of a prominent role of this cytokine and reports of no detectable levels of IFN-γ during the disease have been published. Contrarily, Th2 dominance in patients with SSPE contributing to the persistence of MV and the development of SSPE through reduction of Th1 response has been suggested (Inoue *et al*, 2002).

Although several factors influence the inflammatory response, the role of individual's genetic background has recently received increasing attention. Multigenic influences are assumed to contribute to disease susceptibility and the interaction of several polymorphisms with functional implications is investigated in complex diseases. SSPE is generally considered as a preventable disease and has mostly disappeared in countries with effective vaccination programs. However, it is not very frequent in Turkey

either, although the vaccination was not effectively applied until recently (Onal *et al*, 2006). In this study SSPE has been considered as a disease with ineffective immune response to measles virus and possible contributions of cytokines are evaluated by genetic polymorphisms. Although not sufficient to explain a major contribution, the detected associations with SSPE may have roles in the disease development or disease phenotypes among other factors with possible implications of cytokine-based therapies. However, relative contribution of the studied cytokine polymorphisms awaits replication in other studies.

Considering ethnical differences, we have compared an ethnically matched population control with SSPE patients in respect to immune related genes. However, the control group could not be age-matched with the patients, which may be a limitation for the present comparison. We consider this study of a relatively rare disease as a screening study and interpret our results with caution. The significant findings were modest and most have disappeared frequently after the correction.

Our results indicate that *IL2* and possibly *IL12B* polymorphism are associated with SSPE in Turkey. Future studies on genetics in SSPE may facilitate the understanding development of the disease in some of the children without effective immunization against measles virus.

Methods

Eight-seven SSPE patients were included in the study. The ages of SSPE patients ranged between 1 and 34 years, with a mean of 9.9 ($\pm$ 4.7) and 60 (69%) were boys. All of the patients with SSPE fulfilled the diagnostic criteria as clinical features, anti-MV antibodies in CSF and typical electroencephalography showing slow-wave complexes (Gascon, 1996). Among 81 patients with known clinical staging, 77 patients had diseases at stage 2 (2A: 27; 2B: 23; 2C: 21; and 2D: 6) and 4 patients were at stages 3 and 4 (Ozturk *et al*, 2002). The mean and median age at disease onset was 108 months. Totally 62 of 72 patients had natural measles occurring between the ages of 2 to 108 months (mean: 19 months). Measles vaccination has been applied probably once to 45 of 60 patients and the measles and vaccination history was unknown in the other patients. All of the patients had antibodies against MV in the CSF and sera, and oligoclonal immunoglobulin G (IgG) bands were present in the CSF of all patients. The HCs were randomly selected from 106 individuals between ages of 28 and 64 (mean: 40.7 $\pm$ 7.0 years) and 44 (41.5%) were men. The control group could not be matched for age, measles infection, or vaccination. All parents and adult participants had given their informed consent to donate blood for the study.

Cytokine genotyping
Genomic DNA was extracted from EDTA anticoagulated blood samples by salting-out procedure. Polymerase chain reaction (PCR) with restriction fragment length polymorphism (RFLP) was used to genotype the *IL12B* 3′UTR SNP (+16974 A → C: 1188, *Taq* I, rs3213113) by using the forward 5′-TTTGGAGGAAAAGT-GGAAGA-3′ and reverse primers 5′-AACATTCCATACATCCTGGC-3′ as described before (Huang *et al*, 2000). PCR amplification was carried out in 1× buffer with 2 mM MgCl$_2$, 200 μM dNTP, 2 μM of primer pair, 30 ng of genomic DNA, and 0.7 IU of *Taq* polymerase (Fermentas, Germany). After an initial denaturation step of 2 min at 95°C, PCR was performed with 35 cycles of 20 s at 95°C, 20 s at 55°C, and 30 s at 72°C, and an extension of 2 min at 72°C. The amplified PCR products were digested with *Taq* I enzyme.

For genotyping the polymorphisms of *IFNG* (+874 A → T: rs2430561), and *IL2* (−330 T → G: rs2069762; +160 G → T: rs2069763), PCR–sequence-specific priming (SSP) was applied as described previously. True haplotypes of *IL2* gene with two SNPs could be detected by using modified bispecific PCR primer pairs from method of the XIII International Histocompatibility Working Group (Mytilineos, 2007). *IL2* was amplified with 1 to 1.5 μM specific forward primers 330T (5′-GCTATTCACATGTTCAGTGTAGTTTTAT-3′) or 330G (5′-GCTATTCACATGTTCAGTGTAGTTTTAG-3′) combined with reverse primers 160G (5′-CCATTCAAAATCATCTGTAAATCCAG-C-3′) or 160T (5′-CCATTCAAAATCATCTGTAAATCCAGA-3′) for the SNPs at *IL2* −330+160 in different combinations. Internal control primers (0.3 μM) for human adenomatous polyposis coli gene (5′-ATGATGTTGACCTTTCCAGGG-3′ and 5′-TTCTGTAACTTTTCATC-AGTTGC-3′), 200 μM dNTP, 1.5 mM MgCl$_2$, 0.5 IU *Taq* polymerase (Fermentas, Germany), and 90 ng of genomic DNA were used for each reaction. The cycling parameters were as follows: initial denaturation step of 2 min at 94°C; 10 cycles of 10 s at 94°C, 1 min at 65°C; 20 cycles of 10 s at 94°C; 50 s at 61°C, and 30 s at 72°C. All of the PCR and digestion products were visualized in 2% agarose gels.

Statistical analysis
Each polymorphism was examined in the control population to confirm that the distribution of the genotypes conformed to Hardy-Weinberg expectations. Allele and genotype frequencies were compared between patient and control groups by chi-square and Fisher's exact tests, as appropriate. *P* values less than .05 were considered statistically significant, adjustments for potential multiple testing errors were carried out by Bonferroni correction where appropriate (P_c).

References

Atabani SF, Byrnes AA, Jaye A, Kidd IM, Magnusen AF, Whittle H, Karp CL (2001). Natural measles causes prolonged suppression of interleukin-12 production. *J Infect Dis* **184:** 1–9.

Ayata M, Hayashi K, Seto T, Murata R, Ogura H (1998). The matrix gene expression of subacute sclerosing panencephalitis (SSPE) virus (Osaka-1 strain): a comparison of two sibling viruses isolated from different lobes of an SSPE brain. *Microbiol Immunol* **42:** 773–780.

Baczko K, Lampe J, Liebert UG, Brinckmann U, ter Meulen V, Pardowitz I, Budka H, Cosby SL, Isserte S, Rima BK (1993). Clonal expansion of hypermutated measles virus in a SSPE brain. *Virology* **197:** 188–195.

Bellini WJ, Rota JS, Lowe LE, Katz RS, Dyken PR, Zaki SR, Shieh WJ, Rota PA (2005). Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized. *J Infect Dis* **192:** 1686–1693.

Brajczewska-Fischer W, Iwinska B, Kruszewska J, Korlak J, Czlonkowska A (1989). Interleukin 1 and 2 production by peripheral blood mononuclear cells in subacute sclerosing panencephalitis and exacerbation of multiple sclerosis. *Acta Neurol Scand* **80:** 390–393.

Breschkin AM, Morgan EM, McKimm J, Rapp F (1979). SSPE-BIKEN: a naturally arising hemagglutination-defective mutant of measles virus. *J Med Virol* **4:** 67–80.

Dhib-Jalbut S, Jacobson S, McFarlin DE, McFarland HF (1988). Impaired measles-specific cytotoxic T-cell response in subacute sclerosing panencephalitis. *Ann N Y Acad Sci* **540:** 645–648.

Dyken PR (2001). Neuroprogressive disease of post-infectious origin: a review of a resurging subacute sclerosing panencephalitis (SSPE). *Ment Retard Dev Disabil Res Rev* **7:** 217–225.

Gascon GG (1996). Subacute sclerosing panencephalitis. *Semin Pediatr Neurol* **3:** 260–269.

Graves M (1984). Subacute sclerosing panencephalitis. *Neurol Clin* **2:** 267–280.

Hall MA, McGlinn E, Coakley G, Fisher SA, Boki K, Middleton D, Kaklamani E, Moutsopoulos H, Loughran TP, Jr., Ollier WE, Panayi GS, Lanchbury JS (2000). Genetic polymorphism of IL-12 p40 gene in immune-mediated disease. *Genes Immun* **1:** 219–224.

Hara T, Yamashita S, Aiba H, Nihei K, Koide N, Good RA, Takeshita K (2000). Measles virus-specific T helper 1/T helper 2-cytokine production in subacute sclerosing panencephalitis. *J NeuroVirol* **6:** 121–126.

Huang D, Cancilla MR, Morahan G (2000). Complete primary structure, chromosomal localisation, and definition of polymorphisms of the gene encoding the human interleukin-12 p40 subunit. *Genes Immun* **1:** 515–520.

Ichiyama T, Siba P, Suarkia D, Reeder J, Takasu T, Miki K, Maeba S, Furukawa S (2006). Analysis of serum and cerebrospinal fluid cytokine levels in subacute sclerosing panencephalitis in Papua New Guinea. *Cytokine* **33:** 17–20.

Inoue T, Kira R, Nakao F, Ihara K, Bassuny WM, Kusuhara K, Nihei K, Takeshita K, Hara T (2002). Contribution of the interleukin 4 gene to susceptibility to subacute sclerosing panencephalitis. *Arch Neurol* **59:** 822–827.

Karp CL (1999). Measles: immunosuppression, interleukin-12, and complement receptors. *Immunol Rev* **168:** 91–101.

Karp CL, Wysocka M, Wahl LM, Ahearn JM, Cuomo PJ, Sherry B, Trinchieri G, Griffin DE (1996). Mechanism of suppression of cell-mediated immunity by measles virus. *Science* **273:** 228–231.

Ma X, Reich RA, Gonzalez O, Pan X, Fothergill AK, Starke JR, Teeter LD, Musser JM, Graviss EA (2003). No evidence for association between the polymorphism in the 3′ untranslated region of interleukin-12B and human susceptibility to tuberculosis. *J Infect Dis* **188:** 1116–1118.

Matesanz F, Fedetz M, Leyva L, Delgado C, Fernandez O, Alcina A (2004). Effects of the multiple sclerosis associated −330 promoter polymorphism in IL2 allelic expression. *J Neuroimmunol* **148:** 212–217.

Mytilineos J (2007). Cytokine polymorphisms. In: *HLA 2007: Immunobiology of the Human MHC. Proceedings of the 13th International Histocompatibility Workshop and Congress.* Hansen JA (ed). Seattle, WA: IHWG Press.

Nagano I, Nakamura S, Yoshioka M, Kogure K (1991). Immunocytochemical analysis of the cellular infiltrate in brain lesions in subacute sclerosing panencephalitis. *Neurology* **41:** 1639–1642.

Nagano I, Nakamura S, Yoshioka M, Onodera J, Kogure K, Itoyama Y (1994). Expression of cytokines in brain lesions in subacute sclerosing panencephalitis. *Neurology* **44:** 710–715.

Onal AE, Gurses C, Direskeneli GS, Yilmaz G, Demirbilek V, Yentur SP, Ozel S, Yapici Z, Tumerdem Y, Gokyigit A (2006). Subacute sclerosing panencephalitis surveillance study in Istanbul. *Brain Dev* **28:** 183–189.

Ozturk A, Gurses C, Baykan B, Gokyigit A, Eraksoy M (2002). Subacute sclerosing panencephalitis: clinical and magnetic resonance imaging evaluation of 36 patients. *J Child Neurol* **17:** 25–29.

Saruhan-Direskeneli G, Bicakcigil M, Yilmaz V, Kamali S, Aksu K, Fresko I, Akkoc N, Kiraz S, Ozer HTE, Tunc E, Yucel E, Karaarslan Y, Uyar FA, Doganavsargil E, Inanc M, Direskeneli H (2006). Interleukin (IL)-12, IL-2, and IL-6 Gene Polymorphisms in Takayasu's Arteritis from Turkey. *Human Immunol* **67:** 735–740.

Saruhan-Direskeneli G, Gurses C, Demirbilek V, Yentur SP, Yilmaz G, Onal E, Yapici Z, Yalcinkaya C, Cokar O, Akman-Demir G, Gokyigit A (2005). Elevated interleukin-12 and CXCL10 in subacute sclerosing panencephalitis. *Cytokine* **32:** 104–110.

Schneider-Schaulies J, ter Meulen V, Schneider-Schaulies S (2001). Measles virus interactions with cellular receptors: consequences for viral pathogenesis. *J NeuroVirol* **7:** 391–9.

Schneider-Schaulies J, ter Meulen V, Schneider-Schaulies S (2003). Measles infection of the central nervous system. *J NeuroVirol* **9:** 247–252.

Schnorr J-J, Xanthakos S, Keikavoussi P, Kampgen E, ter Meulen V, Schneider-Schaulies S (1997). Induction of maturation of human blood dendritic cell precursors by measles virus is associated with immunosuppression. *Proc Natl Acad Sci U S A* **94:** 5326–5331.

Seegers D, Zwiers A, Strober W, Pena AS, Bouma G (2002). A TaqI polymorphism in the 3′UTR of the IL-12 p40 gene correlates with increased IL-12 secretion. *Genes Immun* **3:** 419–423.

Tekgul H, Tutuncuoglu S, Kutukculer N, Dizdarer G, Huseyinov A (1999). Lymphocyte subsets and

inflammatory mediators in patients with subacute sclerosing panencephalitis. *J Child Neurol* **14:** 418–421.

Torisu H, Kusuhara K, Kira R, Bassuny WM, Sakai Y, Sanefuji M, Takemoto M, Hara T (2004). Functional MxA promoter polymorphism associated with subacute sclerosing panencephalitis. *Neurology* **62:** 457–460.

Tso H, Lau, YL, Tam CM, Wong HS, Chiang AK (2004). Associations between IL12B polymorphisms and tuberculosis in the Hong Kong Chinese population. *J Infect Dis* **190:** 913–919.

van Els C, Nanan R (2002). T cell responses in acute measles. *Viral Immunol* **15:** 435–450.

Yentur SP, Gurses C, Demirbilek V, Yilmaz G, Onal AE, Yapici Z, Yalcinkaya C, Cokar O, Gokyigit A, Saruhan-Direskeneli G (2005). Alterations in cell-mediated immune response in subacute sclerosing panencephalitis. *J Neuroimmunol* **170:** 179–185.

Yilmaz V, Yentur SP, Saruhan-Direskeneli G (2005). IL-12 and IL-10 polymorphisms and their effects on cytokine production. *Cytokine* **30:** 188–194.