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ORIGINAL ARTICLE

An Association Between Functional Polymorphisms of the Interleukin 1 Gene Complex and Schizophrenia Using Transmission Disequilibrium Test

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Abstract IL1 gene complex has been implicated in the etiology of schizophrenia. To assess whether IL1 gene complex is associated with susceptibility to schizophrenia in Polish population we conducted family-based study. Functional polymorphisms from IL1A (rs1800587, rs17561, rs11677416), IL1B (rs1143634, rs1143643, rs16944, rs4848306, rs1143623, rs1143633, rs1143627) and IL1RN (rs419598, rs315952, rs9005, rs4251961) genes were genotyped in 143 trio with schizophrenia. Statistical analysis was performed using transmission disequilibrium test. We have found a trend toward an association of rs1143627, rs16944, rs1143623 in IL1B gene with the risk of schizophrenia. Our results show a protective effect of allele T of rs4251961 in IL1RN against schizophrenia. We also performed haplotype analysis of IL1 gene complex and found a trend toward an association with schizophrenia of GAGG haplotype (rs1143627, rs16944, rs1143623, rs4848306) in IL1B gene, haplotypes: TG (rs315952, rs9005) and TT (rs4251961, rs419598) in IL1RN. Haplotype CT (rs4251961, rs419598) in IL1RN was found to be associated with schizophrenia. After correction for multiple testing associations did not reach significance level. Our results might support theory that polymorphisms of interleukin 1 complex genes (rs1143627, rs16944, rs1143623, rs4848306 in IL1B gene and rs4251961, rs419598, rs315952, rs9005 in IL1RN gene) are involved in the pathogenesis of schizophrenia, however, none of the results reach significance level after correction for multiple testing.

Keywords Genetics · Polymorphism · Schizophrenia · Transmission disequilibrium test · Interleukin 1 gene complex

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Introduction

Schizophrenia has been associated with a large range of autoimmune diseases, with a history of any autoimmune disease being associated with a 45% increase in risk for the illness (Benros et al. 2012). The etiology of schizophrenia remains unclear, while there has been a growing amount of evidence for the immunogenetics, which are characterized by an increased serum concentration of several pro-inflammatory cytokines (Monji et al. 2009). Cytokines can often act both as immunomodulators and as neuromodulators. The specificity of the response to cytokines is provided by unique cytokine receptors. Cells that express a functional receptor for a cytokine will respond to the presence of that cytokine. These interactions of cytokines and cytokine receptors are a necessary component of the physiologic response to cytokines. Cytokine receptors have also been detected in several areas of the brain (Kronfol and Remick 2000). Cytokines are actively transported through the blood brain barrier and are also produced by neuronal and glial processes in the central nervous system. Furthermore, it has been demonstrated that cytokines are involved in the regulation of many neuronal functions, such

as neurotransmission, neuronal survival and synaptic plasticity (Nawa et al. 2000). The activation of the cytokine systems may be involved in the neuropathological changes occurring in the central nervous system of schizophrenic patients. Numerous studies report that treatment with antipsychotics drugs affects the cytokine network (Drzyzga et al. 2006). It was demonstrated that antipsychotics reduced IL-1B release by activated microglia (Labuzek et al. 2005) and decreased IL-1B plasma levels (Tourjman et al. 2013). The influence of antipsychotics on the cytokine system may be at least partially responsible for their clinical effectiveness. One could expect that antipsychotics with proven effect on cytokines would bring an additional benefit to the patients by normalization of preexisting cytokine aberrations (Drzyzga et al. 2006).

Interleukin (IL)-1 is expressed endogenously by brain cells, such as microglia and astrocytes (Watanabe et al. 2007). IL-1 has been described as an astroglial growth factor and it has been suggested to have a role in the development process of the brain and to be implicated in acute and chronic neurodegeneration (Giulian et al. 1988). IL-1 is considered pro-inflammatory, it augments the immune response to infection and inflammation by promoting leukocyte recruitment to inflammatory sites and/or by activating inflammatory cells. Experimental findings provide contradictory results regarding abnormalities in interleukin production in schizophrenia. The IL-1RN (IL-1 receptor antagonist) is structurally related to IL-1A and IL-1B and competes with these molecules for occupancy of IL-1 cell surface receptors (Lardner 2013) and so it is anti-inflammatory cytokine that contribute to dampen the immune and inflammatory response (Potvin et al. 2008). All three genes of the IL1 gene complex (IL1A, IL1B, IL1RN) are clustered on the long arm of human chromosome 2 in a region q13–q21 (Nicklin et al. 1994).

There are conflicting results of the studies on IL-1A, IL-1B and IL-1RA protein levels in schizophrenia, some of them reported decreased, unchanged or elevated protein levels in serum or cerebrospinal fluid (Miller et al. 2011; Potvin et al. 2008).

Recent genetic studies have revealed that the IL1 gene complex (IL1 alpha, IL1 beta and IL1 receptor antagonist) is associated with schizophrenia, but contradictory findings have also been reported (Xu and He 2010). IL1A have been associated with schizophrenia in genome-wide pharmacogenomic study (McClay et al. 2011) and in high-resolution chromosome ideogram representation study conducted in 2015 (Butler et al. 2015). A few meta-analyses have been conducted on IL1 gene complex polymorphisms. A recent study by Shibuya et al. (2014) of rs16944 and case–control (555 patients with schizophrenia) or family-based study (112 trios) of other 11 single nucleotide polymorphisms (SNPs) in IL1B gene (including rs1143634, rs1143643, rs16944, rs4848306, rs1143623, rs1143633, rs1143627) found no significant association between any of these SNPs and risk of schizophrenia (Shibuya et al. 2014). Meta-analysis conducted by Xu and He (2010) suggests the IL1B gene or the IL1 gene complex may play a moderate role in the etiology of schizophrenia in the Caucasian population. Study of rs16944 in IL1B gene suggests that the C allele confers modest risk for schizophrenia among Caucasian population (Shirts et al. 2006).

The aim of this study was to perform Transmission Disequilibrium Test (TDT) of polymorphisms within IL1A, IL1B and IL1RN on 143 trios of Polish origin diagnosed with schizophrenia. We also performed haplotype analysis of the IL1 gene complex and association of clinical parameters with studied polymorphisms. The polymorphisms from IL1A (rs1800587, rs17561, rs11677416), IL1B (rs1143634, rs1143643, rs16944, rs4848306, rs1143623, rs1143633, rs1143627) and IL1RN (rs419598, rs315952, rs9005, rs4251961) were chosen on the basis of its functionality.

Materials and Methods

The study was performed on a group of 143 trio (patients diagnosed with schizophrenia and theirs healthy parents). There were 64 males (mean age 24.42; SD 6.7) and 79 females (mean age 27.82; SD 6.8) in patient's group. Mean age of onset of first psychotic episode was 22.9 years. In 20 patients family history of schizophrenia and in 42 patients family history of other psychiatric disorders have been confirmed. Clinical description of the studied group is presented in Table 1. Mean age of parents at the recruitment time was: fathers 55.9 (SD 8.44), mothers 53.0 (SD 7.7) years. Both parents were psychiatrically screened using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) and found to be mentally healthy. Inclusion criteria were diagnosis of schizophrenia in patients and availability of their both parents. Patients with any chronic or acute diseases were excluded from the study, also an increased C reactive protein (CRP) was an exclusion criterion (16 patients were excluded from the analysis because of this reasons). Consensus diagnosis of schizophrenia was made for each patient using SCID. All patients were evaluated for lifetime psychiatric symptomatology using the Operational Criteria for Psychotic Illness. Participants were recruited from inpatients, treated at the Department of Psychiatry, Poznan University of Medical Sciences. All subjects were of Caucasian origin and they were native Polish population from Great Poland region. The study was performed in accordance with the ethical standards established in the Declaration of Helsinki

Table 1 Clinical description of the studied subjects

Subjects	143
Males (*n*; mean age)	64; 24.42
Females (*n*; mean age)	79; 27.82
Age of onset ≥18 years old	37
Family history of schizophrenia	20
Family history of other psychiatric disorder	42
Life time diagnosis of alcohol abuse/dependence	5
Life time diagnosis of cannabis abuse/dependence	17
Life time diagnosis of other abuse/dependence	8
Mode of onset	
Abrupt onset definable to within hours or days	10
Acute onset definable to within 1 week	13
Moderately acute onset definable within 1 month	27
Gradual onset over period up to 6 months	29
Insidious onset over period greater than 6 months	55
Unspecified	9
Course of disorder	
Single episode with good recovery	33
Multiple episodes with good recovery between	17
Multiple episodes with partial recovery between	50
Continuous chronic illness	13
Continuous chronic illness with deterioration	20
Unspecified	10

and was approved by the medical ethics committee of the Poznan University of Medical Sciences. All participants gave written informed consent before participating in the study.

DNA was extracted from 10 ml of EDTA anticoagulated whole blood, using the salting out method. The polymorphisms from IL1A (rs1800587, rs17561, rs11677416), IL1B (rs1143634, rs1143643, rs16944, rs4848306, rs1143623, rs1143633, rs1143627) and IL1RN (rs419598, rs315952, rs9005, rs4251961) genes were genotyped with use of TaqMan SNP Genotyping Assays (Applied Biosystems). Characteristic of the analyzed SNPs is provided in Table 2. The amplification for TaqMan SNP genotyping assay plates was done in ABI PRISM® 7900HT Sequence Detection System. Data acquisition and analysis was performed using the allelic discrimination analysis module in SDS v2.4 software (Applied Biosystems). The genotyping was performed without knowing the clinical status of the subjects.

Single polymorphism association and haplotype analysis for family trio data was performed using Haploview v4.2 software (http://www.broadinstitute.org/). Correction of multiple testing was performed for multiple comparisons in haplotype analysis and was done by 10,000 permutations in Haploview. Results were confirmed as well as odds ratios (OR) and confidence intervals (95% CI) were calculated using PLINK whole genome association analysis toolset (http://pngu.mgh.harvard.edu/~purcell/plink/). Two-tailed power analysis was performed using Quanto software (http://biostats.usc.edu/Quanto.html) using case-parent trio design and log-additive inheritance mode.

Results

All polymorphisms did not deviate from Hardy–Weinberg equilibrium. We have found a trend toward an association of rs1143627, rs16944, rs1143623 in IL1B gene with the risk of schizophrenia. Alleles: G [rs1143627; $p = 0.053$;

Table 2 Description of polymorphisms analyzed in this study

Gene	SNP	Chromosome	Chromosome position	MAF	HWE	Taqman assay ID
	rs11677416	2	113245711	0.289	0.9428	Custom
IL1A	rs17561	2	113537223	0.29	0.896	C___9546471_10
	rs1800587	2	113542960	0.289	0.9428	C___9546481_20
IL1B	rs1143643	2	113588302	0.388	0.5405	C___1839949_10
	rs1143634	2	113590390	0.229	1.0	C___9546517_10
	rs1143633	2	113590467	0.388	0.5796	C___1839948_10
	rs1143627	2	113594387	0.322	0.5931	C___1839944_10
	rs16944	2	113594867	0.32	0.6541	C___1839943_10
	rs1143623	2	113595829	0.249	1.0	C___1839941_10
	rs4848306	2	113598107	0.48	0.9084	C__11725735_10
IL1RN	rs4251961	2	113874467	0.332	0.2049	C__32060323_10
	rs419598	2	113887207	0.299	0.4051	C___8737990_10
	rs315952	2	113890304	0.357	0.2183	C__11512470_10
	rs9005	2	113891412	0.32	0.8855	C___3133528_10

MAF minor allele frequency, *HWE* Hardy–Weinberg equilibrium

Table 3 Association of IL1 gene complex (IL1A, IL1B, IL1RN) polymorphisms with schizophrenia in Polish population

Gene	SNP	A1	A2	T:U	OR	95% CI	CHISQ	*p*	*p* corrected	Power (%)
IL1A	rs11677416	C	T	59:57	0.9667	0.6738–1.387	0.034	0.8527	1	5.3
	rs17561	A	C	60:60	1	0.7012–1.426	0.0	1.0	1	5
	rs1800587	A	G	60:59	0.9836	0.6887–1.405	0.008	0.927	1	5
IL1B	rs1143643	T	C	73:69	1	0.7213–1.386	0.113	0.7371	1	5
	rs1143634	A	G	55:46	0.8214	0.5561–1.213	0.802	0.3705	1	15.8
	rs1143633	T	C	71:69	1.014	0.7291–1.411	0.029	0.8658	1	5
	rs1143627	G	A	76:54	1.389	0.9789–1.971	3.723	0.0537#	0.558	48.3
	rs16944	A	G	75:54	1.37	0.9649–1.946	3.419	0.0645	0.6305	44.9
	rs1143623	G	C	63:43	1.465	0.9943–2.159	3.774	0.0521#	0.556	57.5
	rs4848306	A	G	76:63	0.8421	0.6039–1.174	1.216	0.2702	0.9898	17.8
IL1RN	rs4251961	C	T	83:53	0.6667	0.4754–0.9349	6.618	0.0101*	0.1435	59.5
	rs419598	C	T	68:57	1.158	0.8124–1.65	0.968	0.3252	1	12.7
	rs315952	C	T	77:65	1.149	0.8283–1.595	1.014	0.3139	0.9964	12.9
	rs9005	A	G	67:59	1.153	0.8132–1.633	0.508	0.476	1	12.6

A1 rare allele, *A2* common allele, *T* transmitted, *U* undertransmitted, *OR* odds ratio, *95% CI* confidence interval (95%)

* $p < 0.05$

\# Trend toward an association

OR = 1.389; 95% CI = (0.9798–1.971)], A [rs16944; p = 0,064, OR = 1.37; 95% CI = (0.9649–1.946)], G [rs1143623; $p = 0.052$; OR = 1.465; 95% CI = (0.9943–2.159)] were significantly more frequent transmitted by parents to their children with schizophrenia. Our results show a protective effect of allele T of rs4251961 in IL1RN against schizophrenia [$p = 0.01$, OR = 0.6667; 95% CI = (0.4754–0.9349)]. After correction for multiple testing by 10000 permutations in Haploview program associations did not reach significance level. Results of association analysis are presented in Table 3.

Single polymorphisms analyses with family history of schizophrenia and other psychiatric disorders, life time diagnosis of alcohol, cannabis or other substances abuse/dependence, onset and course of disorder did not show any positive findings.

We also performed haplotype analysis of IL1 gene complex using Haploview statistic program. In Polish population all studied polymorphisms: rs11677416, rs17561, rs1800587 in IL1A gene are in linkage disequilibrium (block 1). Polymorphisms in IL1B gene formed two haplotypes composed of: rs1143643, rs1143634, rs1143633 (block 2) and rs1143627, rs16944, rs1143623, rs4848306 (block 3). Polymorphisms in IL1RN gene formed two haplotypes composed of: rs4251961 and rs 419598 (block 4) and rs315952, rs9005 (block 5) (Fig. 1).

We found a trend toward an association ($p = 0.052$) with schizophrenia of GAGG haplotype in block 3 (IL1B gene), TT haplotype ($p = 0.085$) in block 4 (IL1RN gene) and TG haplotype ($p = 0.072$) in block 5 (IL1RN gene). Haplotype CT of block 4 within IL1RN gene was found to be associated with schizophrenia ($p = 0.006$). After correction for multiple testing associations did not reach significance level. Results of haplotype analysis with schizophrenia are presented in Table 4.

Discussion

Among the polymorphisms investigated in our study, −511C/T (rs16944) has been the most extensively examined. Association studies of −511C/T (rs16944) provide contradictory results. Papiol et al. (2004) examined Spanish population and detected an excess of allele 1 (−511C) close to statistical significance when allelic frequencies of the −511C/T polymorphism were analysed in schizophrenic patients compared to controls (Papiol et al. 2004). Zanardini et al. (2003) examined 169 northern Italian schizophrenic patients and noticed that frequencies of IL1B −511C was significantly higher in patients with schizophrenia compared to controls. Shirts et al. (2006) performed a meta-analysis of IL1B −511C/T and noticed that the C allele of IL1B −511C/T polymorphism was significantly associated with schizophrenia in the Caucasian samples. However, other studies (Watanabe et al. 2007) and recent meta-analysis by Shibuya et al. (2014) failed to find an association. Also Sasayama et al. (2011) examined tagging polymorphism of IL1B gene, rs16944 and found no association with schizophrenia ($n = 533$ patients). When the analysis was performed separately in each gender the A allele of rs16944 showed a trend towards

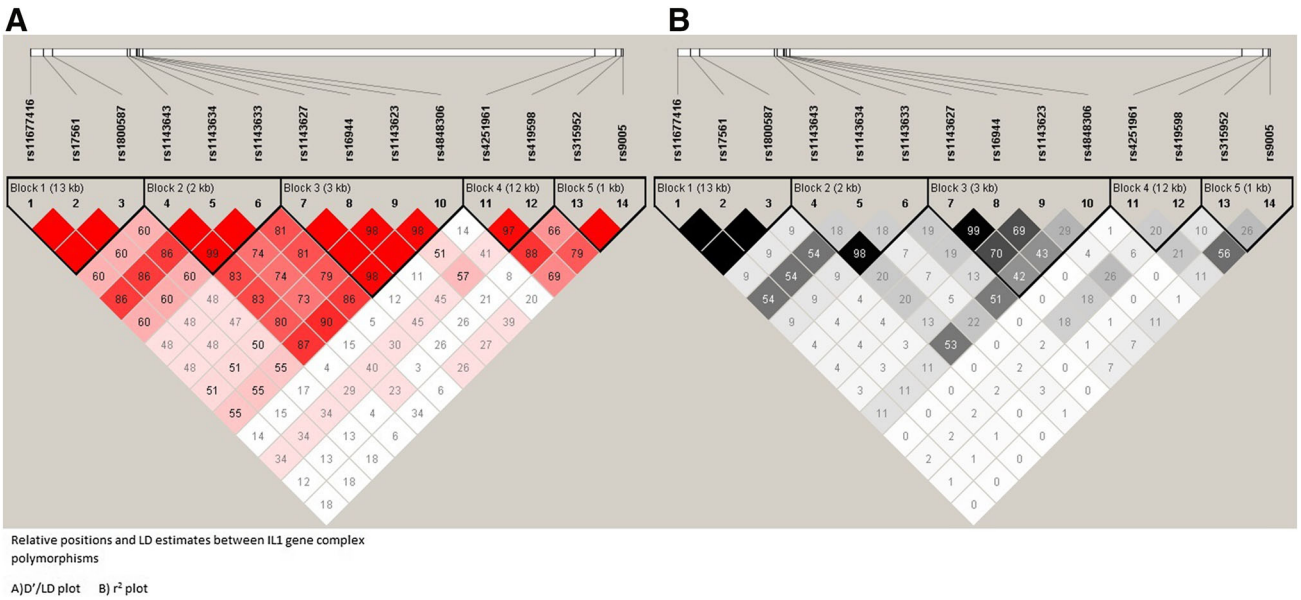

Fig. 1 Relative position and LD estimates between IL1 gene complex polymorphisms. **a** D'/LD plot, **b** r2 plot

Table 4 Haplotype association of IL1 gene complex (IL1A, IL1B, IL1RA) polymorphisms with schizophrenia in Polish population

Gene	SNP	Haplotype block	Haplotype frequency	χ^2	*p*	*p* corrected
IL1A	rs11677416	Block 1				
	rs17561	TCG	0.710	0.034	0.8539	1
	rs1800587	CAA	0.290	0.034	0.8539	1
IL1B	rs1143643	Block 2				
	rs1143634	TGT	0.386	0.064	0.8005	1
	rs1143633	CGC	0.381	1.029	0.3103	0.9952
		CAC	0.229	0.802	0.3705	1
	rs1143627	Block 3				
	rs16944	AGCA	0.478	1.476	0.2244	0.9707
	rs1143623	GAGG	0.248	3.774	0.0521#	0.556
	rs4848306	AGCG	0.200	0.577	0.4477	1
		GACG	0.072	0.027	0.8694	1
IL1RN	rs4251961	Block 4				
	rs419598	TT	0.373	2.957	0.0855#	0.7206
		CT	0.328	7.427	0.0064*	0.091
		TC	0.297	0.796	0.3724	1
	rs315952	Block 5				
	rs9005	CG	0.357	1.014	0.3139	0.9964
		TG	0.323	3.219	0.0728#	0.6792
		TA	0.320	0.638	0.4245	1

* $p < 0.01$

Trend toward an association

association with schizophrenia in female subjects. Authors suggest the possibility that the influence of IL1B gene variations on susceptibility to schizophrenia may be greater in females than in males (Sasayama et al. 2011). Rosa et al. (2004) analyzed the −511C/T polymorphism among 89 nuclear families using TDT method and revealed a trend for biased transmission of the T allele from heterozygous parents to offspring with schizophrenia. In a second

approach, they divided patients into six symptom dimensions and found a preferential transmission of the −511T allele only for the depressive symptom dimension (Rosa et al. 2004). Xu and He (2010) investigated the polymorphism rs16944 using meta-analytic techniques and found moderate significant association of schizophrenia risk in Caucasian population with −511T allele. The study suggests the IL1B gene or the IL1 gene complex may play a moderate role in the etiology of schizophrenia in the Caucasian population (Xu and He 2010). Meisenzahl et al. (2001) reported that the rs 16944 T allele (genotype T/T, C/T) was associated with bifrontal-temporal gray matter volume deficits and generalized white matter tissue deficits in patients with schizophrenia. Papiol et al. (2007) in the study on 19 schizophrenic patients of Spanish origin found a significantly lower metabolic activity in the left dorsolateral prefrontal cortex (DLPFC) in those patients with at least one allele −511T of IL1B gene with respect to patients homozygous for allele C and no significant differences in the right DLPFC. Allele −511T promotes a higher transcriptional and translational activity and expression of the gene with respect to allele −511C (Chen et al. 2006; El-Omar et al. 2000; Fatjo-Vilas et al. 2012). −511C/T polymorphism has a role in regulating the levels of IL1B gene expression, in which case it would influence neuronal activity dependent on the protein availability (Fatjo-Vilas et al. 2012). It could be hypothesized that changes in IL1B expression, maybe mediated by functional polymorphisms like −511C/T, may lead to subtle differences in neurons relevant to dopaminergic system neurotransmission (Papiol et al. 2007) and may manifest in vulnerability to schizophrenia due to the fact that dopamine system has functional importance in schizophrenia symptoms. In our study, allele A (rs16944) was significantly more frequent transmitted by parents to their children with schizophrenia.

El-Omar et al. (2000) reported that the presence of both the T allele at −511 and the C allele at promoter polymorphism (−31T/C, rs1143627) is associated with a substantially increased transcriptional activity of the gene. Polymorphism −31T/C is characterized as a transcriptional regulatory variant (El-Omar et al. 2000) and is located in the TATA-box within the core promoter of the gene and it may thus represent an interesting regulatory SNP to explain inter-individual differences in IL1B expression (Landvik et al. 2012). The presence of the variant allele C, results in disruption of the TATA-box which may modulate the binding abilities of transcription factors and regulate gene expression (Landvik et al. 2012). Borkowska et al. (2012) showed that genotypes T/C and C/C of rs1143627 in IL1B gene exerted a significant protective effect decreasing the risk of the development of paranoid schizophrenia, and allele T of rs1143627 led to an increase in the risk of paranoid schizophrenia in Polish population. Shirts et al. (2006) examined 478 cases (272 diagnosis of schizophrenia and 206 diagnosis of schizoaffective disorder) and found no association of rs1143627 with schizophrenia in the Caucasian samples. Also the results of recent case–control and family-based studies of rs1143627 by Shibuya et al. (2014) were negative. In our study, allele G [rs1143627; $p = 0.053$; OR = 1.389; 95% CI = (0.9798–1.971)] was significantly more frequent transmitted by parents to their children with schizophrenia.

We have found a trend toward an association of rs1143623 in IL1B gene with the risk of schizophrenia. Allele G [rs1143623; $p = 0.052$; OR = 1.465; 95% CI = (0.9943–2.159)] was significantly more frequent transmitted by parents to their children with schizophrenia. The results of recent case–control and family-based studies of rs1143623 by Shibuya et al. (2014) were negative. Chen et al. (2006) reported that polymorphism rs1143623 (−1464G/C) influenced transcriptional activity of the IL1B promoter. Polymorphism rs1143623 is interesting in that the rarer allele G was associated with weaker promoter activity and decreased gene expression which could be explained by lower binding at the GATA motif. In the study on the four functional IL1B promoter SNPs (−3737, −1464, −511, −31) indicated that the effect of individual SNPs on reporter gene transcription varied according to which alleles of the three other SNPs were present in the promoter construct. This fact may be one of the explanation of the inconstant results of different association studies of these polymorphisms (Chen et al. 2006).

Another commonly analyzed polymorphism was IL1B +3953C/T (rs1143634). Xu and He (2010) investigated the association of this polymorphism using meta-analytic techniques and found moderate significant associations of schizophrenia risk in Caucasian population with 3953C/T polymorphisms in the IL1B gene. No significant differences in genotype or in allelic distribution of these polymorphism were found in some case–control studies (Sasayama et al. 2011; Watanabe et al. 2007). Yang et al. (2003) investigated the TaqI polymorphism in IL1B gene (rs1143634) among 132 Chinese families (schizophrenic patients and their biological parents) of Han descent using the TDT and found no association with schizophrenia. Also the results of recent case–control and family-based studies by Shibuya et al. (2014) and the results of our study of +3953C/T (rs1143634) polymorphism were negative.

Sasayama et al. (2011) examined tagging polymorphism of IL1B gene rs1143633 for association with schizophrenia. The C allele of rs1143633 was significantly more common in patients than in controls. When the analysis was performed separately in each gender, significant difference between patients and controls in allele distribution of rs1143633 was observed only in females. Authors suggest the possibility that the influence of IL1B gene variations on

susceptibility to schizophrenia may be greater in females than in males (Sasayama et al. 2011). Earlier study in a United States population (Caucasian origin) by Shirts et al. (2006) found no significant difference in allele frequencies of rs1143633 between patients (272 diagnosis of schizophrenia and 206 schizoaffective disorder) and controls. Results of recent case–control and family-based studies by Shibuya et al. (2014) showed no significant association between rs1143633 polymorphism and schizophrenia. Also in our study we found no association of this polymorphism with schizophrenia. The inconsistent results regarding the effect of rs1143633 may be attributable to the ethnic differences (Sasayama et al. 2011).

Because four IL1B promoter SNPs (−3737, rs4848306, −1464, rs1143623, −511, rs16944, −31, rs1143627) have been indicated to regulate the transcriptional activity of the IL1B gene (Chen et al. 2006) we also performed haplotype analysis of IL1B gene and found a trend toward an association with schizophrenia of GAGG haplotype (rs1143627, rs16944, rs1143623, rs4848306) in IL1B gene.

Polymorphism at position −889 of IL1A (rs1800587) has also been extensively investigated among schizophrenic patients. The regulatory effect of the IL1A −889C/T polymorphism on basal IL1B production (Hulkkonen et al. 2000) and a possible overexpression of IL1A associated with the −889T allele was reported (Du et al. 2000). Significant case–control differences in allele or genotype frequencies were not detected (Watanabe et al. 2007; Xu and He 2010). The results of our study of –889 of IL1A (rs1800587) are also negative.

McClay et al. (2011) performed genome-wide association study and noticed that SNP rs11677416 in IL1A gene mediated the effect of olanzapine on working memory. The authors mentioned that another SNP rs17561 in IL1A gene was almost genome-wide significant and gave rise to a nonsynonymous amino acid substitution of alanine to serine at protein position 114 and suggested it as a target for future study (McClay et al. 2011). We examined both these polymorphisms (rs11677416, rs17561) and found no association with schizophrenia. Also analysis of haplotypes consist of rs11677416, rs17561, rs1800587 showed no association with schizophrenia.

We have examined other functional polymorphisms in the IL1RN gene (rs4251961, rs419598, rs315952, rs9005) and found that allele T of rs4251961 has a protective effect against schizophrenia which is enhanced by the concomitant presence of allele C (rs419598). Reiner et al. (2008) reported an association between rs4251961 with the peptidoglycan-induced production of the IL1RN protein in whole-blood samples, suggesting a potential role for this SNP in the regulation of IL1RN in response to inflammatory stimuli. They found that allele C of rs4251961 was associated with lower IL1RN production in response to the innate immune stimulus peptidoglycan (Reiner et al. 2008). Rafiq et al. (2007) found suggestive evidence that the C allele at rs4251961 that lowers IL1RN levels is associated with an increased IL1B level. Tekola Ayele et al. (2012) successfully replicated rs4251961 to be associated with IL1RN levels among African Americans population. Shirts et al. (2006) in their study did not detect any significant association of rs4251961 with schizophrenia. Case–control association studies for IL1RN rs315952 in Japanese subjects with schizophrenia (Watanabe et al. 2007) and in schizophrenia/schizoaffective disorder Caucasian samples (Shirts et al. 2006) found no association between this polymorphism and schizophrenia. As regards rs315952 we also found no association of this polymorphism with schizophrenia.

We also performed haplotype analysis of IL1RN gene and found that haplotype CT (rs4251961, rs419598) is associated with schizophrenia ($p = 0.006$).

Our results might support theory that polymorphisms of IL1 complex genes are involved in the pathogenesis of schizophrenia, however, none of the results reach significance level after correction for multiple testing. It seems advisable to carry out further examinations of the role of these polymorphisms in schizophrenia by means of TDT method and classical (case–control) association method.

To overcome the stratification problem, we used family-based analysis (TDT method) in this study. Family-based association may be less prone to false-positive findings than the approach of selecting ethnically similar controls, but because of potentially reduced power, it may be more prone to false-negative results. Focus on case-parent trios may result in a slightly different sample of cases than in other genetic studies that focused on either multiply affected families only or on unrelated cases and controls, the cases in trios usually had a younger age at onset. Patients who have both mentally healthy parents available for the study might have better social support than cases who have not mentally healthy parents available for the study. On the other hand younger age at onset is a worse prognostic factor for the course of the disorder. Most of the patients recruited for the study were young and had no general medical problems but we also excluded from the analysis 16 patients because of chronic/acute diseases or increased CRP. Exclusion the patients with comorbidity might have affected the results. This slightly different sample of cases may be the reason that some of our results are not coincident with previous studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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