Brief report

Lack of association of NALCN genetic variants with schizophrenia

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Abstract

NALCN (sodium leak channel, non-selective) is located on chromosome 13q (suggested linkage region for schizophrenia). We analyzed 21 polymorphisms in 464 schizophrenia subjects, 220 controls subjects and 119 small nuclear families. We observed nominal association with rs9518320 and rs9518331, suggesting that NALCN is not related to schizophrenia risk.

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1. Introduction

Schizophrenia affects about 1.0% of the population worldwide. Evidence increasingly suggests that schizophrenia is a disorder of brain development and plasticity (Eichhammer et al., 2004). Genetic studies have recently begun to identify strong candidate risk genes for schizophrenia, and neurobiological studies of the normal and variant forms of these genes are advancing (Chumakov et al., 2002). Linkage and association studies have implicated several loci in the genome that likely harbor genes conferring risk for schizophrenia. A meta-analysis suggested the existence of susceptibility genes on chromosomes 8p, 13q and 22q (Badner and Gershon, 2002). Among other genes, the 13q region contains G72 (or DAOA at 13q33.2). Several individual replication studies and a meta-analysis have supported the association of G72 with schizophrenia, although the associated alleles and haplotypes are not identical across studies and some polymorphic variants are located outside of the gene.

In this region, 13q33.1, 4.1Mb upstream of G72 is located in the NALCN (also known as VGCNL1). NALCN is a highly conserved protein in mammals (99% identity between human and rat). Close homologues are also found in invertebrates (Humphrey et al., 2007; Yeh et al., 2008).

NALCN mRNA expression has been shown in the cerebral cortex and hippocampus in all neurons and layers (Lee et al., 1999; Lu et al., 2007). NALCN mutant mouse neonates do not display gross abnormalities in embryonic development, righting responses, spontaneous limb movement, and toe/tail pinch responses, but do not survive beyond 24 h after birth (Lu et al., 2007). NALCN encodes a voltage-independent, non-selective, non-inactivating cation channel permeable to sodium, potassium and calcium when exogenously expressed in HEK293 cells (Lu et al., 2007). In vivo, the NALCN channel appears to be the main source of the background sodium leak in the hippocampal neurons at rest and is important for neuronal excitability (Lu et al., 2007). Both hippocampal activity and neuronal excitability are processes strongly altered in schizophrenia (Eichhammer et al., 2004; Oxley et al., 2004). Because the function of NALCN is consistent with that manifested in some schizophrenia symptoms, and its location is within a suggestive chromosomal linkage region for schizophrenia, we hypothesized that NALCN may show a genetic association with schizophrenia. To test this hypothesis, we performed an association study using case-control and family-based approaches.

2. Methods

All recruitment and clinical assessments were conducted with written informed consent in accordance with the Declaration of Helsinki and approval of the institutional ethics review board. We recruited 464 subjects (male/female ratio = 2; age 36 ± 8, 82% Caucasians) with a DSM-III-R or DSM-IV diagnosis of schizophrenia at the Centre for Addiction and Mental Health (n = 321), Case Western Reserve University (n = 94) and
We implemented transmission disequilibrium test haplotype analysis and 1000 permutations were performed using Haploview 4.1. Single marker analysis showed two variants nominally associated with schizophrenia in the case-based sample (data not shown).


