A sex-specific role of CACNA1C in longitudinal functioning in major psychiatric disorders

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Abstract

Longitudinally defined phenotypes are instrumental in finding a genetic basis for disease severity and the degree of recovery from episodes of psychiatric disturbance. Past studies have reported on a sex-specific role for CACNA1C in the field of psychiatric genetics. Here, we investigated a potential sex-specific role of CACNA1C in functional recovery. Our results indicate CACNA1C to play a strong sex-specific role in recovery from schizophrenia-spectrum (SZspec) but not bipolar disorder (BD) episodes. In women, but not men, suffering from SZspec disorders, the CACNA1C minor allele was associated with worse recovery from illness episodes. These results underscore the need for longitudinal and sex-specific analyses in psychiatric genetics.

Introduction

For several decades, psychiatric genetic research has focused on cross-sectionally defined phenotype definitions. However, course of illness in psychiatric disorders has long been recognized to vary substantially between individuals and diagnoses. Studying the genetic underpinnings of the longitudinal course may thus serve as an avenue into disentangling the genetic heterogeneity of major psychiatric disorders. A well-known gene in the field of psychiatric genetics is CACNA1C on chromosome 12p13, coding for a subunit of the L-type calcium channel. Genome-wide association studies (GWAS) have demonstrated a role of the CACNA1C single-nucleotide polymorphism (SNP) rs1006737 in susceptibility to BD and schizophrenia. Furthermore, we could recently report on a distinct sex-specific relationship of CACNA1C with potentially illness-associated endophenotypes in the general population, such as resilience factors (Strohmaier et al., 2013). Given the general role of CACNA1C in psychopathology, we hypothesized that the aforementioned SNP may also affect functional improvement following episodes of bipolar and SZspec disorder.

Table 1: Descriptive statistics of samples and the CACNA1C proxy SNP rs10774035

	SZspec	BD
Sample size (n)	306	530
Sex (% females)	45.1	54.5
Recovery (GAS differential, mean±SD)		
All	37.4±15.3	49.2±16.3
Males	35.4±14.7	48.8±15.9
Females	40.0±15.7	49.5±16.6
CACNA1C proxy SNP *rs10774035*		
Genotype counts (CC/CT/TT)	125/140/41	235/233/62
MAF (95% CI)	0.36 (±0.04)	0.34 (±0.03)
HWE p	0.902	0.698

Table 2: Parametric test for a sex-specific influence of CACNA1C rs10774035 on recovery, assuming an additive mode of inheritance and adjusted for age

	SZspec		BD	
	Estimate (GAF units)	p	Estimate (GAF units)	p
CACNA1C rs10774035	0.662	0.707	0.099	0.950
Sex	**8.351**	**0.001**	0.312	0.878
Sex**CACNA1C* rs10774035	**-4.816**	**0.059**	0.486	0.819

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Methods

CACNA1C polymorphism

We used the SNP rs10774035 to assess variations in CACNA1C. This SNP is located in an intronic region of the CACNA1C gene (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=10774035) and is in complete linkage disequilibrium (SNAP database http://www.broadinstitute.org/mpg/snap/) with the SNP rs1006737 (r2=1 and d'=1) for which several psychiatric associations have been reported (e.g. Green et al., 2010; Roussos et al., 2011; Green et al., 2012; Roussos et al., 2013). Genotyping and quality control have been described in detail elsewhere (Cichon et al., 2011; Rietschel et al., 2012). Briefly, DNA was extracted from whole blood using standard methods. Genotyping was performed using Illumina HumanHap550v3, Illumina Human610, and Illumina Human 660w quad bead chips (Illumina San Diego, CA, USA).

Phenotype

The Global Assessment of Functioning (GAF) scale is an instrument used to assess psychosocial functioning. We used GAF values collected at different time points (see below) as the phenotype of interest.

The GAF scale was initially developed by Luborsky (1962), a modified version was included in the DSM-III-R (axis V; Cooper & Michels, 1988). The GAF scale measures psychological, social and vocational functioning on a hypothetical health-illness continuum ranging from 0 to 100. Briefly, values of 100 to 91 correspond to superior psychosocial functioning, whereas values of 10 to 0 are used to describe the low end of this continuum in which an individual needs constant supervision.

In the present study, we used GAF information obtained for two time points:

(1) Current status. If the interview took place during an illness episode, psychosocial functioning was assessed prior to this illness episode.

(2) The worst value ever present during an illness episode.

The difference between these two values ("current status" minus "worst ever") served as a simple measure for the degree of recovery from episodes of psychiatric disorder. The following predictors were present for all subjects: age at the time of interview, sex and rs10774035 genotype.

Statistical analyses

All statistical analyses were carried out using the R language (version 2.14.1; R Development Core Team, 2009). The BD and the SZspec sample were each tested for sex*genotype interaction using a parametric model with additive mode of inheritance for rs10774035. If evidence for a sex*genotype interaction (p<0.1) was established, men and women were subsequently analyzed separately with a non-parametric maximum test (Konietschke et al., 2012) implemented in the R package nparcomp (analogous to the approach of Strohmaier et al., 2013). The non-parametric maximum test includes the additive, recessive and dominant modes of inheritance and is robust against variance heterogeneity).

Samples

We analyzed the SZspec (N=306) and the BD sample (N=530) separately. Details of the samples and rs10774035 are given in Table 1.

Results

The parametric model suggested a sex*genotype interaction in the SZspec sample (p=0.06) but not in the BD sample (p=0.82; Table 2). Sex-stratified analyses of SZspec with the non-parametric maximum test (R package nparcomp) suggest a dominant effect of rs10774035 in SZspec women (overall p-value <0.001, Figure 1) but no significance was reached in SZspec men (overall p-value: 0.250, Figure 2)

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Figure 1: CACNA1C genotype is associated with functional recovery in SZspec females

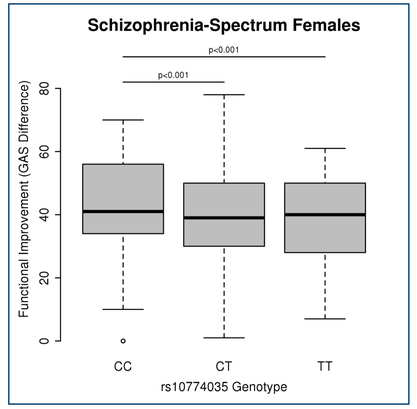
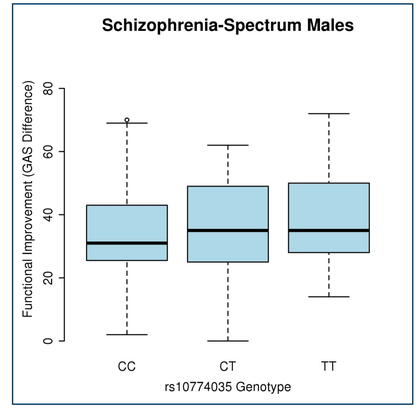


Figure 2: CACNA1C genotype is not associated with functional recovery in SZspec males



Discussion

In line with previous findings on sex-specific effects of CACNA1C, we could also observe such effect to be present in longitudinal measures of recovery in female but not male SZspec patients. Whereas in the general population, the minor allele of CACNA1C has been described to be associated with protective personality traits such as resilience factors (Roussos et al. 2011, 2013; Strohmaier et al., 2013), the present study suggests that the same allele has a negative effect on recovery following illness episodes. This suggests different CACNA1C-mediated effects for disease vulnerability in the general population vs. recovery in psychiatric patients. Besides, we found higher recovery values for women, independent of genotype status, which is well known (e.g. McGlashan & Bardenstein, 1990; Grossman et al., 2006). Notably, the effect size of the genotype*sex interaction is -4.8 GAF units per risk allele, about the same magnitude as the mean difference in recovery between men and women. Our investigation underscores the need for longitudinal and sex-specific analyses in psychiatric genetics.

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