

Evidence for the impact of the CACNA1C risk allele rs1006737 on 2-year cognitive functioning in bipolar disorder

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A recent 2-year naturalistic study on cognitive functioning in bipolar patients showed significant variations in cognitive functioning over time, largely independent of clinical factors (Arts *et al.*, 2011). The CACNA1C (α 1C subunit of the L-type voltage-gated calcium channel) risk allele (rs1006737) is associated with a risk of bipolar disorder across samples, with highly consistent replications in recent GWAS studies (Lett *et al.*, 2011).

The aim of the present study was to examine the association of the CACNA1C risk allele (rs1006737) with longitudinal cognitive functioning in a European sample of patients with bipolar disorder and in two groups at a high and an average genetic risk for bipolar disorder: first-degree relatives and healthy controls.

Individuals were participants in the BIPOLCOG (BIPOLar and COGnition) study (Jabben *et al.*, 2009). The final risk set for analysis included 51 patients, 34 first-degree relatives and 50 healthy controls. Genetic material was collected at the first visit.

Patients were examined at 2-monthly intervals over a period of 2 years, yielding 12 assessments of cognitive functioning over the 2-year period. Cognitive measures were standardized; raw test scores were converted into standardized z -scores against the means and SD of the healthy control group (tested twice over 4 months). The final composite measure of neurocognition was based on the means of the five domain scores (verbal memory, sustained attention, selective attention, attentional span and working memory).

Regression analyses were carried out using the statistical software program STATA (version 11.2) (StataCorp, 2002). The Bonferroni correction for multiple testing yielded a corrected P -value of less than 0.0045 (0.05/11).

Genotype effects under a – statistically most conservative – recessive genetic model were estimated by comparing the differences between GG versus AG and GG versus AA.

Analysis of SNP rs1006737 showed the following in bipolar patients: six patients were homozygous for the risk allele (A/A), 21 patients were heterozygous (A/G)

and 24 individuals belonged to the nonrisk group (G/G). In the group of first-degree relatives (assessed twice over 4 months), only one patient was homozygous for the risk allele; 15 relatives were heterozygous and 18 belonged to the nonrisk group. Finally, two healthy controls were homozygous for the risk allele, 24 were heterozygous and 24 carried the nonrisk allele. Genotypes in all groups were in Hardy–Weinberg equilibrium ($P > 0.1$ for all).

The AG genotype was not associated with any of the cognitive measures in bipolar patients. The AA genotype, however, was associated with poorer cognitive performance on several tasks, particularly in the area of speed of processing ($-0.27 < \beta < -0.18$; $0.048 < P < 0.011$). However, none of the individual cognitive tests survived Bonferroni correction. The composite cognitive measure, however, survived correction with a moderate effect size of -0.26 ($P = 0.003$; $N_{\text{obs}} = 392$).

The finding of a negative association between the AA genotype and the composite cognitive measure could be replicated in neither relatives ($N_{\text{obs}} = 62$; $\beta = 0.06$; $P = 0.647$) nor controls ($N_{\text{obs}} = 91$; $\beta = -0.03$; $P = 0.82$).

Patients with bipolar disorder showed a negative effect of the CACNA1C risk allele rs1006737 on a composite cognitive measure, only apparent in the group homozygous for this allele, fitting a recessive model. This finding could not be replicated in a group of first-degree relatives or in healthy controls, indicating interactions with background genetic factors associated with bipolar disorder.

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Conflicts of interest

Jim van Os is/has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, AstraZeneca, Pfizer and Servier, companies that have an interest in the

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