Schizophrenia Research 154 (2014) 42–47

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The CSMD1 genome-wide associated schizophrenia risk variant rs10503253 affects general cognitive ability and executive function in healthy males

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ARTICLE INFO

Article history:
Received 6 September 2013
Received in revised form 24 January 2014
Accepted 17 February 2014
Available online 11 March 2014

Keywords:
Cognition
Executive function
Endophenotypes
CSMD1 gene
Schizophrenia

ABSTRACT

Background: The single-nucleotide polymorphism (SNP) rs10503253, located within the CUB and Sushi multiple domains-1 (CSMD1) gene on 8p23.2, has reached genome-wide support as a risk factor for schizophrenia. There is initial but inconclusive evidence for a role of this variant in aspects of cognition.
Methods: We investigated the neurocognitive effects of the CSMD1 rs10503253 (C/A) polymorphism in a large, demographically homogeneous sample of young, healthy Greek Caucasian males (n = 1149) phenotyped for a wide range of neuropsychological measures, most of which have been shown to be reliable endophenotypes for schizophrenia.
Results: The risk 'A' allele was associated with poorer performance on measures of general cognitive ability, strategy formation, spatial and visual working memory, set shifting, target detection and planning for problem solving but not for emotional decision making. Most of these effects were dependent on risk "A" allele dose, with AA and CC homozygotes being the worse and the best respectively, while CA individuals were intermediate. Potential genotype effects in Stroop and verbal memory performance were also suggested by our dataset.
Discussion: These results underline the relevance of the risk "A" allele to neurocognitive functioning and suggest that its detrimental effects on cognition, may be part of the mechanism by which the *CSMD1* mediates risk for schizophrenia.

1. Introduction

General cognitive dysfunction is a core stable trait-like feature of the schizophrenia (SCZ) syndrome, that follows the pattern required of an endophenotype (Gottesman and Gould, 2003): it is observed in SCZ patients prior to illness onset, is largely independent of clinical state and medication status, and is familial in nature (Keshavan et al., 2010; Lewandowski et al., 2011; Keefe and Harvey, 2012). Extensive family and twin data support the role of shared additive genetic factors underpinning both SCZ and cognitive deficits (e.g., Toulopoulou et al., 2010). Also, it has been recently demonstrated, that SCZ polygenic risk scores can predict the total brain and white matter volume (Terwisscha van Scheltinga et al., 2013) and general cognitive ability in the general population (McIntosh et al., 2013), suggesting that, general cognitive ability shares genetic risk with the disease, and may be part of the neural mechanism by which risk is mediated. Several genetic variants that are associated with SCZ have emerged from genome-wide association studies (GWAS) (Ripke et al., 2011; Smoller et al., 2013), but their role in illness pathophysiology remains unclear. One important direction of research effort in the post-GWAS era is the characterisation of the functional effects of novel and poorly understood risk variants on critical 'intermediate' phenotypes such as general cognitive ability. Healthy subjects drawn from the general population are a good model to study the effects of SCZ risk variants on the central nervous system, as they are devoid of confounds related to illness process and state. This research effort has already provided important insights into the neural mechanisms by

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http://dx.doi.org/10.1016/j.schres.2014.02.017
0920-9964/

which these variants increase risk for disease (Meyer-Lindenberg, 2010; Roussos et al., 2011a, 2011c, 2012a, 2013a).

From the five novel variants identified in the largest SCZ GWAS to date (Ripke et al., 2011), the SNP rs10503253 located within the CUB and Sushi multiple domains-1 (CSMD1) gene on 8p23.2, seems important given previous evidence of its association with risk for multiple neurodevelopmental disorders (Shimizu et al., 2003; Glancy et al., 2009; Håvik et al., 2011). Furthermore, a recent, joint analysis in five major psychiatric illnesses (autism, ADHD, MDD, BD and SCZ) reported a disorder-specific effect for the rs10503253 and SCZ (Smoller et al., 2013). These results support a "central" role of the rs10503253 as a risk factor of SCZ. In a recent study, the CSMD1 SCZ risk 'A' allele at rs10503253 was associated with poorer performance on neuropsychological measures of general cognitive ability (IQ) and memory function but not attentional control (Donohoe et al., 2013) in two independent case-controlled cohorts. However, the effects of the risk "A" allele were subtle and varied between samples in a non-task specific manner, raising the likelihood of false positives due to small sample sizes.

This interesting but inconclusive first evidence motivated us to investigate the effects of rs10503253 on neuropsychological function in a large, demographically homogeneous sample of young, healthy Greek Caucasian males from the LOGOS study (Roussos et al., 2011a, 2011b, 2011c; Jutras-Aswad et al., 2012; Roussos et al., 2012a; Giakoumaki et al., 2013; Roussos et al., 2013a, 2013b). We tested the hypothesis that the risk allele would be associated with reduced IQ and executive function/memory performance.

2. Methods

2.1. Study participants

Subjects were recruited from the first wave of the LOGOS (Learning On Genetics Of Schizophrenia Spectrum) study. The LOGOS project examined 1149 randomly selected young male conscripts from the Greek Army (mean age 21.95 ± 3.5; range: 18–29), who met the inclusion/exclusion criteria (see below) between June 2008 and December 2010. The study took place between 9 am and 3 pm in the medical quarters of the Military Training Camp of Candidate, Supply Army Officers (SEAP) in Heraklion, Crete. For this purpose, two adjacent rooms in the medical quarters were converted into testing rooms. Following public presentation of the study's methods and goals in each consecutive series of new conscripts, all participants willing to volunteer, had a detailed information sheet and gave written informed consent before screening. All subjects were tested on one single occasion at some point during their two month military training in this establishment. The study was approved by the Ethics Committee of the University of Crete, the Executive Army Bureau and the Bureau for the Protection of Personal and Sensitive Data of the Greek State, and was carried out in accordance with The Declaration of Helsinki. All subjects had been recently screened for current physical and mental health status by the army medical authorities and were physically healthy and free from serious mental illnesses. However, they all underwent a review of their medical history, Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998), urine toxicology and IQ testing with the Raven's Progressive Matrices. Inclusion criteria were (i) healthy male recent conscripts; (ii) right handed; and (iii) informed consent (met by 1254 subjects). Exclusion criteria were (i) personal history of head trauma and medical or neurological conditions; (ii) current use of prescribed drugs or a positive recreational drug screen; and (iii) personal history of DSM-IV Axis I disorders. Based on these criteria, 105 subjects were excluded [38 subjects (3.3%) with a history of head trauma and medical or neurological conditions and 67 subjects (5.34%) with a history or presence of an Axis-I disorder (4.3% with recent history of substance/alcohol abuse and 1.04% with panic, anxiety, depression, insomnia)].

2.2. Genotyping

DNA was extracted from blood or cheek swab samples, using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). For N = 833 subjects, the rs10503253 genotype was extracted from available genome-wide genotyping SNP profiling with the Illumina HumanOmniExpress BeadChip (San Diego, CA, USA) (Roussos et al., 2013a). The genotype for another 316 subjects was determined by direct sequencing on the Applied Biosystems (ABI) 3100 genetic analyzer (Applied Biosystems, Foster City, CA, USA). Primers and conditions for polymerase chain reaction (PCR) amplification are described in Supplement. Genotyping was performed blind to phenotype measures. Genotyping quality control was performed in 50 randomly selected samples (N = 40 included in the genome-wide profiling; N = 10 included in the direct genotyping) by duplicate checking (rate of concordance in duplicates 100%). The call rate across all samples was 95.7% (N = 1099/1149). All subjects were of Caucasian ancestry on the basis of self-report, which was confirmed for the subset of our cohort with genome-wide profiling based on EIGENSOFT analysis (Patterson et al., 2006; Price et al., 2006). Based on these data, the self-report identification of the Caucasian ancestry is highly reliable in our cohort, which makes genetic inhomogeneity of the tested population unlikely.

2.3. Neurocognitive assessment

Subjects underwent cognitive testing using the Cambridge Neuropsychological Test Automated Battery (CANTAB), which includes nonverbal tests administered with the aid of a high-resolution touch-sensitive screen (Advantech) and /or a response key to all subjects in the same order. Working memory and strategy formation were assessed with the Spatial Working Memory task (SWM) (Owen et al., 1990), planning for problem solving was assessed with the Stockings of Cambridge (SoC) (Owen et al., 1990) and sustained attention and vigilance were assessed with the Rapid Visual Information Processing task (RVIP) (Park et al., 1994). We also assessed Visual working memory with the N-Back Sequential Letter Task (Braver et al., 1997), selection of appropriate response and the effects of interference with the Stroop Color/Word Interference Test (Golden, 1978) and set-shifting/rule learning abilities with a computerized version of the Wisconsin Card Sorting Test (WCST) (Birkett et al., 2008). Verbal learning and memory was assessed with the Word Lists (WL) subtest of the Wechsler Memory Scale-Revised (Wechsler, 1997). Finally, all subjects were administered the Iowa Gambling Task (IGT) (Bechara et al., 1994) to assess planning based on emotional processing and integration of incentive information for decision-making. For a detailed description of the tests see Supplementary data.

2.4. Situational mood and feelings

On arrival to the testing room, following acclimatization and instructions about the study, subjects self-rated their moods and feelings on a 16-item visual analog scale (VAS) originally developed for measuring drug-induced changes in mood and alertness. Subsequently, these scales were found to be very sensitive to momentary changes in psychological states caused by verbal instructions and experimental manipulations (Bitsios et al., 1996, 1998a, 1998b).

2.5. Group statistical analyses

For the sake of data reduction and variable classification we submitted the outcome variables from the neuropsychological tasks to principal component analysis (PCA). For PCA, the varimax rotation method was used and components with eigenvalues >1 and factor loadings >0.5 were accepted. QTPHASE (https://sites.google.com/site/fdudbridge/software/), from the UNPHASED package version

3.1.7, was used for the association analysis (Dudbridge and Gusnanto, 2008). To correct for multiple testing and reduce the probability of type I error, p values were Bonferroni corrected by dividing 0.05 by 10 (the number of comparisons used: IQ and 9 factors resulting from the PCA) (see below). Genotype group effects with Bonferroni corrected p values (0.05/10 = 0.005) are considered significant. Genotype effects at 0.05 are only reported as "suggested significance" for future studies. We estimated the power based on an additive mode of inheritance and α value set at 0.005 − 2-sided [Bonferroni corrected: 0.05/10]. In our cohort (n = 1099 subjects and MAF = 16.5%), we have 80% power to detect small effects (Cohen's d = 0.205; effect size r = 0.1).

3. Results

A full description of the PCA analysis for the cognitive variables is provided in the Supp. Table 1. A total of 22 key cognitive outcome variables were included in the analysis and nine factors were extracted which explained 77.64% of the variance. These were grouped into meaningful dimensions: Declarative memory, problem solving, sustained attention, inattention, set shifting/rule learning, emotional decision making, verbal working memory, strategy formation/spatial working memory and planning time (Supp. Table 1).

Genotype distributions were: CC: 772, CA: 291, AA: 36 (allele frequencies: C 1835, A 363 and MAF: 16.5). The genotypic distribution was consistent with the Hardy–Weinberg expectations (p = 0.19). There were no differences in demographic variables, or mood on the day of testing for the genotype groups (Table 1). Table 2 shows the association of *CSMD1* with IQ and the nine PCA factors as revealed by the QTPHASE. The rs10503253 risk A-allele was significantly associated with lower IQ and worse strategy formation/spatial working memory, planning time, set shifting/rule learning problem solving verbal working memory and sustained attention before or after covarying for age, education and smoking habits (cigarettes/day). These PCA factor dimensions are also shown across the three genotypes in Table 3. The pattern in most dimensions suggests a clear A allele dose effect (CC better than CA better than AA).

For the PCA factors that survived Bonferroni corrections (strategy, planning, set shifting) we provide detailed neuropsychological performance of the three genotype groups in the SWM, SoC and WCST tasks (Supplemental Figs. 1 and 2 and Table 2). There were significant genotype main effects in both outcome measures of the SWM (errors and strategy scores) with post hoc tests confirming the A-allele dose effect (CC better than CA better than AA) (Supplemental Fig. 1). In the SoC, A allele carriers solved fewer problems correctly with post hoc tests confirming an A allele dose effect (CC > CA > AA). CA and AA individuals had shorter initial thinking (planning) times (time required to think out the solution), longer subsequent (execution) times and a greater number of moves required to reach the solution, a pattern suggesting poorer planning abilities for problem solving (Supplemental Fig. 2). Also, the risk A allele carriers performed worse in almost all measures of the WCST, namely, categories achieved, unrelated cards, total errors, Nelson non-perseverative errors and Milner type errors, as revealed by non-parametric Kruskal–Wallis comparisons (Supplemental Table 2).

Table 1
Demographic and testing characteristics of the genotype groups.

Group	C/C (n = 772)	C/A (n = 291)	A/A (n = 36)	P
Age[a]	22.3 ± 3.7	22.4 ± 3.9	21.7 ± 3.4	>0.6
Education[a]	14.7 ± 2.5	14.6 ± 2.4	14.6 ± 2.5	>0.6
Smokers/non-smokers[b]	332/440	136/155	16/20	>0.5
Smokers: Cig per day[a]	16.6 ± 8.1	16.7 ± 10.2	15.9 ± 9.5	>0.7
VAS anxiety[a]	2.24 ± 1.6	2.23 ± 1.8	2.17 ± 1.4	>0.9
VAS alertness[a]	4.97 ± 1.0	5.07 ± 1.1	5.02 ± 1.2	>0.3
VAS discontentment[a]	2.00 ± 1.2	2.00 ± 1.3	1.94 ± 1.4	>0.8

[a] Non-parametric Kruskal–Wallis comparison.
[b] Chi square comparison.

4. Discussion

This is the first report of the potential effects of the *CSMD1* rs10503253 polymorphism on an extended battery of executive function and memory in a large cohort of healthy males. The risk A-allele carriers had lower IQ and poorer strategy formation in a spatial working memory task, set shifting/rule learning and planning for problem solving. They also had poorer sustained attention and verbal working memory although these differences did not survive correction for multiple testing (however, see discussion for type II error below).

Specifically, in the SWM task, individuals' ability to form appropriate search strategies [a "pure" executive function in working memory tasks (Owen et al., 1996) and produce fewer between-errors in the difficult SWM problems became worse the greater their risk A allele "dose" (AA being the worse, CC the best and CA intermediate). Equally, the participants' ability to solve problems correctly in the SoC task declined linearly depending on the presence of the risk A allele (CC being the best, CA intermediate and AA being the worse). The risk A allele was associated with shorter planning, but longer execution times with more moves in the execution phase, suggesting that these subjects had to reassess and even plan new solutions during execution of the task, as a result of less efficient planning strategies. Complex (trials involving moves of 3 and above) problem solving depends on the integrity of the frontal lobes (Owen et al., 1990; Newman et al., 2003). Finally, the risk A allele carriers performed worse in almost all measures of the WCST. All the above taken together suggest that the risk A allele is associated with less efficient prefrontal function. Importantly, working memory, set shifting and sustained attention deficits have been shown to be among the most reliable endophenotypes for SCZ, producing the largest effect sizes in first degree relatives vs control comparisons in a recent meta-analysis (Snitz et al., 2006). Our results extend the findings by Donohoe et al. (2013) on the association of the CSMD1 gene with reduced general cognitive ability and agree with very recent fMRI findings of reduced cortical activation during a working memory task in risk A-allele carriers (Rose et al., 2013).

While the CSMD1 rs10503253 (C/A) polymorphism affects planning ability for non-emotional problem solving [a dorsolateral prefrontal cortex (DLPFC)-based task (Owen et al., 1990; Rowe et al., 2001; Newman et al., 2003)], it did not affect planning ability in the IGT which involves planning based on emotional processing of incentive information for decision-making. Given that the IGT is predominantly dependent on the function of the ventrolateral/orbitofrontal (VLPFC/OFC) cortex (Bechara et al., 1998; Collette et al., 2001; Ernst et al., 2002; Horn et al., 2003; Fukui et al., 2005), it is possible that this polymorphism does not affect VLPFC/OFC functions, as much as it affects DLPFC functions, at least in healthy males.

We did not find genotype effects on verbal memory which is interesting given the relevance of this endophenotype for SCZ (Snitz et al., 2006) and the GWAS-supported status of the CSMD1 rs10503253 genotype as a risk factor for this disorder. It may be that the CSMD1 rs10503253 is not essential for this function at least in healthy young males, and that such putative effects may be conditional to the presence of other risk genes. This latter possibility needs to be investigated in light of some evidence for disease specific CSMD1 genotype effects (Donohoe et al., 2013) and other reports suggesting that risk genes may interact with disease status (Prata et al., 2009; Wirgenes et al., 2010). More research in larger healthy populations and high risk individuals is required, before safe conclusions can be drawn on the effects of this genotype on verbal learning/memory.

The function of CSMD1 gene is not well studied. It has been associated with multiple neurodevelopmental disorders such as epilepsy, speech delay and learning difficulties (Shimizu et al., 2003; Kraus et al., 2006; Glancy et al., 2009; Håvik et al., 2011) where cognition

Table 2
Adjusted p-values from permutation test for association of general cognitive ability (IQ) and the nine factors from the principal component analysis of the cognitive variables for CSMD1 rs10503253 polymorphism. p values < 0.005 (Bonferroni corrected) are in bold. P' refers to p values derived after age, education and cigarettes per day were taken as covariates. The minus symbol signifies lower score in the risk allele A.

rs1050325 [CSMD1]	P	Beta (SE)	95%CI	P'
IQ	**0.00025**	−0.03316 (.009)	−0.051/−0.015	**0.00019**
Strategy formation	**0.001333**	0.184 (0.058)	0.071/0.297	**0.001654**
Planning	**9.17E−05**	−0.247 (0.063)	−0.371/−0.123	**0.000113**
Set shifting	**0.001849**	−0.167 (0.054)	−0.273/−0.061	**0.003001**
Problem solving	0.01628	−0.134 (0.056)	−0.244/−0.025	0.01841
Verbal working memory	0.01639	−0.128 (0.054)	−0.234/−0.023	0.02044
Sustained attention	0.01965	−0.133 (0.057)	−0.245/−0.021	0.02924
Inattention	0.06025	−0.121 (0.065)	−0.247/0.006	0.0606
Declarative memory	0.3207	−0.057 (0.057)	−0.170/0.056	0.3834
Emotional decision making	0.9286	−0.005 (0.058)	−0.119/0.108	0.9678

is affected. In situ hybridization and neuron immunolabeling show that rat Csmd1 was synthesized in the developing central nervous system and in epithelial tissues, with particular enrichment in the nerve growth cone (Kraus et al., 2006). Csmd1 knockout mice do not differ from wild-type littermates for sensorimotor gating (measured as prepulse inhibition), social interaction, anhedonia (measured by sucrose preference), or sensitivity to the locomotor stimulant effects of the dopaminergic agent d-amphetamine (Distler et al., 2012). These findings indicate that gain-of-function mutations or loss-of-function mutations targeting alternative transcripts of Csmd1 might be associated with schizophrenia like phenotypes in animal models (Distler et al., 2012).

Using the Genotype Tissue Expression (GTEx) data (GTEx Consortium, 2013) we examined the distribution of CSMD1 expression in different brain regions and peripheral tissues. CSMD1 is abundantly expressed in cortical regions (Supplemental Fig. 3). Given that rs10503253 is an intronic variant, we examined in the GTEx data whether rs10503253 affects gene expression of CSMD1, based on expression quantitative trait loci (eQTL) analysis (GTEx Consortium, 2013). No cis eQTL effect was observed for rs10503253 (or any other SNP for CSMD1) in the brain or any other tissue included in the GTEx project. Using a previous published gene coexpression analysis in human postmortem tissue of cases with schizophrenia and controls (Roussos et al., 2012b), we found that CSMD1 gene is coexpressed in a neuronal module [module membership Pearson's $r = 0.49$; $p = 9.3E-8$]. More specifically, by using multiple brain related annotations as described previously Roussos et al. (2012b), we found that the module is enriched for markers related to neuronal function, PV + interneurons and synaptic transmission. In the gene expression data, there was a trend [$p = 0.06$] for upregulation of CSMD1 in schizophrenia. Overall, the CSMD1 is abundantly expressed in cortical regions and is coexpressed in neuronal related modules; however, we could not draw any conclusions about the mechanism through which the risk allele affects CSMD1.

Our highly genetically and demographically homogeneous cohort of healthy males with limited age range restricts spurious associations with our multimodal phenotypic assessment. Moreover, type I error was controlled by strict Bonferroni correction to correct for multiple testing. These results cannot be attributed to age, education, smoking habit or state mood. However our results cannot generalize to a wider age range or female gender and future studies should examine and extend these findings. In summary, the risk 'A' allele was associated with deleterious effects in general cognitive ability and a range of executive function tests. These results highlight its potential relevance to neural functioning and suggest that the deleterious effects of the risk "A" allele on neurocognitive function may be part of the mechanism by which the *CSMD1* gene mediates risk for schizophrenia.

Role of funding source
None.

Contributors
SGG, PR and PB designed the study. EK, MP, PR and SGG collected and processed the data. PB and PR undertook the statistical analyses. EK and PR wrote the first draft of the manuscript. TL, AM, LJS, SGG and PB commented and supplemented the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest
All authors reported no biomedical financial interests or potential conflicts of interest.

Acknowledgments
The authors wish to thank the participants and the personnel of the Military Training Camp of Candidate, Supply Army officers (SEAP) in Heraklion, Crete for their help with the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.02.017.

Table 3
IQ and the PCA factor dimensions across the three genotype groups. Values represent group means (±S.E.M.).

	C/C (n = 772)	C/A (n = 291)	A/A (n = 36)	
IQ	50.415 ± 0.277	48.495 ± 0.514	48.138 ± 1.446	CC > CA***, CC > AA†, CA > AA^{ns}
Strategy formation[a]	−0.061 ± 0.035	0.054 ± 0.058	0.469 ± 0.161	CC < CA^{ns}, CC < AA***,CA < AA*
Planning	0.071 ± 0.037	−0.199 ± 0.048	−0.166 ± 0.149	CC > CA***,CC > AA†, CA-AA^{ns}
Set shifting	0.072 ± 0.034	−0.116 ± 0.063	−0.210 ± 0.187	CC > CA**,CC > AA^{ns}, CA > AA^{ns}
Problem solving	0.051 ± 0.036	−0.054 ± 0.056	−0.306 ± 0.176	CC > CA†, CC > AA*, CA > AA^{ns}
Verbal working memory	0.030 ± 0.035	−0.047 ± 0.062	−0.420 ± 0.196	CC > CA^{ns}, CC > AA**, CA > AA*
Sustained attention	0.048 ± 0.035	−0.114 ± 0.057	−0.098 ± 0.199	CC > CA**, CC > AA^{ns}, CA-AA^{ns}

ns: non-significant after post hoc Mann–Whitney tests.
[a] The higher the score, the worse the strategy formation.
*** $p < 0.001$.
** $p < 0.01$.
* $p < 0.05$.
† $0.05 < p < 0.09$.

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