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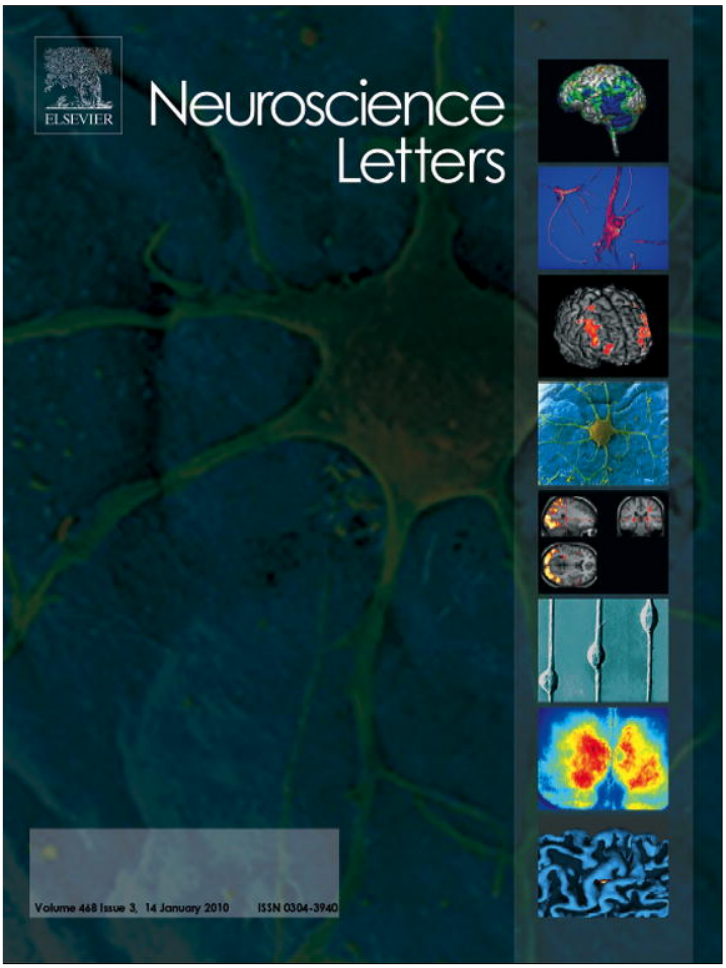

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Neuroscience Letters 468 (2010) 330–333

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Genetic variants of IL-6 and its receptor are not associated with schizophrenia in Taiwan

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ARTICLE INFO

Article history:
Received 15 September 2009
Received in revised form 30 October 2009
Accepted 7 November 2009

Keywords:
IL-6
IL-6 receptor
Schizophrenia
Tetra-primer ARMS
RFLP

ABSTRACT

The pathophysiological process of schizophrenia is still unclear. The levels of interleukine-6 (IL-6) and its receptor, soluble IL-6R, have been reported to be elevated in the plasma and cerebrospinal fluid of schizophrenic patients. In this study, we tested the association of genetic variants of IL-6 and IL-6R with schizophrenia. Genotyping of three single nucleotide polymorphisms (SNP) for each IL-6 (IL-6-1, IL-6-2, and IL-6-3) and IL-6R (rs4845617 = IL-6R1, rs4553185 = IL-6R2, and rs4379670 = IL-6R3) gene was performed in 100 patients with schizophrenia and 113 normal controls. The polymorphisms of IL-6R2 were genotyped using Tetra-primer ARMS PCR. IL-6R3 polymorphisms were genotyped using restriction fragment length polymorphism (RFLP) with Apo I enzyme as the restriction enzyme. All other polymorphisms were genotyped using the direct sequencing method. We found a di-nucleotide haplotype block and a tri-nucleotide haplotype block in the genes of IL-6 and IL-6R, respectively. All six SNPs and their haplotypes failed to show a significant association with schizophrenia. The IL-6-2 SNP showed a nominally significant association with the positive symptoms of schizophrenia ($p = 0.0472$). We conclude that the genetic variants of IL-6 and IL-6R are not associated with schizophrenia. In order to verify this result, further study using a larger sample size and exploring the association between the genotype of IL-6-2 and plasma level of IL-6 is recommended.

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Schizophrenia is a complex mental disorder affecting 1% of all populations. The disease primarily affects the central nervous system, but immune alterations have been actively proposed to play a role in the pathogenesis of schizophrenia [10,16,18]. An autoimmune involvement in schizophrenia has been suggested by several cellular and humoral cytokine changes in patients [22]. Among these altered cytokines, interleukine-6 (IL-6; online Mendelian Inheritance in Man (MIM) number *147620) has been most consistently found to be related to schizophrenia [6,9,14–15,26].

IL-6 is a pleiotropic cytokine released both from peripheral immune cells and from neurons and microglia of the central nervous system (CNS) [24,27]. In the CNS, soluble IL-6 receptor (sIL-6R; MIM number *147880) levels in the CSF have increased in schizophrenic patients with a marked paranoid-hallucinatory syndrome [17]. In the periphery, IL-6 has been found to be persistently elevated in the plasma of patients in different ethnic groups [1,11,19,26]. High IL-6 levels have been found to be related to duration and treatment resistance in schizophrenia [11,19]. These results suggested that an elevated plasma level of IL-6 was associated with an unfavorable course of schizophrenia with a longer duration of illness, greater treatment resistance, and more marked paranoid-hallucinatory symptoms.

We selected single nucleotide polymorphisms (SNPs) located within these two genes and genotyped them in 113 normal controls and 100 schizophrenic patients to decipher the potential genetic association of IL-6 and IL-6 receptor in schizophrenia. Endophenotypes are recommended to define the role of the gene in the complex traits of schizophrenia [5]. In this study, we used the sus-

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doi:10.1016/j.neulet.2009.11.026

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tained attention endophenotype of schizophrenia as measured by the continuous performance test (CPT) and the severity of the positive and negative symptom dimensions to assess the potential association of these endophenotype indicators with IL-6 and its receptor in the disease.

We collected the DNA of schizophrenic patients, fulfilling criteria defined by the Diagnostic and Statistical Manual 4th edition (DSM-VI) [2] from the Department of Psychiatry of the National Taiwan University Hospital and normal controls without a history of any psychotic symptoms or family history of psychotic disorder from hospital staff and community subjects. All individuals were screened for the presence of acute infectious disease. The average age was 33.3 ± 10.6 years for normal controls and 34.5 ± 11.3 years for patients. The male to female ratios were 50:62 in normal controls and 48:52 in patients. Clinical symptoms were rated using the schedule for assessment of negative symptoms (SANS) [4] and the schedule for assessment of positive symptoms (SAPS) [3]. The sum score of negative symptoms (SUMN) was the sum of the global scores of four negative symptom dimensions, including affective blunting, alogia, avolition-apathy, and anhedonia-asociality. The sum score of positive symptoms (SUMP) was the sum of the global scores of hallucinations and delusions. The sum score of disorganizing symptoms (SUMDIS) was the sum of the global scores of Bizarre behavior and positive formal thought disorder. The patients were recruited from the outpatient clinics and their psychiatric status was stable as they received maintenance neuroleptic treatment due to the potential fluctuations in positive symptoms. Their mean positive symptom score was 1.44 ± 1.18, mean disorganizing symptom score 1.27 ± 0.97, and mean negative symptom score 1.80 ± 0.96 using the SAPS and SANS scales (rating range 0–5).

After signing informed consent, the study subjects took the continuous performance task (CPT) in the morning and 10 cc of blood was drawn from the antecubital vein in the morning after overnight fasting.

A CPT machine from Sunrise System, v. 2.20 (Pembroke, MA, USA), was used to assess sustained attention. The procedure has been described in detail elsewhere [7]. Briefly, numbers from 0 to 9 were randomly presented for 50 ms each, at a rate of one number per second. Each subject undertook two CPT sessions: the undegraded 1–9 task and the 25% degraded 1–9 task. Subjects were asked to respond whenever the number "9" preceded by the number "1" appeared on the screen. A total of 331 trials, 34 (10%) of which were target stimuli, were presented over five minutes for each session. During the 25% degraded session, a pattern of snow was used to toggle the background and foreground so that the image was visually distorted. Each test session began with 2 min of practice (repeated if subjects required). One signal-detection index of performance on the test, sensitivity (d'), was derived from the hit rate (probability of response to target trials) and false-alarm rate (probability of response to nontarget trials) [20]. Sensitivity is an individual's ability to discriminate target stimuli from nontarget stimuli. In a 1-week test–retest reliability study [7] of the CPT versions used in this study, the intraclass correlation coefficients or reliability of d' were 0.83 and 0.82 for the undegraded and the 25% degraded 1–9 task, respectively.

The SNP markers were selected according to the potential proteomic function alterations which include the exon and the promoter regions of the loci with average distance of 31 kb for IL-6R (IL-6R1, IL-6R2, and IL-6R3) and 6 kb for IL-6. We initially selected 3 SNPs (rs1800797, rs3087236, and rs3087236) of IL-6 and 3 SNPs (rs4845617, rs4553185, and rs4379670) of IL-6R from the NCBI SNP database (dbSNP). However, no polymorphisms were found at the originally selected SNP_ID in IL-6 and we found three novel SNPs (IL-6-1, IL-6-2, IL-6-3) in the region near the originally selected three SNPs, respectively, using direct sequencing. The chromosome position of each SNP marker on each gene was genotyped with the primer pairs as shown in Table 1. The SNP of IL-6R2 was genotyped by Tetra-primer ARMS PCR [25], the IL-6R3 was genotyped by RFLP with Apo I enzyme, and the others were genotyped by direct sequencing. All polymerase chain reactions (PCRs) were carried out according to the protocol of the Pro Taq (Protech Technology, Taiwan) on a DNA Thermal Cycler ABI 9700. The PCR for IL-6R2 Tetra-primer was performed with an initial denaturation step at 95 °C for 2 min, followed by two rounds; 16 cycles of denaturing at 95 °C for 1 min, annealing at 71 °C for 1 min and extension at 72 °C for 1 min, and 20 cycles with initial 95 °C for 1 min, annealing at 57 °C for 1 min and extension at 72 °C for 2 min. The PCR products of direct sequencing were purified to remove reaction buffer and remaining primers with PCR DNA Fragments Extraction Kit (Geneaid, Taiwan). The sequences of PCR products were directly determined by BigDye Terminator Cycle Sequencing kit (Applied Biosystems, CA, USA).

The Hardy–Weinberg equilibrium was assessed using the ALLELE procedure in SAS/GENETICS release 8.2 [8] for each SNP. We used Haploview software to construct haplotype blocks constituted by "strong LD" markers [12]. The genotype and allele-type association analyses were performed by using the CASECONTROL procedure in SAS/GENETICS release 8.2 with 10000 permutation resamples between the normal controls and the schizophrenic patients. The phenotype and genotype association analyses were performed by the Kruskal–Wallis non-parametric one-way analysis of variance.

Three SNPs of both IL-6 receptor (at chromosome 1q21) and IL-6 (at chromosome 7p21) were designed with specific primer pairs for genotyping and were validated in this study (Table 1). The SNPs at the IL-6 region (IL-6-1, IL-6-2 and IL-6-3) are novel compared to the IL-6R. The polymorphism of IL-6-1 is 25 bps at the 3′-end on the rs1800797 locus, IL-6-2 is 38 bps at the 3′-end on the rs3087236 and IL-6-3 is 63 bps at the 3′-end on the rs3087236.

No polymorphisms were found at the rs1800797 and the rs3087236 in these subjects.

The genotype frequency and minor allele frequency of each SNP in both control and schizophrenia groups are presented in Table 2. All SNPs were compatible with Hardy–Weinberg's equilibrium distribution, except IL-6R2 ($p = 0.022$ in control, and $p = 0.0171$ in schizophrenia). However, considering multiple testing, the SNP IL-6R2 was still compatible with Hardy–Weinberg's equilibrium. We found no significant associations of these SNP genotypes with schizophrenia.

The intermarker linkage disequilibrium analyses for haplotype block revealed a three-SNP block of IL-6 with D' of 0.81 and a two-SNP block of IL-6R with D' of 0.95 (Fig. 1). The haplotype frequencies

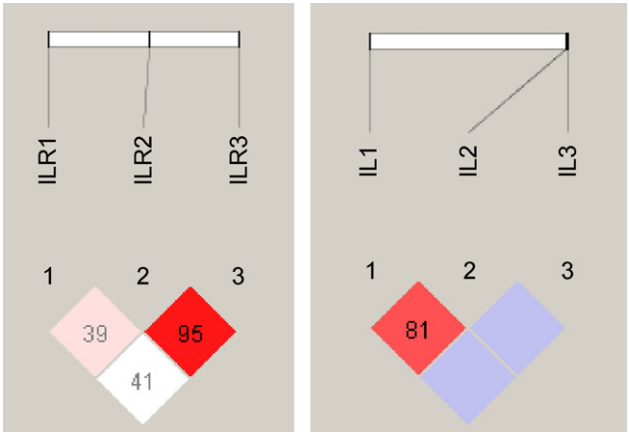

Fig. 1. Haploview linkage disequilibrium (D') displays the haplotype structures of both IL6-R and IL-6 genes. The number in each square is $D' \times 100$ between two SNPs.

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Table 1
SNP genotyping on three IL-6 and three IL-6 receptor markers.

Genetic SNP (SNP_ID)	Gene position (allele type) (exon/intron)	Primer Sequence (from 5′- to 3′-end) F: forward R: reverse
IL-6R1 (rs4845617)	−208 (A = 1/G = 2) (5′-UTR,exon 1)	F: CGCCGCTCTGAGTCATGTG R: CCATGGAGTGGTAGCCGAG
IL-6R2 (rs4553185)	32850 (C = 1/T = 2) (intron 6)	F: (inner primer for T allele): TTCTAGCCCTGTGGCGTAGTTGACCT R: (inner primer for C allele): CTGCCAAGTATTTAAGAATGATTAATGTG F: (outer primer (5′–3′)): AGATCTAGAATGCAAGAATCTCCCTGAC R: (outer primer (5′–3′)): CCCATAGATAAAAGCCTTCTCTCCCT
IL-6R3 (rs4379670)	61760 (A = 1/T = 2) (3′-UTR,exon 10)	F: CTGCAAGAATTGAAGCAGGA R:GTGATTTTCATTGCTGGGCT
IL-6-1 (rs1800797 + 25)	−636 (C = 1/G = 2) (promoter)	F: CTGGCACAGAGAGCAAAGTCCTCACTGG R: TGCGATGGAGTCAGAGGAAACTCAGTTCA
IL-6-2 (rs3087236 + 38)	5379 (A = 1/G = 2) (3′-UTR)	F: TGCCAGGCATCATTAAATGTGTTGC R: CCCAGATTTGAAATCCAAGTCTACC
IL-6-3 (rs3087236 + 63)	5404 (G = 1/T = 2) (3′-UTR)	F: TGCCAGGCATCATTAAATGTGTTGC R: CCCAGATTTGAAATCCAAGTCTACC

SNP_ID + number: the SNP is located at the number of nucleotides after the SNP_ID locus.

Table 2
Minor allele frequency (MAF) and association analyses of the SNPs of IL-6R and IL-6.

SNP	Control				Schizophrenia				Association Test (*p*-value)	
	11	12	22	MAF	11	12	22	MAF	Genot[a]	Allele[b]
IL-6R1	0.16	0.59	0.25	(A) 0.46	0.14	0.62	0.24	0.45	0.90	0.90
IL-6R2	0.21	0.62	0.17	(T) 0.48	0.19	0.64	0.17	0.49	0.89	0.74
IL-6R3	0.67	0.30	0.028	(T) 0.18	0.63	0.31	0.068	0.22	0.38	0.29
IL-6-1	0.61	0.35	0.045	(G) 0.22	0.58	0.35	0.070	0.25	0.72	0.52
IL-6-2	0.47	0.42	0.11	(G) 0.32	0.43	0.43	0.14	0.36	0.76	0.46
IL-6-3	0	0.021	0.98	(G) 0.011	0	0.010	0.99	0.0051	0.54	0.54

[a] Genot: genotype frequency association test.
[b] Allele: allele type frequency association test.

of all compositions in either IL-6 or IL-6R showed no significant association with schizophrenia ($p = 0.3495$ for IL-6 and $p = 0.158$ for IL-6R).

Table 3 shows the results of association of all SNP genotypes and the phenotypes of the severity of positive symptom dimension (SUMP), the severity of negative symptom dimension (SUMN), the severity of disorganization (SUMDIS) and endophenotype of the sustained attention indicators (the d' of degraded CPT and the d' of undegraded CPT). Only the IL-6-2 showed a borderline significant association with the positive symptom dimension phenotype ($p = 0.0472$), where the positive symptom dimension phenotype is more severe in the recessive model of patients carrying A allele.

In this study, there was a statistically marginally significant association between the SNP of IL-6-2 genotype and the severity of the positive symptom dimension of schizophrenia. It has been reported that high IL-6 levels were related to the duration and the treatment resistance of schizophrenia [11,19]. The patients in this study were stable schizophrenics followed in the outpatient department and receiving regular maintenance neuroleptic treatment. As the IL-6-2 is located within the 3′-UTR, it is possible that the SNP was responsible for the elevation of IL-6 during the active pathological process of schizophrenia with prominent positive symptoms [19,24]. However, we have no plasma level of IL-6 to demonstrate the association between the genotype of IL-6-2

Table 3
Association analyses of quantitative phenotype indicators of schizophrenia and SNPs genotypes of IL-6R and IL-6 using Kruskal–Wallis Test.

Phenotype	SNPs (*p*-value)							
	Case							
	IL-6R1	IL-6R2	IL-6R3	IL-6-1	IL-6-2	IL-6-3	IL6-H[6]	IL6R-H[7]
SUMN[a]	0.49	0.88	0.76	0.053	0.61	0.31	0.17	0.74
SUMP[b]	0.97	0.68	0.17	0.15	0.047	0.72	0.34	0.56
SUMDIS[c]	0.060	0.97	0.97	0.38	0.84	0.75	0.63	0.65
Undegraded[d] CPT d'	0.36	0.49	0.26	0.54	0.77	0.58	0.56	0.72
Degraded[e] CPT d'	0.49	0.94	0.61	0.38	0.15	0.14	0.13	0.48
	Control							
	IL-6R1	IL-6R2	IL-6R3	IL-6-1	IL-6-2	IL-6-3	IL6-H[f]	IL6R-H[g]
Undegraded CPT d'	0.28	0.24	0.86	0.36	0.57	0.58	0.73	0.85
Degraded CPT d'	0.40	0.080	0.26	0.22	0.35	0.35	0.40	0.29

[a] SUMN: the severity of negative symptom dimension.
[b] SUMP: the severity of positive symptom dimension.
[c] SUMDIS: the severity of disorganization dimension.
[d] Undegraded CPT: the sustained attention indicator tested by unmasked CPT.
[e] Degraded CPT: the sustained attention indicator tested by masked CPT.
[f] IL-H: IL6 haplotype;
[g] ILR-H: IL6 receptor haplotype.

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and plasma level of IL-6. Hence, it is worth exploring the association between the genotype of IL-6-2 and plasma level of IL-6 in the future.

Although our results failed to find an association between the genotype of IL-6 or IL-6R and schizophrenia, two results from Asian populations have shown that the significant genetic region is primarily located at IL-6R of exon 9 and promoter region [13,23]. One study even showed an association between the genotype and the serum soluble IL-6R level in schizophrenia [13]. In a large meta-analysis, IL-6 was found to be increased in schizophrenia [21]. In comparison to these results, our IL-6R SNPs were not located in exon 9 or its promoter region. This may be one of the reasons for this difference. Another reason may be a different sample composition resulting from the heterogeneity of schizophrenia. Further study should consider the genetic region and factors related to cytokine alterations such as stress, weight gain and different kinds as well as different dosages of antipsychotic medication in order to verify the potential etiological relations between the cytokine and schizophrenia.

In summary, SNP markers of IL-6 (rs1800797 + 25 at promoter, rs3087236 + 38 at the 3′-UTR, and rs3087236 + 63 at the 3′-UTR) and IL-6R (rs4845617 at exon 1 of 5′-UTR, rs4553185 at intron 6, and rs4379670 at exon 10 of 3′-UTR) showed no significant associations with schizophrenia in both single locus and haplotype analyses. Verifying this result using a larger sample size and exploring the association between the genotype of IL-6-2 and plasma level of IL-6 is recommended. This study suggested that genes of IL-6 or IL-6 receptor are likely to be environmental mediators rather than genes that predispose susceptibility to schizophrenia.

Acknowledgements

We acknowledge the help from the Department of Medical Research in National Taiwan University Hospital. This study was supported by grants from the National Science Council, Taiwan (NSC-91-3112-B-002-011; NSC-92-3112-B-002-019; NSC-93-3112-B-002-012; NSC-94-3112-B-002-020, NSC 95-3112-B-002-011, NSC 96-3112-B-002-011, NSC 97-3112-B-002-046), the National Health Research Institute, Taiwan (NHRI-90-8825PP; NHRI-EX91, 92, 93, 94-9113PP; IRO1 MH59624-01), National Taiwan University (EPP-97R00066-47), and the Department of Health, Taiwan (DOH94-TD-G-111-035).

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