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ORIGINAL PAPER

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Interleukin-1 beta gene polymorphism and its interactions with neuregulin-1 gene polymorphism are associated with schizophrenia

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Abstract Interleukin-1β (IL-1β) and neuregulin-1 (NRG-1) have an important role in development of the central nervous system. Several recent studies suggest that their genetic polymorphisms are associated with schizophrenia. We studied the effects of the IL-1β gene (IL-1B) -511 and NRG-1 SNP8NRG221533 polymorphisms and their interactions on the risk and age of onset of schizophrenia in 113 Finnish schizophrenic patients and 393 healthy controls. The allele and genotype frequencies of IL-1B and NRG-1 did not differ between schizophrenic patients and healthy controls, but the risk of schizophrenia was more than 10 times higher (odds ratio 10.20, 95% CI 2.53–41.09, $p = 0.001$) among subjects with the IL-1B 2.2, NRG-1 CC genotypes compared to subjects with the IL-1B 2.2, NRG-1 T-allele carriage. There was also a trend for an association between the interaction between IL-1B and NRG-1 polymorphisms and the age at onset of schizophrenia ($\chi^2 = 2.80$; df = 1; $p = 0.09$, log rank test). IL-1B-511 allele 1 homozygotes had a significantly higher age of onset than allele 2 carriers (mean age of onset 25.9 ± 7.7 and 22.7 ± 5.4 years, t-test: $t = 2.46$; $p = 0.032$). Our results suggest that there is an interaction between the IL-1B and NRG-1 genes in schizophrenia. In addition, the IL-1B-511 polymorphism seems to be associated with the age at onset of schizophrenia.

Key words schizophrenia · polymorphism · interleukin-1β · neuregulin-1 · genetics

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Introduction

Interleukin-1beta (IL-1β) is a pleiotropic cytokine contributing to inflammation, cell growth, and tissue repair [40]. In addition, cytokines have been shown to modulate the dopaminergic neurotransmission in the central nervous system (CNS), which is thought to be aberrant in schizophrenia [29]. Numerous recent studies have provided evidence for abnormal levels of interleukin-1 (IL-1) complex cytokines in the blood of schizophrenic patients, indicating dysregulation of these cytokines in schizophrenia [1, 15, 39]. The neurodevelopmental hypothesis of schizophrenia suggests that changes in the CNS that sensitize an individual to schizophrenia are present in utero or later in CNS development. There is a good deal of evidence that IL-1β affects CNS development. IL-1β has been shown to stimulate astrocyte to proliferation

and produce a variety of cytokines and trophic factors, including nerve growth factor [28]. Marx et al. [23] demonstrated that IL-1β produces dose-dependent decreases in the number of neurons in embryonic rat cortical slices, suggesting decreased cerebral cortical neuron survival. Gilmore et al. [9] showed that high levels of IL-1β reduce dendrite development and neuron survival in vitro. These data suggest that IL-1β plays an important role in prenatal exposure to infection and a heightened risk of schizophrenia.

The IL-1β gene (IL-1B) has a single nucleotide polymorphism (SNP) in the promoter region at position -511 [5]. Several studies show that this SNP has an impact on the levels of IL-1 gene complex cytokines [11, 12]. We previously demonstrated an association between an allele combination of the IL-1 gene complex (i.e., IL-1alpha-889 allele 2, IL-1B-511 allele 1, IL-1 receptor antagonist (IL-1RN) variable number of tandem repeats (VNTR) allele 1) and schizophrenia, suggesting that the cytokine aberrations seen in schizophrenia might be partly genetically determined [16]. Our finding was not confirmed in two independent Chinese populations [4].

Neuregulin-1 (NRG-1) belongs to a family of neuregulins that consists of four growth factor genes that are structurally related to the epidermal growth factor genus of cell-to-cell signalling molecules [19]. NRG-1 is localized to widespread areas of the brain, including frontal cortex, hippocampus, midbrain, and cerebellum [18]. NRG-1 has a broad range of bioactivities in the CNS, including synapse formation, regulation of *N*-methyl-D-aspartate and gamma-aminobutyric acid-A receptor subunit expression, as well as neuron differentiation, proliferation, and migration [2, 20, 30, 33–35]. These activities are partly developmental, but NRG-1 continues to be expressed in the adult brain [19]. Leading theories about the pathogenesis of schizophrenia suggest a neurodevelopmental origin of the disease [24] or aberrant signalling in glutamatergic and dopaminergic pathways [3]. This makes NRG-1 an interesting candidate in the etiopathogenesis of schizophrenia.

The NRG-1 gene localizes to chromosome 8p22. It was in this region that Stefansson et al. [36] identified an NRG-1 at-risk haplotype of seven markers and one SNP in the 5′ region of the NRG-1 gene (SNP8NRG221533) that was significantly different in schizophrenic patients compared to controls in a large Icelandic sample. The same group found associations with three SNPs and the entire haplotype in a Scottish case-control sample, providing support for the initial association [37]. Williams et al. [41] examined three markers from Stefanssońs haplotype and reported an association with the haplotype but not with any of the individual markers. Yang et al. [42] investigated the single most significant SNP from the study by Stefansson et al. [36] in Chinese Han case-parent families and confirmed Stefansson's results. On the other hand, in a Finnish case-control study, the NRG-1 SNP 221533 was examined in schizophrenic patients and healthy controls, and no group differences in genotype or allele were found [14]. Nor was there any association between the polymorphism and the age of onset of schizophrenia. However, genotype distributions differed between responders and non-responders to conventional antipsychotics [14].

The purpose of the present study was to compare the allele frequencies of the IL-1B-511 polymorphism and the 8NRG221533 SNP of NRG-1 in Finnish schizophrenic patients and healthy controls and analyze the effects of these polymorphisms on the age at onset of schizophrenia. In addition, since IL-1B and NRG-1 are both candidate genes for schizophrenia and play an important role in CNS development, we studied interactions between the IL-1B-511 polymorphism and the NRG-1 SNP 221533 in the risk of schizophrenia and the age at onset of schizophrenia. The patient population in the present study was an expansion of our previous study [16] and was different from that of Kampman et al. [14].

Methods

Subjects

The patient sample consisted of 113 patients (69 males, 44 females; age 18–76 years, mean ± SD 39.7 ± 12.0 years) that met the DSM-IV criteria for schizophrenia. About 48 patients met the criteria for paranoid, 37 for undifferentiated, 22 for disorganized, three for residual, and three for catatonic acute or chronic schizophrenia. A family history was available for 97 patients: 24 patients had a schizophrenic first-degree relative, 13 patients had schizophrenia in more distant relatives, and 60 patients had no family history of schizophrenia. The diagnoses were assigned based on a Structured Clinical Interview for DSM-IV Axis I Disorders-clinician version (SCID-I/CV) [7] by two experienced psychiatrists (KH and HK). The following exclusion criteria were applied: an additional axis I diagnosis (substance abuse, organic mental disorder, affective disorder), neurological illness, or diabetes mellitus. The mean age ± SD of onset of schizophrenic psychosis was 23.7 ± 6.1 years. We defined the age of onset as the first occurrence of positive psychotic symptoms [26]. We acquired this information from patients' medical records and interviews with the patients and their relatives. The age of onset in one patient was unknown. The mean duration ± SD of schizophrenia was 16.3 ± 11.2 years. Patients were recruited from the Departments of Psychiatry at Helsinki University Central Hospital and South Karelia Central Hospital. All patients had been hospitalized because of acute or chronic schizophrenic psychosis. The patients were of Caucasian Finnish origin and residents of southern Finland. The control group consisted of 393 (213 males, 180 females) healthy blood donors (age range 19–65 years; mean ± SD 44.5 ± 11.1 years) from the Finnish Red Cross Blood Transfusion Service, Tampere, Finland. The controls were Caucasian Finnish citizens.

To determine interactions between IL-1B and NRG-1 polymorphisms, we divided patients and controls into four groups according to their genotype status. The groups were (1) a combination of IL-1B 1.1/1.2, NRG-1 CT/TT (frequencies in patients and controls n = 87, n = 287, respectively); (2) IL-1B 1.1/1.2, NRG-1 CC (n = 12, n = 50); (3) IL-1B 2.2, NRG-1 CT/TT (n = 7, n = 51); and (4) IL-1B 2.2, NRG-1 CC (n = 7, n = 5).

The study was approved by local hospital ethics committees and was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All subjects received

a full explanation and a written description of the procedures. The investigators determined that all subjects understood the procedures, and written informed consent was obtained.

Genotyping

From each subject, 10 ml of blood was drawn into EDTA vacuum tubes and immediately frozen at −20°C. Genomic DNA was isolated from blood samples by the salting-out method [27]. Methods for screening IL-1B-511 gene polymorphisms have been described [16]. Allele assignments were made as follows: allele 1, C (cytosine); allele 2, T (thymine).

Neuregulin-1 SNP8NRG221533 was genotyped by employing the 5′ nuclease assay for allelic discrimination [21] using the ABI Prism 7000 Sequence Detection System (Applied Biosystems, Foster City, CA). The nucleotide sequences of primers and fluorogenic allele-specific oligonucleotide probes were deduced from sequences found on the deCODE Genetics Web site (http://www.decode.com/nrg1/markers) and the GenBank Database. They were synthesized by Applied Biosystems using the Assays-by-Design tool. A PCR reaction containing genomic DNA, 1× Universal PCR Master Mix, 900 nM of each primer and 200 nM of each probe was performed in 96-well plates using the standard protocol for TaqMan (Applied Biosystems) MGB probes in a total volume of 25 µl.

Statistical analysis

Differences between the allele and genotype frequencies in the control and patient groups were determined with a χ^2 test. Differences in genotypes were calculated with *t*-tests, one-way ANOVAs, and Kaplan–Meier log rank tests. The interaction analyses were performed with a logistic regression model, and odds ratios (OR) with 95% confidence intervals (CI) were calculated with the −2 log likelihood test. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the SPSS/Win software (Version 12.0, SPSS Inc., Chicago, IL).

Results

The genotype distributions in controls and patients followed the Hardy–Weinberg equilibrium. The distributions of IL-1B genotypes and the allele frequencies in patients and controls are shown in Table 1. There were no differences in genotype distributions between schizophrenic patients and controls ($p = 0.53$), and there were no differences in allele frequencies between the two groups ($p = 0.28$). There was no association between NRG-1 genotype or allele frequencies and schizophrenia ($p = 0.66$ and 0.36, respectively) (Table 1).

Interactions of IL-1B and NRG-1 polymorphisms were associated with the incidence of schizophrenia ($\chi^2 = 11.77$; df = 3; p = 0.008, −2 log likelihood test) (Table 2). The risk of schizophrenia was more than 10 times higher (OR 10.20, 95% CI 2.53–41.09, $p = 0.001$) for the IL-1B 2.2, NRG-1 CC-genotype combination compared to the IL-1B 2.2, NRG-1 T-allele carriage (Fig. 1).

There was no difference in the age at onset between the IL-1B-511 allele 1 carriers and 2.2 homozygotes (*t*-test: $t = 0.86$; $p = 0.39$). We also divided the patients into IL-1B-511 1.1 homozygotes and allele 2 carriers. It showed that allele 1 homozygotes had a significantly higher age of onset of schizophrenia than allele 2 carriers. The mean ± SD age of onset was 25.9 ± 7.7 years in 1.1 homozygotes and 22.7 ± 5.4 years in allele 2 carriers (*t*-test: $t = 2.46$; $p = 0.032$ (after Bonferroni correction); mean difference 3.2 years; 95% CI 0.6–5.8 years. Log rank test: $\chi^2 = 6.25$; $p = 0.012$) (Fig. 2). The NRG-1 polymorphism was not associated with the age at onset of schizophrenia ($F = 0.79$; $p = 0.46$, one-way ANOVA).

There was a trend for an association between the interaction between IL-1B and NRG-1 polymorphisms and the age at onset of schizophrenia (log rank test $\chi^2 = 2.80$; df = 1; $p = 0.09$) (Fig. 3). The mean difference in the age at onset between subgroups according to IL-1B/NRG-1 combination (subgroup I, combination of IL-1B allele 1 carriage and NRG-1 CC-genotype, $n = 11$; subgroup II, any other combination of IL-1B/NRG-1 genotypes; $n = 101$) was 4.7 years (subgroup I, mean ± SD 28.2 ± 4.2 years, subgroup II, mean ± SD 23.5 ± 6.7 years; $t = 2.2$; $p = 0.027$, *t*-test).

Table 1 The genotype and allele frequencies of IL-1B-511 and NRG-1 polymorphisms in 113 schizophrenic patients and 393 healthy controls

Polymorphism	Schizophrenic patients	Controls	χ^2-test *p*-value*
Number of subjects	113 (%)	393 (%)	
IL-1B-511 genotype			
1.1	47 (42)	141 (36)	
1.2	52 (46)	196 (50)	
2.2	14 (12)	56 (14)	0.53
IL-1B-511 alleles			
Allele 1	146 (65)	478 (61)	
Allele 2	80 (35)	308 (39)	0.28
NRG-1 genotype			
TT	33 (29)	129 (33)	
CT	61 (54)	209 (53)	
CC	19 (17)	55 (14)	0.66
NRG-1 alleles			
T-allele	127 (56)	467 (59)	
C-allele	99 (44)	319 (41)	0.36

* *p*-value refers to the difference between schizophrenic patients and controls

Table 2 Risk of schizophrenia in relation to IL-1B and NRG-1 genotypes ($n = 113$). Genotype interaction $p = 0.008$ (−2 log likelihood test)

Genotype combination	Odds ratio	95% CI	*p*-value
IL-1B2.2 + NRG-1TT/CT ($n = 7$)	1		
IL-1B1.1/1.2 + NRG-1CC ($n = 12$)	1.74	0.64–4.80	0.28
IL-1B1.1/1.2 + NRG-1TT/CT ($n = 87$)	2.21	0.97–5.04	0.06
IL-1B2.2 + NRG-1CC ($n = 7$)	10.20	2.53–41.09	0.001

Discussion

The main finding in the present study was an interaction between the IL-1B and NRG-1 genes that has implications for the genes in schizophrenia. More

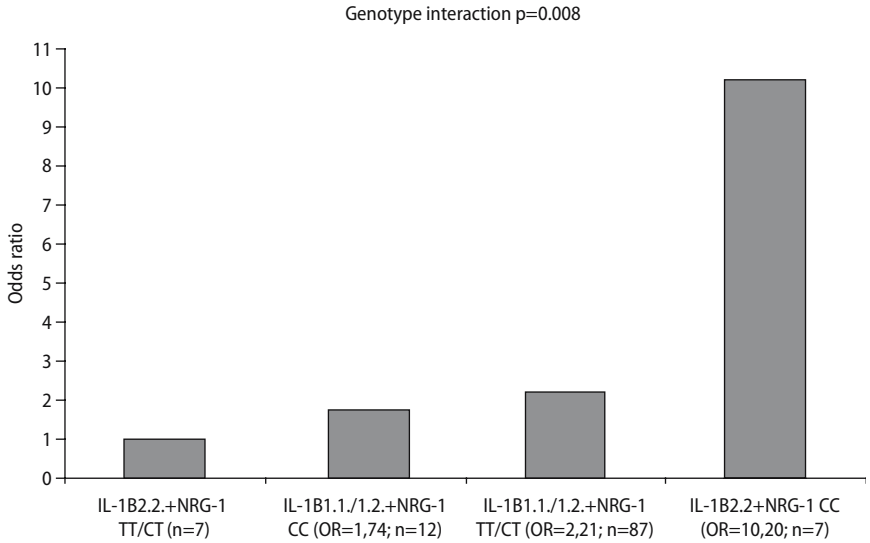

Fig. 1 Odds ratios for having schizophrenia in relation to IL-1B and NRG-1 genotypes (n = 113). Patients that were IL-1B 2.2 homozygotes and NRG-1 T-allele carriers formed a comparison group

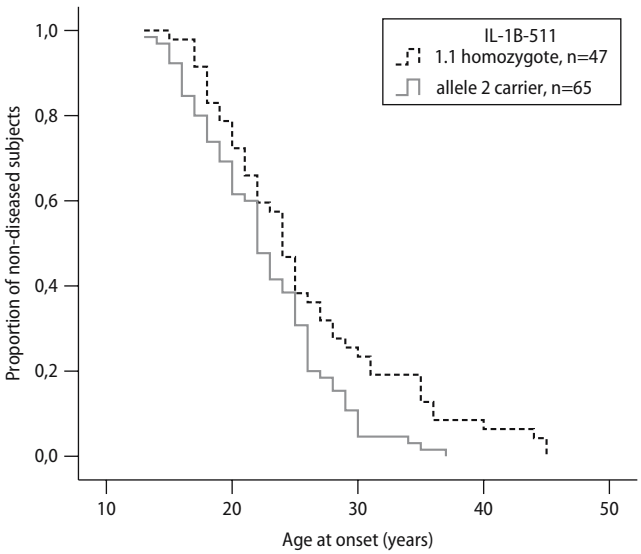

Fig. 2 Survival plot showing the age at onset of schizophrenia in 112 patients relative to the IL-1B-511 genotype (p = 0.012, log rank test)

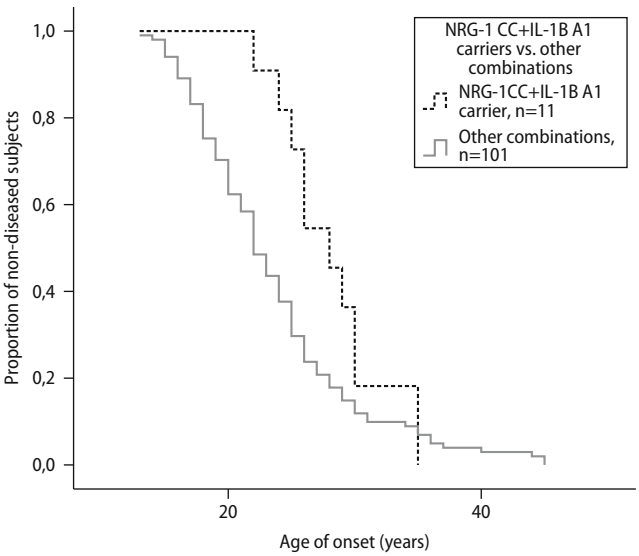

Fig. 3 Survival plot showing the age at onset of schizophrenia in patients with the combination NRG-1 CC and IL-1B allele 1 carrier vs. all other combinations (p = 0.09, log rank test) (n = 112)

specifically, our results demonstrate that the interactions affect both the risk of schizophrenia and the age of onset of the disease. The interaction has not been described previously. The risk of schizophrenia was 10 times greater in patients with the IL-1B 2.2 genotype that were NRG-1 CC-homozygotes than those that were T-allele carriers. Furthermore, our results suggest that the combination of IL-1B allele 1 carriage and NRG-1 CC homozygotism is a modifier for late onset of schizophrenia, the mechanism of which is not clear. However, there is evidence that IL-1B allele 2 is associated with enhanced IL-1β production [6, 12], and in vitro studies have demonstrated that high IL-1β concentrations can decrease neuronal survival and may modulate the neuroanatomical alterations that are observed in schizophrenia [23]. In addition, magnetic resonance imaging (MRI) studies have demonstrated bifrontal-temporal gray matter volume deficits and generalized white matter deficits in schizophrenic IL-1B-511 allele 2 carriers [25]. We speculate that the elevated levels of IL-1β in allele 2 carriers interact with NRG-1 in the developing brain, causing morphological and functional aberrations which might sensitize a person to a schizophrenic psychosis. Correspondingly, IL-1B allele 1 could have a protective effect for schizophrenia by delaying the onset of illness. However, it is remarkable that post-mortem studies of human dorsolateral prefrontal cortex suggest that the NRG-1 SNP 221533 appears

not to be functional, at least in terms of regulating NRG-1 expression [10].

We found no association between the IL-1B-511 polymorphism and the risk of schizophrenia. This is consistent with several previous studies [16, 17, 25, 38, 42]. However, Zanardini et al. [43] and Papiol et al. [31] reported increased IL-1B allele 1 in schizophrenia that was nearly significant. Evidence for an effect of the IL-1B-511 polymorphism on the risk of schizophrenia is weak, but haplotype analyses in the IL-1 gene complex have revealed a stronger association with schizophrenia. Zanardini et al. [43] detected a protective effect of the IL-1RN VNTR allele 2 combined with the IL-1B-511 allele 2 against schizophrenia. Papiol et al. [31] reported a significant excess of the haplotype combination of the IL-1B-511 allele 1 and the IL-RN VNTR allele 2 in schizophrenic patients compared to controls. Thus, it seems unlikely that the IL-1B-511 polymorphism is pathogenic per se, but there is evidence that its interactions with polymorphisms in other genes (e.g., other IL-1 complex genes and NRG-1) might confer an increased risk of schizophrenia.

In our study IL-1B-511 allele 1 homozygotes had a significantly higher age of onset of schizophrenia than allele 2 carriers, which suggests that this polymorphism has a modulatory effect in schizophrenia. We are not aware of any other studies that have examined the association between the IL-1B-511 polymorphism and the age at onset of schizophrenia.

There is evidence that polymorphisms of the NRG-1 gene are associated with the risk of schizophrenia [22, 36, 37, 41, 42]. In addition, Petryshen et al. [32] reported associations between a haplotype that overlaps the risk haplotype originally reported in an Icelandic population and two haplotypes located on the 3′ end of NRG-1 in a Portuguese population, but they did not detect an association with the original Icelandic risk haplotype. Fukui et al. [8] tested a four SNP haplotype, which shared three SNPs of the Stefanssoń original risk haplotype in a Japanese sample, and found a positive association. Zhao et al. [44] found an association with the risk haplotype in a Chinese Han sample. However, Iwata et al. [13] did not report a relationship in a Japanese population. Thus, the results are conflicting, and no specific mutation responsible for an association has been identified to date. The most significant association is with the SNP 8NRG221533 compared with the other six markers of the at-risk haplotype [36, 37, 42]. We did not find an association between the SNP 221533 and risk of schizophrenia in our Finnish population, which is in line with several previous studies [13, 14, 41, 44]. Nor did we find an association between the SNP 221533 and the age at onset of schizophrenia. These negative results may be due to the small sample size, which is the primary limitation of our investigation, particularly since we used the SNP 221533 as the only genetic marker, rather than a haplotype of several genetic markers.

In conclusion, we showed an interaction of IL-1B and NRG-1 polymorphisms that has an effect on the risk of schizophrenia and the age at onset of schizophrenia. In addition, we suggest that the IL-1B-511 polymorphism is a modulatory factor that affects the age of onset of schizophrenia. It is, however, important to note that the background of our findings has not been clearly verified, and is partly hypothetical. Thus, the results should be viewed cautiously. This is especially true because no gene variant in our study showed an increased risk for schizophrenia. Further studies with larger groups are needed to confirm our findings.

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