

# The rs10503253 CSMD1 gene may mediate risk for schizophrenia through reduction of cognitive ability

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## INTRODUCTION

- Extensive family and twin data support the role of shared additive genetic factors underpinning both SCZ and cognitive deficits.
- SCZ polygenic risk scores can predict the general cognitive ability in the general population, suggesting that, general cognitive ability shares genetic risk with the disease, and may be part of the neural mechanism by which risk is mediated.
- 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 learning difficulties, autism and schizophrenia.
- The CSMD1 SCZ risk 'A' allele at rs10503253 was associated with poorer performance on neuropsychological measures of general cognitive ability (IQ) and memory function in two independent case-controlled cohorts, although due to small samples the results were inconclusive.
- **AIM:** To test the effects of CSMD1 on neuropsychological function in a large and homogeneous sample. **Hypothesis:** The risk A allele would be associated with reduced IQ and executive function/memory performance.

## SUBJECTS & METHODS

**Subjects:** We recruited 1149 randomly selected young males conscripts from the Greek Army (mean age 22.32±3.78; range: 18-29). Of these 50 individuals were excluded because of axis I pathology, left handedness, history of head trauma, medical and neurological conditions, positive recreational drug screen or current use of prescribed drugs.

**Genotyping:** Subjects were grouped according to genotype in three groups CC (n=772), CA (n=291) and AA (n=36).

### Phenotyping

#### Neurocognitive test

- Raven's Matrices
- Spatial Working Memory (SWM)
- N-Back Task
- Stockings of Cambridge (SoC)
- Word Lists (WL)

#### Domain

- IQ
- Spatial Working Memory & Strategy formation
- Visual Working Memory
- Planning for problem solving
- Verbal Learning & Memory
- Sustained Attention & Vigilance
- Set-Shifting and Rule Learning abilities
- Selection of appropriate responses and the effects of Interference
- Planning based on emotional processing and integration of incentive information for decision-making

- Rapid Visual Information Processing (RVIP)
- Wisconsin Card Sorting Task (WCST)
- Stroop Color-Word Interference Test

- Iowa Gambling Task (IGT)

**Statistics:** ANOVAs and Kruskal-Wallis tests were used to analyse the phenotypic variables. To correct for multiple testing and reduce the probability of type I error, p values were Bonferroni corrected (0.05/9 = 0.0055).

## CONCLUSIONS

- The risk A-allele carriers were worse in IQ and executive function domains such as spatial and visual working memory, strategy formation, sustained attention and set shifting/rule learning (which have all emerged as the most relevant SCZ cognitive endophenotypes in recent meta-analyses)
- For the working memory and set shifting/rule learning domains, we observed an A allele "dose" effect in several measures (SWM between-errors and strategy, n-back accuracy, and the Milner's perseverative errors in the WCST), AA being the worse, CC the best and CA intermediate.
- The risk A-allele carriers were also worse in DLPFC-mediated planning for non-emotional problem solving (SoC) but not in VLPFC/OFC-mediated planning which involves emotional processing of incentive information for decision-making (IGT task). Thus, it is possible that this polymorphism does not affect VLPFC/OFC functions, as much as it affects DLPFC functions, at least in healthy males.
- 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.

## RESULTS

**Table 1:** Demographic characteristics and state mood prior to testing of the genotype groups. a non-parametric Kruskal-Wallis, b chi square comparison, VAS: Visual Analogue Scales

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

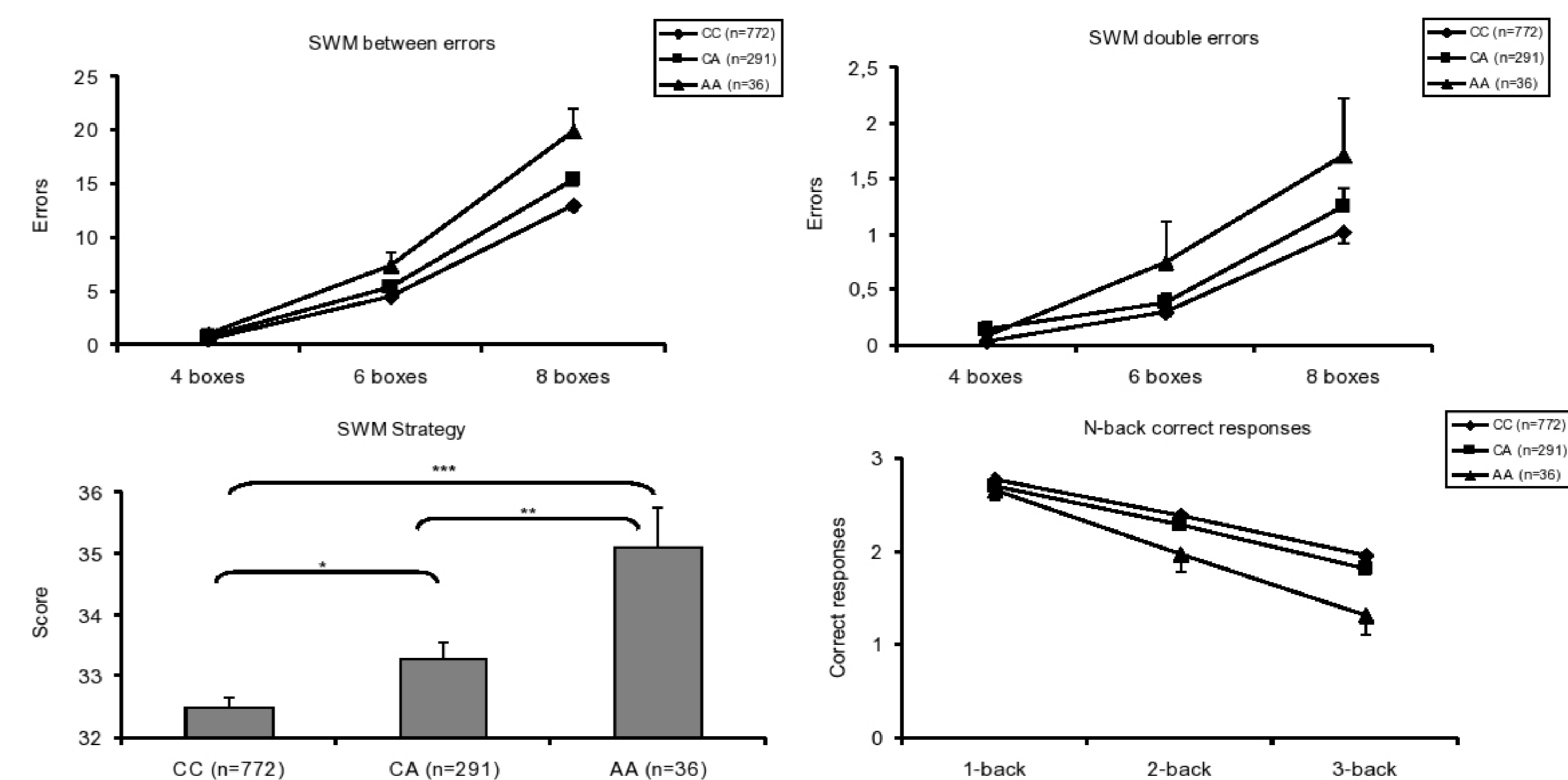
**Table 2:** Mean (±SD) for all RVIP and WCST performance metrics for the three genotype groups. Significant findings from Kruskal-Wallis comparisons with a p<0.005 are shown in bold and p<0.05 are shown in underlined italics. Post Hoc refer to Mann-Whitney follow up comparisons of significant findings.

		C/C	C/A	A/A	P	Post Hoc
IQ	Raven's Raw Score	50.1±7.3	48.5±7.5	48.1±7.8	<b>0.005</b>	CC>CA, AA
RVIP	A'	0.925±0.05	0.915±0.05	0.908±0.05	<b>0.002</b>	CC>CA, AA
	Probability of Hit	0.70±0.18	0.67±0.18	0.63±0.21	<b>0.002</b>	CC>CA, AA
	Total Hits	19.1±4.8	18.1±4.9	17.4±5.6	<b>0.003</b>	CC>CA, AA
	Total Misses	7.9±4.9	8.9±4.9	9.7±5.4	<b>0.003</b>	CC>CA, AA
	Total CR	254.9±10.3	252.5±10.6	251.5±11.5	<b>0.001</b>	CC>CA, AA
	B'	0.977±0.03	0.978±0.03	0.971±0.03	>0.5	
	Probability of FA	1.7±2.6	1.7±2.6	2.1±2.7	>0.3	
	Total FA	0.55±0.79	0.56±0.80	0.74±0.90	>0.3	
	Mean Latency	417.8±67.0	423.1±74.8	419.0±69.1	>0.6	
WCST	Categories	5.45±1.1	5.24±1.1	5.03±1.3	<b>0.001</b>	CC>CA, AA
	Total Errors	7.12±6.5	8.5±6.7	10.4±8.5	<b>0.001</b>	CC<CA, AA
	Unrelated Cards	0.93±2.2	1.17±2.3	1.67±2.6	<b>0.002</b>	CC<CA, AA
	Nelson NP Errors	4.2±3.4	5.0±3.6	5.5±3.4	<b>0.001</b>	CC<CA, AA
	Milner NP Errors	3.4±3.2	4.0±3.3	3.7±2.3	<u>0.007</u>	CC<CA
	Nelson-type Errors	1.96±2.8	2.25±2.7	3.31±6.3	0.06	
	Milner-type Errors	2.81±3.1	3.34±3.3	5.08±6.7	<b>0.001</b>	CC<CA<AA

**Figure 1:** Between errors, double errors and strategy score from the SWM test and accuracy from the N-back test across the three groups.

**SWM:** The graphs (between and double errors) represent the number of errors in the three different levels of difficulty (4, 6, 8 boxes) and bars represent S.E.M. Columns in SWM strategy score represent group means and bars represent S.E.M. Pair-wise group comparisons were performed using the Mann-Whitney test. \*\*\* p<0.001 \*\* p<0.015 \*p<0.015

**N-back(accuracy):** The graph represents the number of correct responses in the three different conditions (1-back, 2-back, 3-back) and bars represent S.E.M.



**Figure 2:** SoC Initial Thinking Time (planning time prior to execution of the first move), Subsequent Thinking Time (time taken to execute the solution), Mean Moves (number of moves taken to execute the solution) and Problems Solved correctly from the SoC test across the three groups. Bars represent S.E.M. In the case of SoC problems solved, pair-wise group comparisons were performed using the Mann-Whitney test. \*\*\* p<0.001 \*\* p<0.01 \*p<0.05

