Brief Report

Association of an Interleukin-1β Genetic Polymorphism With Altered Brain Structure in Patients With Schizophrenia

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Objective: This study investigated the effect on brain morphology of an interleukin-1 β genetic polymorphism (C \rightarrow T transition at position –511) in patients with schizophrenia.

Method: In vivo magnetic resonance imaging and genotype analysis were used in the examination of 44 male schizophrenic patients and 48 healthy male comparison subjects.

Results: No association between the interleukin-1 β polymorphism and schizophrenia was detected. Within the patient group, bifrontal-temporal gray matter volume deficits and generalized white matter tissue deficits in allele 2 carriers (genotype T/T or C/T) were found. In contrast, the interleukin-1 β polymorphism had no influence on brain morphology within the healthy subjects.

Conclusions: The data suggest that allele 2 within the promoter region of the interleukin-1 β gene at position -511 contributes to structural brain alterations in patients with schizophrenia.

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also plays a crucial role in the development of the central nervous system. Interleukin-1 β has previously been shown to stimulate astrocytes to proliferate and produce a variety of cytokines and trophic factors, including nerve growth factor (4). Moreover, it is involved in acute and chronic neurodegeneration (5).

TABLE 1. Association of Interleukin-1 β Genotype and Allele Frequency With Diagnosis in Patients With Schizophrenia and Healthy Comparison Subjects

Genotype ^a							Allele Frequency							
							Analysis ^b							Analysis ^c
	1/1		1/2		2/2		Odds	95% Confidence	1		2		Odds	95% Confidence
Group	Ν	%	Ν	%	Ν	%	Ratio	Interval	Ν	%	Ν	%	Ratio	Interval
Schizophrenic patients (N=44)	21	47.7	18	40.9	5	11.4	0.78	0.34-1.78	60	68.2	28	31.8	0.78	0.42-1.43
Comparison subjects (N=48)	20	41.7	20	41.7	8	16.6			60	62.5	36	37.5		

^a Hardy-Weinberg equilibrium was present (χ^2 =0.41, df=2, p<0.82).

^b For genotype 1/1 versus 1/2 and 2/2 (χ^2 =0.34, df=1, p<0.56).

^c For allele 1 versus 2 (χ^2 =0.65, df=1, p<0.42).

TABLE 2. Effects of Diagnosis, Interleukin-1ß Genotype ^a , Brain Region, and Hemisphere on Gray and White Matter Volume	es
for 44 Patients With Schizophrenia and 48 Healthy Comparison Subjects	

	Gray	y Matter Volui	White Matter Volume				
Effect	F	df	р	F	df	р	
Main effects							
Diagnosis	1.13	1, 88	0.29	3.25	1, 88	0.08	
Genotype	1.90	1, 88	0.17	0.34	1, 88	0.56	
Brain region ^b	7257.20	6, 528	0.0001	3242.50	6, 528	0.0001	
Hemisphere	39.50	1, 88	0.0001	2.40	1, 88	0.13	
Interaction effects							
Diagnosis by genotype	2.25	1, 88	0.14	5.63	1, 88	0.02	
Brain region by diagnosis ^b	1.80	6, 528	0.17	0.96	6, 528	0.46	
Brain region by genotype ^b	0.71	6, 528	0.50	0.36	6, 528	0.67	
Brain region by diagnosis by genotype ^b	4.94	6, 528	0.007	0.75	6, 528	0.61	
Brain region by hemisphere ^b	86.00	6, 528	0.0001	69.70	6, 528	0.0001	
Hemisphere by diagnosis	0.23	1, 88	0.64	0.48	1, 88	0.49	
Hemisphere by genotype	1.43	1, 88	0.23	0.87	1, 88	0.35	
Hemisphere by diagnosis by genotype	0.04	1, 88	0.85	0.06	1, 88	0.80	

^a Homozygous for allele 1 versus allele 2 carrier at position –511.

^b Greenhouse-Geisser corrected.

Two biallelic base-exchange polymorphisms, which are in nearly complete linkage disequilibrium, have been reported at positions –511 and –31 in the promoter region of the interleukin-1 β gene (6). There is growing evidence that allele 2 at position –511 is associated with enhanced interleukin-1 β production (6, 7). The interleukin-1 β polymorphisms and a repeat polymorphism in the neighboring interleukin-1Ra gene are in much weaker linkage disequilibrium. Nevertheless, there is an interaction: interleukin-1 β –511 allele 2 is associated with higher levels of interleukin-1Ra, while allele 2 (IL1RN*2) in the interleukin-1Ra gene is associated with higher levels of interleukin-1B (7, 8).

We investigated the effect on brain morphology of the interleukin-1 β genetic polymorphism (C \rightarrow T transition at position –511) in patients with schizophrenia and healthy comparison subjects.

Method

For this study we examined 44 male right-handed medicated schizophrenic inpatients (mean age=30.2 years, SD=8.8, range= 18–47). Demographic information and clinical history were obtained by using a semistructured interview. The patients had been ill for 6 months to 25 years (mean=7.1 years, SD=7.1). The comparison group consisted of 48 right-handed healthy male subjects who were recruited from the general population (mean age=30.3 years, SD=8.9, range=18–47). They were matched to the patients in a one-to-one fashion for age (range plus or minus 3 years) and educational achievement.

Neither the healthy subjects nor their first-degree relatives had a history of neurological or mental illness. Exclusion criteria for both groups were a history of serious neurological disorder, use of benzodiazepine or cortisol medication in the last 3 months, any mental disorder other than schizophrenia, or previous treatment with ECT. All patients and comparison subjects provided written informed consent after the procedures had been fully explained. Magnetic resonance imaging (MRI) data were acquired by using coronal T_2 and proton-density-weighted dual-echo sequences and a three-dimensional magnetization-prepared rapid gradient echo sequence, described in detail elsewhere (9). Volumetric measurement was performed on the MRI data sets by using the software program BRAINS (10).

Genomic DNA was prepared from 10 ml blood by using the QIAamp DNA Blood Maxi Kit (Quiagen, Hilden, Germany). The promotor region of the interleukin-1 β gene contains a polymorphic site at position -511 caused by a C \rightarrow T transition, the C allele completing an AvaI restriction site. Genotyping was performed as described previously (7).

Frequency data were analyzed with chi-square tests. Possible confounding variables were compared by using t tests for independent data. Morphometric data were normally distributed. Results were subjected to univariate analyses of variance (ANO-VAs) that assessed main and interaction effects, with brain region (frontal, temporal, parietal, occipital, subcortical, cerebellum) and hemisphere (left, right) as within-subject factors and diagnosis (schizophrenia, healthy) and genotype (1/1, 1/2, or 2/2) as between-subject factors. Significant interactions were resolved by separate analyses for each region and each diagnostic group.

Results

An overview of the results is given in Table 1. Two allelic subgroups within each diagnostic group were formed by placing subjects homozygous for allele 1 into one group and collapsing allele 2 carriers (1/2 and 2/2) into the other. These subgroups (1/1 versus 1/2 and 2/2) did not differ significantly with respect to age, height, weight, education, verbal IQ, nicotine or alcohol consumption, age at onset of illness, or duration of illness (each t<1.05, df=90, p>0.30). Interleukin-1 β genotype was not associated with diagnosis. The sample size allowed for sufficient power (0.80) to correctly accept the null hypothesis if the effect size was 0.60 (Cohen's d) or larger.

Diagnosis and genotype had no main effects on either gray or white matter across the whole brain (Table 2). However, for gray matter volumes, the three-way interaction of diagnosis, genotype, and region indicated that there could be a region-specific effect. Separate three-factorial ANOVAs for each region revealed interaction effects of diagnosis and genotype in the frontal lobe (F=5.31, df= 1, 88, p<0.03) and temporal lobe (F=4.26, df=1, 88, p=0.04). Further F tests showed that there was no genotype effect in the comparison subjects for frontal gray matter (F=0.97, df=1, 46, p=0.33) or temporal gray matter (F=0.07, df=1, 46, p=0.80), but among the schizophrenic patients allele 2 carriers had significantly smaller gray matter volumes in these areas than did 1/1 homozygotes (frontal: F=6.06, df= 1, 42, p<0.02; temporal: F=11.62, df=1, 42, p=0.001). The ANOVA for white matter volumes showed a diagnosis-bygenotype interaction that was independent of brain region. Again, white matter volumes in comparison subjects were not affected by interleukin-1 β genotype (F=1.36, df= 1, 46, p=0.25), whereas schizophrenic patients had overall white matter deficits if they were allele 2 carriers (F=5.54, df=1, 42, p<0.03).

Discussion

To our knowledge, this is the first study to examine the relationship between cytokine genetics and MRI brain structure in schizophrenia. Interleukin-1 β -511 allele 2 carriers showed bifrontal-temporal gray matter volume deficits and generalized white matter tissue deficits. The data suggest that genetically determined interindividual differences in interleukin-1 β may influence brain morphology in schizophrenia. The same presumably high-activity allele 2 in the promoter region of interleukin-1 β (position –511) is associated with two other conditions that lead to altered brain morphology: Alzheimer's disease and hippocampal sclerosis in temporal lobe epilepsy (11, 12).

We found no association between schizophrenia and the interleukin-1 β genetic polymorphism at position-511. Since previous findings have suggested a lack of association with this polymorphic site, it is improbable that the allele 2 has a pathogenic effect per se (3). It is tentatively speculated that elevated levels of interleukin-1 β interact with schizophrenia-specific risk factors, resulting in frontal-temporal gray matter deficits and more widespread white matter deficits.

It remains to be clarified whether the effect emerges during CNS development, or later, e.g., as a result of neurotoxicity caused by presumably high levels of pro-inflammatory cytokines. The present findings emphasize the interaction of disease-specific genetic risk factors with nonspecific environmental and other genetic vulnerability factors, leading in concert to altered neuronal networks.

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