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Research paper

Association of interleukin 3 (IL-3) polymorphisms with schizophrenia in Han Chinese population

Zichao Liu[a,1], Liang Huang[b,1], Dingkang Wang[a,*], Lichuan Wu[c,**]

[a] Key Laboratory of Special Biological Resource Development and Utilization of Universities in Yunnan Province, Department of Biological Science and Technology, Kunming University, Kunming, Yunnan, PR China
[b] First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi, PR China
[c] School of Chemistry and Chemical Engineering, Guangxi University, Nanning, Guangxi, PR China

HIGHLIGHTS

- We analyzed six single nucleotide polymorphisms in IL-3 with schizophrenia in Chinese population.
- We used two independent samples, including a total of 901 schizophrenia patients and 1417 healthy controls.
- The IL-3 has been reported conferring risk of schizophrenia in Irish populations, but is not significant in our Han Chinese samples.

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ABSTRACT

Schizophrenia has been observed to be associated with various abnormalities in multiple cytokines. Recent genetic analyses showed that the interleukin 3 (IL-3) gene and its receptors are significantly associated with schizophrenia, especially in Irish populations. To examine the associations of the Irish-risk single nucleotide polymorphisms (SNPs, e.g., rs3916441) in the IL-3 gene with schizophrenia in Chinese population, we utilized two independent samples from Southwestern China, including a total 901 schizophrenia patients and 1417 healthy controls. However, no statistically significant differences were observed in allelic or genotypic frequencies of the tested 6 SNPs in IL-3 between cases and controls in any sample. Therefore, the results of our analyses were not able to confirm the association of IL-3 SNPs with schizophrenia. The absence of the IL-3's association in Chinese population suggest a potential genetic heterogeneity in the susceptibility of schizophrenia on this locus and also demonstrate the difficulties in replicating associations of schizophrenia across different ethnic populations.

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1. Introduction

Schizophrenia is one of the most severe complex psychiatric disorders, and a lifetime prevalence of schizophrenia is estimated at 0.70–1.10% in general populations worldwide [7]. The essential characteristics of this disease include various psychotic symptoms, such as delusions and hallucinations, affective response, social withdrawal, apathy, and cognitive impairment [1]. Family, twin, and adoption studies have unequivocally shown a strong genetic component in schizophrenia, with the estimation of heritability at about 80% [15].

The chromosome 5q22-33 region is one of the genomic regions likely to contain risk genes for schizophrenia. Previous linkage studies have implicated chromosome 5q21-33 as a potential susceptibility region for schizophrenia [2,16,19,20,23]. There are several genes in this genomic region including SPEC2, PDZ-GEF2, ACSL6 and interleukin-3 (IL-3). Through fine-scale genetic mapping analysis using single nucleotide polymorphisms (SNPs), Chen et al. [5] found that the IL-3 gene is associated with schizophrenia in three independent samples including family and case-control samples from Irish populations, and the associations are female-specific.

IL-3, spanning 2.7 kb on human chromosome 5 and containing 5 exons, plays critical roles in both neurodevelopmental and immune systems. Interleukin 3, the protein product of IL-3, is a cytokine that induces growth and differentiation of hematopoietic stem cells and a variety of cell types originating in the bone marrow [14]. Recent studies have also demonstrated the important role of IL3 in the

* Corresponding author.
** Corresponding author.
E-mail addresses: wdk117@163.com (D. Wang), wulichuan@126.com (L. Wu).
[1] These authors contributed equally to this work.

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Table 1
Comparison of the demographic characteristics of Kunming and Yuxi samples.

	Kunming sample			Yuxi sample			*P*-value
	Case	Control	*P*-value	Case	Control	*P*-value	
Sample size	439	934	NA	462	483	NA	NA
Mean age (s.d.)	36.0 (9.1)	36.5 (7.0)	n.s.	38.7 (10.7)	37.8 (7.7)	n.s.	NA
Male/female (gender ratio)	196/243 (0.446/0.554)	419/515(0.449/0.551)	n.s.	236/226(0.511/0.489)	200/283(0.414/0.586)	<0.05	n.s.

NA—not available; n.s.—not significant.

central nervous system (CNS) [25]. A lately report found that IL-3 could promote the proliferation and survival of neural progenitors, which could finally result in human brain volume variation among healthy general populations, further confirming its important role in brain development [13]. In addition, recent investigations indicated that IL-3 can stimulate cell growth and suppress apoptosis, and dysfunction of apoptosis may be involved in the pathophysiology of schizophrenia [8]. Furthermore, abnormal activities and serum levels of interleukin 3 have been observed in schizophrenia patients compared with normal controls [21,26].

All these lines of evidence suggest that IL-3 is a plausible susceptibility gene for schizophrenia, however, most of the studies were conducted in the Irish populations, and reports in other ethnic populations were rather limited. Here, to evaluate whether IL-3 is a risk gene for schizophrenia in Han Chinese population, we conducted an association analysis of 6 SNPs in IL-3 in two independent case-control Chinese samples.

2. Material and methods

2.1. Case–control subjects

The Kunming sample consists of 439 unrelated schizophrenia patients (243 females and 196 males; mean age 36.0 ± 9.1 years) and 934 unrelated control individuals (515 females and 419 males; mean age 36.5 ± 7.0 years). Schizophrenia patients were recruited from Yunnan Mental Health Hospital and diagnosed with schizophrenia by at least two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Detailed information on the clinical onset, symptoms (positive symptoms such as delusions and hallucination, a low level of co-presence of depressive or mania symptoms due to affective dysregulations, and negative symptoms such as lack of motivation and social withdrawal etc.), the presence of personality disorders, and family history of mental illness have been recorded. Patients with head injuries, substance induced psychotic disorders, alcoholic psychosis, and other symptomatic psychoses were excluded from the present study. For the control subjects, we recruited healthy volunteers from local communities. These individuals were all asked to provide detailed information about medical and family psychiatric histories. Those people who had history of major mental disorders, drug abuse, or family history of psychiatric disorders were excluded.

The Yuxi sample is comprised of 462 unrelated schizophrenia patients (226 females and 236 males; mean age 38.7 ± 10.7 years) and 483 unrelated healthy control subjects (283 females and 200 males; mean age 37.8 ± 7.7 years). The patients were recruited from the Second People's Hospital of Yuxi City and diagnosed as having schizophrenia by at least two psychiatrists according to The International Classification of Diseases 10 (ICD-10) criterion. Detailed information on the course of clinical disorders, onset age, symptoms and family history of psychiatric illnesses were obtained. Potential participants who have history of alcoholism, epilepsy, neurological diseases, or drug abuse were excluded from this study. Meanwhile, unrelated healthy volunteers were recruited from the local communities as control subjects. These control individuals were all asked to provide detailed information about medical and family psychiatric histories. Those who had history of psychiatric disorders, psychiatric treatment, and drug abuse, alcohol dependence, or relatives having history of mental illnesses were excluded.

All the patient and control subjects are of Han Chinese origin from southwestern China. Partial of these samples have been published in previous studies [9,10,12]. All individuals were provided with written informed consent for participation, and the research protocol was approved by the internal review board of Kunming University. Demographic characteristics of these two samples are presented in Table 1.

2.1.1. SNP selection and genotyping

We chose six SNPs for genotyping in the IL-3 gene, one was located in exon 1 (rs40401, Serine to Proline), one in intron 2 (rs31481), one in the promoter (rs31480), and three in the upstream region (rs3846726, rs3916441 and rs31400). These SNPs spanned a genomic region of 38.2 kb covering IL-3 gene and its upstream. These SNPs (or haplotypes comprised by these SNPs) have shown association with schizophrenia in Irish populations [5], and in a recent study conducted by Luo et al., they also showed significant associations with brain volume [13], a biological phenotype related to schizophrenia [22]. Among these genetic markers, Luo et al. [13] demonstrated that rs31480 is a functional SNP affecting IL-3 promoter activity and expression using *in vitro* assays.

For genotyping of the SNPs, venous blood was collected from all participants. Genomic DNA was extracted from the blood sample using phenol-chloroform method. DNA samples of the cases and controls were randomly distributed in the DNA plates. The primers were designed to amplify the regions containing the selected SNPs. Details of all primers and assay conditions are available on request. The PCR reactions were performed in the 96-well plates with a total volume of 25 μl, including 10ng of genomic DNA. Genotyping was conducted using SNaPShot method on an ABI 3130 automatic sequencer, which has already been described in previous studies [11]. The genotypes of the tested SNPs were automatically called by ABI GeneMapper 4.0 and verified manually, and any assay with low quality was PCR amplified and genotyped again. To make sure of the accuracy of genotyping, we used bi-directional sequencing on randomly selected 60 individuals and no genotyping errors were found. The genotyping success rate for the three tested SNPs was more than 99.0%.

2.1.2. Statistical analysis

The Haploview program (version 4.1, Broad Institute of MIT and Harvard, Cambridge, Massachusetts) was applied to test the genotypic distribution of SNPs for Hardy-Weinberg equilibrium (HWE) between paired SNPs, and to define the haplotype blocks using the r^2 confidence interval (CI) algorithm. Allelic and genotypic associations were accessed with PLINK [17], and the results were considered significant when the corrected p-value is smaller than 0.05. To detect the significance of the difference in association separately in female or male samples, we conducted statistical analysis in each single sex group. Power calculations were performed using the software G* power.

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