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Association analysis of a functional variant in ATXN2 with schizophrenia

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ABSTRACT

Schizophrenia (SZ) is a severe mental disorder characterized by multiple neurodevelopmental dysfunctions including a breakdown of thinking process and a deficit of typical emotional responses. Ataxin-2 (ATXN2) plays vital roles in cell proliferation and growth, and functional mutations of ATXN2 cause neurodegenerative phenotypes, including spinocerebellar ataxia type 2 (SCA2) and amyotrophic lateral sclerosis (ALS). To explore the possible role of ATXN2 in SZ, we conducted a two-stage study to examine the association of ATXN2 polymorphisms with SZ in the Han Chinese population. Association analysis of seven SNPs in 768 patients and 1348 controls revealed two associated SNPs, including rs630511 (P = 1.76E−4) and rs7969300 (P = 5.08E−4). We examined these two SNPs in a validation sample of 1957 patients and 1509 controls, and observed an association of rs7969300 with SZ (P = 5.03E−3). The SNP rs7969300 is a non-synonymous SNP causing a Ser to Asn substitution, which is predicted to increase the protein stability of ATXN2. Our data suggest that the ATXN2 gene may confer vulnerability for SZ, adding further evidence for the genetic variants within the developmental pathway in the illness.

1. Introduction

Schizophrenia (SZ) is a severe mental disorder characterized by profound disruption in cognition and emotion, affecting the most fundamental human attributes: language, thought, perception, affect, and sense of self. The onset of the illness is typically in late adolescence or early adulthood. The neurodevelopmental hypothesis has received much support from epidemiological, developmental and neuroimaging studies [24] and has been the dominant paradigm for SZ research over the past two decades [16]. This hypothesis posits that SZ has its origins in disturbed development of the nervous system, in which cerebral insults occur during early brain development, long before the full-blown of the illness.

It has been shown that ATXN2 protein plays a direct role in translational regulation by associating with polyribosomes [21] and is mainly localized at the rough endoplasmic reticulum [23]. ATXN2 also participates in the formation of stress granules (SGs), where untranslated mRNAs are translationally inhibited during conditions of cell stress [15,19]. Animal studies showed that over-expression of ATXN2 potentiates toxicity from neurodegenerative disease proteins [2], while the deficiency of ATXN2 could cause mice to grow to excessive size and weight, through modulation of insulin signaling [11,12]. Thus, ATXN2 is a relevant regulator of general cell growth.

A majority of human population carry a repeat size of 22–23 CAG triplets coding for glutamine in ATXN2 exon 1 [17], and only individuals having a polyQ-repeat of 32 CAGs or more may develop SCA2, with larger repeat sizes resulting in a more severe disease course and earlier manifestation [1], while triplets between 27 and 33 are viewed as intermediate size expansions which result in a higher risk for related neurodegenerative diseases such as ALS and progressive supranuclear palsy [4,8,20]. In addition, ATXN2 has been shown to be associated with longevity among human centenarians [22], microcirculation [10] and blood pressure [6].

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Recently, we detected an association of a polymorphism within the breast cancer suppressor protein associated protein (BRAP) gene with SZ (P = 1.43E−6, unpublished data). BRAP lies at the upper stream of ATXN2. Given the recognized link between neurodevelopmental abnormalities and SZ, we hypothesized that the ATXN2 gene may influence the genesis of SZ. In this work, we aimed to evaluate the association of BRAP polymorphisms with SZ in a two-stage study. In the screening stage, we derived relevant data from our GWAS data [25], involving seven SNPs in 768 SZ cases and 1348 healthy controls. In the validation stage, we aimed to replicate the two significant SNPs in 1957 cases and 1509 controls. Finally, we sought to predict the potential functions of rs7969300.

2. Materials and methods

2.1. Subjects

All participants were unrelated Han Chinese recruited from northern China. The initial GWAS sample consisted of 768 unrelated subjects with SZ (360 males and 408 females) and 1348 control subjects (658 males and 690 females). For validation, an independent sample consisting of 1957 cases (1037 males and 920 females) and 1509 controls (360 males and 1149 females) was recruited from northern China. The SZ cases were recruited from inpatients of hospitals. The consensus diagnoses were made by at least two experienced psychiatrists according to the Diagnosis and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for SZ. Patients with other major psychosis, including major depression, bipolar disorder, or severe medical complications, including stroke, epilepsy, and diabetes mellitus, were excluded from the study. Healthy controls were recruited by advertisements during physical examination from communities with simple non-structured interview performed by psychiatrists, who excluded individuals with history of mental health and neurological diseases. The controls were paid for their participation.

The study was approved by the Medical Research Ethics Committee of the Institute of Mental Health, Peking University. All participants enrolled in the study signed written informed consent.

2.2. Genotyping

Peripheral blood samples were collected from all subjects. Genomic DNA was extracted using the Qiagen QIAamp DNA Mini Kit. In the screening stage, we derived genotypes of seven SNPs in ATXN2 from our GWAS data [25], involving rs2301621, rs6490162, rs630512, rs607316, rs616668, rs7969300, and rs653178. In the validation stage, the genotypes of rs630512 and rs7969300 were determined using the Sequenom MassARRAY system (Sequenom iPLEX). 1957 cases and 1059 controls were successfully genotyped, the calling rate being 99.91%.

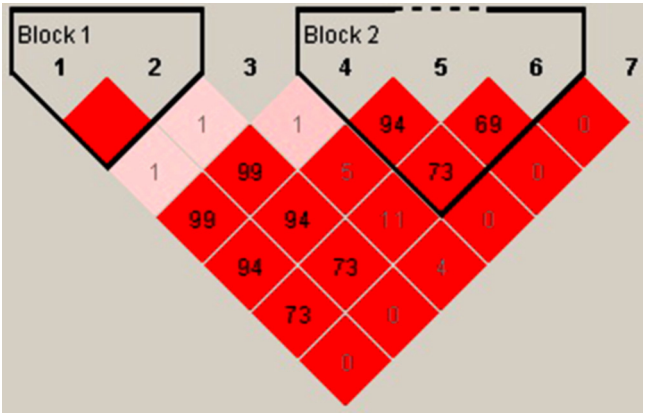

Fig. 2. LD pattern of the six SNPs. rs2301621 and rs6490162 are in complete LD, while rs607316, rs616668, and rs7969300 are in a block.

2.3. Bioinformatics analysis

Genetic association tests were analyzed using PLINK v1.07 [18]. Genetic power was estimated by PS [3]. Protein–protein interaction network was predicted using STRING v9.1 [5]. Finally, we predicted the function of rs7969300 via the on-line tool F-SNP (http://compbio.cs.queensu.ca/F-SNP/) [13] and iPTREE-STAB (http://210.60.98.19/IPTREEr/iptree.htm) [9].

3. Results

3.1. Genetic association

As seen in Fig. 1, the six genotyped SNPs span most part of the ATXN2 gene. Genotypic distributions of the ATXN2 SNPs in the two samples did not deviate from Hardy–Weinberg equilibrium (HWE) in either the patient group or the control group (P > 0.01). The linkage disequilibrium (LD) of the six SNPs is shown in Fig. 2. Two SNPs were found to be associated with SZ, including rs630512 (P = 1.76E−4, OR = 1.51) and rs7969300 (P = 5.08E−4, OR = 1.25) (Table 1). One SNP, rs7969300, was replicated in the validation data set, with the G-allele conferred risk for SZ (P = 5.03E−3, OR = 1.15), while the other SNP failed to be replicated (Table 1). Thus, rs7969300 was considered be consistently associated with SZ across the two samples. In the combined sample, rs7969300 G-allele conferred risk for SZ (P = 3.65E−7), with an OR of 1.21 (Table 1).

3.2. Protein interaction network

ATXN2 can interact with other proteins, direct interacting partners including SH3GL2 (SH3-domain GRB2-like 2), SH3GL3

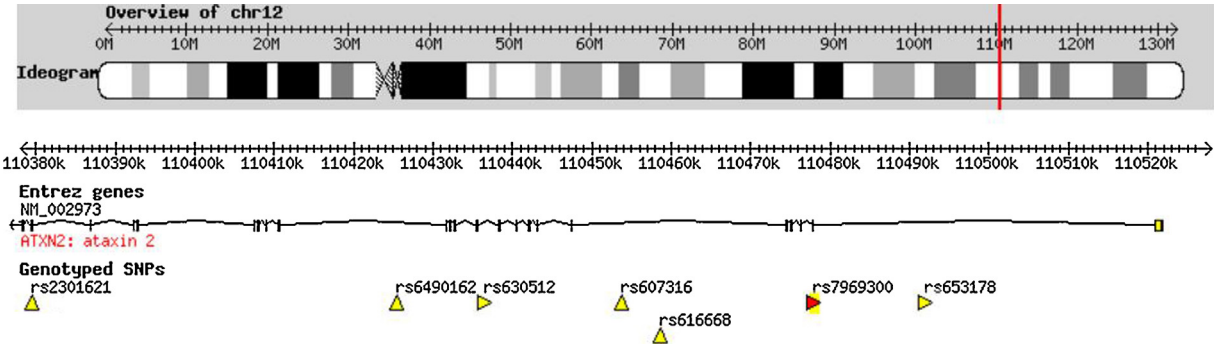

Fig. 1. Chromosome location of the six genotyped SNPs.