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CACNA1C as a risk factor for schizotypal personality disorder and schizotypy in healthy individuals

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To the Editors:

The *CACNA1C* gene codes for the pore-forming a1C subunit of the L-type voltage-gated calcium channel and plays an important role in synaptic plasticity, memory formation, learning and behavior (Bhat et al., 2012). The *CACNA1C* rs1006737 variant has been associated with bipolar disorder (BD) (Ferreira et al., 2008) and schizophrenia (Nyegaard et al., 2010). Furthermore, the same allele has been associated with increased hippocampal and

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Author contributions

P.R., P.B. and L.J.S. conceptualized the study, and performed statistical analyses. P.R., P.B and S.G.G. performed behavioral analyses in the LOGOS cohort. M.M.M., E.A.H., A.S.N. and L.J.S. performed behavioral analyses in the schizotypal personality cohort. All authors contributed to the interpretation of data, drafting the Letter and final approval of the manuscript. P.R. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

prefrontal activity during emotional processing and executive cognition, respectively (Bigos et al., 2010), reduced bilateral hippocampal activation during episodic memory recall (Erk et al., 2010), increased paranoid ideation (Roussos et al., 2011), and increased expression of *CACNA1C* mRNA in human brain (Bigos et al., 2010). Psychosis is an overlapping feature of both schizophrenia and BD, and it has been suggested to represent a clinical manifestation of shared genetic liability between these two psychiatric illnesses (Craddock et al., 2009). In this study, we provide further support of this notion by replicating our previous findings (Roussos et al., 2011) and demonstrating that rs1006737 is also a risk factor for schizotypal personality disorder (SPD).

Healthy subjects were recruited from the first (n=530) and second (n=334) wave of the Learning on Genetics of Schizophrenia (LOGOS) study. The recruitment of healthy controls (n=48) and SPD patients (n=50) has been described elsewhere (McClure et al., 2008). Briefly, the majority of SPD patients (90%) were recruited through advertisement in local newspapers and the remaining through referrals from outpatient psychiatric clinics at the Bronx Veterans Affairs Medical Center and Mount Sinai Medical Center. Participants provided written informed consent in accordance with the Institutional Review Board guidelines. All participants were evaluated by doctoral-level clinical psychologists with the Structured Interview for DSM-IV Personality (SIDP-IV) (Pfohl et al., 1997), and diagnoses were reached in a consensus meeting with an expert diagnostician (M.M.M.). The overall symptom-severity score for the cohort of patients with SPD was calculated based on each of the nine DSM-IV symptom criteria for SPD on a 4-point Likert-type scale (0=absent, 0.5=mild, 1.0=moderate, and 2.0=severe) grouped into three composite scores: cognitive impairment, interpersonal deficits, and paranoia. Subjects in the LOGOS cohort were assessed with the Schizotypal Traits Questionnaire (STQ). Table 1 describes the demographic characteristics of the LOGOS and SPD cohorts. All subjects were of Caucasian ancestry on the basis of self-report, as well as using a panel of ancestry informative unlinked markers.

Genotyping was performed blind to phenotype measures by K-Biosciences (Herts, UK; <http://www.kbioscience.co.uk/>) as described elsewhere (Roussos et al., 2011). Call rate was 0.992, and no deviation from the Hardy–Weinberg Equilibrium was observed in any cohort (Table 2). Association analysis for qualitative (disease status in the SPD cohort) and quantitative traits (STQ in the LOGOS, and cognitive impairment, interpersonal deficits and paranoia in the SPD cohorts) was conducted with the UNPHASED package (<http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/>) (Dudbridge 2008). Analysis of the demographic variables was performed based on Student's t-test or the nonparametric Mann–Whitney–Wilcoxon test using SPSS (version 20; IBM, Armonk, NY).

The rs1006737 'A' allele was associated with the Paranoid Ideation subscale in the LOGOS I (p=5.0 × 10^{-4}) and II (p=0.03) cohorts. Combined analysis of both cohorts showed a significant association for Paranoid Ideation (p=5.0 10^{-5}) and Unusual Experiences (p=0.03). The same allele increased the risk for SPD (p=0.03, OR=1.91) and was associated at a trend level with Paranoia in the SPD patient group (p=0.053) (Table 2).

The rs1006737 is associated with increased paranoid ideation as measured by the STQ in two distinct cohorts of healthy individuals, with SPD, and with the subphenotype of paranoia within the SPD patient group at a trend level. One limitation of our study is the small size of the SPD cohort, and further examination of the relationship between this single nucleotide polymorphism (SNP) and the schizotypal domains is warranted in future studies. However, the replication of previous results (Roussos et al., 2011) of increased schizotypy, as well as the same directionality of the effect (same risk allele), in all our cohorts and the existing literature in schizophrenia and BD, makes less likely that our SPD findings are a statistical artifact. These findings are consistent with the notion that common genetic risk factors for psychiatric disorders are penetrant in non-clinical and spectrum individuals. Furthermore, they provide a plausible link between enhanced genetic risk through inheritance of *CACNA1C* genotypes and the development of schizophrenia and BD through a "psychosis pathway", which involves increased schizotypy in the clinical phenotype.

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Table 1

Demographic and clinical characteristics of the LOGOS cohorts I and II and the SPD patients group.

	LOGOS cohort		SPD cohort		
	LOGOS I	**LOGOS II**	**SPD**	**CON**	***p*-Value**
Sample size	527	331	50	48	–
Age (years)	23.2 (0.2)	23.6 (0.2)	33.8 (1.5)	33.1 (1.5)	0.7
Gender (male/female)[b]	527/0	331/0	31/19	28/20	0.8
Education (years)[a]	15.3 (0.1)	15.6 (0.2)	14.4 (0.5)	17.4 (0.8)	0.003

LOGOS, Learning on Genetics of Schizophrenia; SPD, schizotypal personality disorder; CON, control individuals. Data are expressed as mean (SEM).

[a] For these measures, the nonparametric Mann–Whitney–Wilcoxon procedure was applied.

[b] Chi square comparison.

Table 2

Association analysis of rs1006737 and STQ in the LOGOS cohorts I and II and the SPD patients group.

LOGOS cohort		**LOGOS I (*n*=527)**		**LOGOS II (*n*=331)**		**Combined LOGOS I/II**	
A/G allele counts (MAF)		287/767 (0.27)		191/471 (0.29)		478/1238 (0.28)	
HWE: χ^2 (*p*-value)		1.17 (0.3)		0.01 (0.9)		3.14 (0.08)	
		χ^2 (*p*-value)	Add value	χ^2 (*p*-value)	Add value	χ^2 (*p*-value)	Add value
STQ	Paranoid ideation	**12.2 (0.0005)**	0.09	**4.5 (0.03)**	0.07	**16.6 (0.00005)**	0.08
	Magical thinking	1.7 (0.19)	0.04	1.9 (0.17)	0.05	3.5 (0.06)	0.04
	Unusual experiences	**3.7 (0.052)**	0.06	0.9 (0.35)	0.04	**4.6 (0.03)**	0.05
SPD cohort		SPD (*n*=50)	CON (*n*=48)	Symptom-severity score		χ^2 (*p*-value)	Add value
A/G allele counts (MAF)		44/56 (0.44)	28/68 (0.29)	Cognitive impairment		2.4 (0.12)	0.21
HWE: χ^2 (*p*-value)		0.01 (0.9)					
χ^2 (*p*-value)		**4.6 (0.03)**		Interpersonal deficits		0.1 (0.73)	0.05
OR (95% CI)		1.91 (1.06–3.45)		Paranoia		3.7 (0.053)	0.26

The rs1006737 allele is located at chromosome 12: 2345295 (NCBI Build 37, February 2009). *p* Values are calculated from chi square based on d.f.=1. Add value represents the estimated additive genetic value for the minor allele relative to the more common allele. The *p*-values <0.05 are in bold. HWE, Hardy–Weinberg equilibrium; STQ, Schizotypal Traits Questionnaire; LOGOS, Learning on Genetics of Schizophrenia; schizotypal personality disorder; CON, control individuals; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval.

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