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The one and the many: Effects of the Cell Adhesion Molecule Pathway on Neuropsychological function in Psychosis

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Abstract

Background—Genetic studies of single gene variants have been criticised as providing a simplistic characterisation of the genetic basis of illness risk that ignores the effects of other variants within the same biological pathways. Of candidate biological pathways for schizophrenia (SZ), *cell adhesion molecule* (CAM) pathways have repeatedly been linked to both psychosis and neurocognitive dysfunction. Here we tested, using risk allele scores derived from the Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ), whether alleles within the CAM pathway were correlated with poorer neuropsychological function in patients.

Method—424 patients with psychosis were assessed in areas of cognitive ability typically found to be impaired in SZ: IQ, memory, working memory and attentional control. CAM pathway genes were identified using the KEGG database. Alleles within these genes identified as significantly associated with SZ risk in the PGC-SCZ were then used to calculate a CAM pathway based polygenic risk allele score for each patient and these scores were tested for association with cognitive ability.

Results—Increased CAM pathway polygenic risk scores were significantly associated with poorer performance on measures of memory and attention, explaining 1–3% of variation on these measures. Notably, the most strongly associated SNP in the CAM pathway (rs9272105 within *HLA-DQA1*) explained a similar amount of variance in attentional control but not memory as the polygenic risk analysis.

Discussion—These data support a role for the CAM pathway in cognitive function, both at the level of individual SNPs and the wider pathway. In so doing these data highlight the value of pathway-based polygenic risk score studies as well as single gene studies for understanding SZ associated deficits in cognition.

Introduction

The involvement of cell adhesion molecules (CAMs) in the pathophysiology of schizophrenia (SZ) has long been hypothesised. Genes encoding CAMs play an important role in neurodevelopmental processes including axonal and dendritic growth and brain segmentation (e.g. *CDH4*; Wang et al. 2009), cell-cell binding (e.g. *CDH7*; Soronen et al. 2010), and synapse formation (e.g. neurexin; Dean et al. 2003). Disruption of several CAM genes has been reported in patients with psychosis, including *de novo* copy number variants (CNVs) in neurexin-1 (Kirov et al. 2012, Rujescu et al. 2009), neuroligin-2 (Sun et al. 2011) and several others (including members of the DLG gene family; Kirov et al. 2012), each of which has been associated with increased illness risk.

Genes encoding CAMs have also been shown to impact cognitive function. A synthetic peptide derived from the neuronal cell adhesion molecule (NCAM) has been found to influence memory consolidation in an animal model at both a behavioural and hippocampal neuron phenotypes (Cambon et al. 2004). In patients, Soronen and colleagues (Soronon et al 2010) found that the gene cadherin 7 (*CDH7*) is associated with variation in performance on measures of working memory and visual attention in patients with bipolar disorder. Contactin-associated protein-like 2 (*CNTNAP2*), which encodes a member of the neurexin family has been implicated in SZ, in associated with epilepsy and intellectual disability (Friedman et al. 2008). The mechanism by which CAMs influence cognition is unknown, particularly whether this occurs via the same biological pathway as is associated with increased psychosis risk.

In addition to the study of single variants, researchers have recently begun to focus on methods to extract data from multiple variants. These include approaches that examine whether associated SNPs are more likely to come from biologically related genes, termed pathway analysis. In a recent pathway analyses by our group of three independent GWAS datasets, we identified using an enrichment of genetic association signals in psychosis for SNPs that were tagged to genes defined as members of the Cell adhesion molecules (CAMs) pathway (KEGG Identifier: HSA04514; O'Dushlaine et al. 2011). Evidence for involvement of CAM pathways has also emerged from two other recent studies taking different analytical approaches (Jia et al. 2012, Lips et al. 2012). A second approach, termed polygenic risk score analysis, has been designed to investigate whether illness associated SNPs from one study (e.g. of schizophrenia) can explain phenotypic variance in an independent sample using either the same illness phenotype (Purcell et al. 2009), or a related phenotype (e.g. cognition, McIntosh et al. 2013). This analysis approach indicates that the composite effect of many small genetic variants contribute substantially to schizophrenia variance (~25%; Purcell et al. 2009, Kirov et al. 2012). Polygene analysis has also provided further evidence of genetic overlap between related phenotypes; for example, McIntosh and colleagues (2013) recently reported that polygenic schizophrenia risk scores could be used to explain variance in longitudinal measures of age related changes in cognitive function.

The purpose of the present study was to investigate the effects of common variants within the CAM pathway on neuropsychological function in patients with psychosis using a combination of pathway and polygenic analysis. We hypothesised that an additive effect of

risk allele load from genetic variants located within the CAM pathway would account for a significant percentage of the variance in neuropsychological function in patients. To test this hypothesis we based our analysis on recent case-control analysis from the PGC schizophrenia GWAS.¹⁵ Selecting all SNP variants located within genes from the CAM pathway (defined in our previous work (KEGG Identifier: HSA04514)), we calculated a pathway-specific polygenic risk score based on the number of risk alleles they carried. We then determined the amount of variance in patients' neuropsychological function explained by these scores. Finally, we compared the amount of variance explained from the full polygene analysis to the amount of variance explained by individual variants from four CAM-related genes that were most strongly associated with SZ risk in the PGC case-control analysis - *HLA-DQ1A*, *CDH4*, *NRXN1* and *CNTNAP2*. In doing so we sought to determine both whether polygenic risk scores from the CAM pathway was significantly associated with neuropsychological performance and if so, how the amount of variance explained compared to that explained by individual risk variants within the pathway. Given the previous use of polygene analysis in schizophrenia and psychosis more broadly, a secondary question for our study was whether any significant associations observed were specific to schizophrenia cases, or were shared across the broader psychosis phenotype.

Method

Neuropsychological sample characteristics

424 cases who had completed a full neuropsychological assessment battery and for whom full genome-wide SNP data was available were analysed (Irish Schizophrenia Genomics Consortium 2012). Cases consisted of clinically stable patients with a DSM-IV diagnosis of schizophrenia (SZ), schizoaffective disorder (SZA), bipolar disorder (BP), major depressive disorder with psychotic features (MDD) or psychosis not otherwise specified (PNOS) (see Table 1 for details) recruited from five sites across Ireland. Inclusion criteria required that participants were clinically stable at the time of neuropsychological assessment, aged 18 to 65 years, had no history of co-morbid psychiatric disorder, no substance abuse in the preceding six months, no prior head injury with loss of consciousness and no history of seizures. Diagnosis was confirmed by trained psychiatrists using the Structured Clinical Interview for DSM-IV Axis 1 Diagnoses (SCID; First et al, 2002). Due to the range of psychotic illness present in the sample and differences in cognitive deficits associated with these, we based our analysis on both (1) a narrow definition of SZ and SZA (n=340) and (2) a broad definition of psychosis which encompassed all those meeting the criteria for psychosis (n=424). Additional diagnostic details and clinical sample characteristics ascertained at time of interview include medication dosage and symptom severity. This was calculated based on a factor analysis of Operational Criteria Checklist for Psychotic Illness (OPCRIT; McGuffin et al. 1991), as previously described for this sample (Cummings et al. 2013). All assessments were conducted in accordance with the relevant ethics committees' approval from each participating site. All patients were of Irish ancestry (i.e. four grandparents born in Ireland) and all provided written informed consent.

Cognitive assessment

All patients completed a full neuropsychological assessment battery designed to target the cognitive deficits typically reported in SZ – namely deficits in general cognitive function, memory function, working memory and attentional control. Where possible both a verbal and a visuo-spatial measure of each construct were included.

Pre-morbid and current General cognitive functioning (IQ) was measured using the Wechsler Test of Adult Reading (WTAR) and selected subtests (Vocabulary, Similarities, Block Design and Matrix Reasoning) from the Wechsler Adult Intelligence Scale, 3rd edition (Wechsler 1997a). Verbal and visual **episodic memory** were assessed using the logical memory subtest from the Wechsler Memory Scale, 3rd edition (WMS-III; Wechsler 1997b) and the Paired Associate Learning (PAL) task from the Cambridge Automated Neuropsychological Test Battery (CANTAB; Robbins et al. 1994) respectively. **Working memory** was assessed using the spatial working memory task (SWM) from the CANTAB and letter number sequencing (LNS) from WMS-III. **Attentional control** was assessed using the continuous performance task identical pair's version (CPT-IP; Cornblatt et al. 1988) and the sustained attention to response task (SART; Robertson 1994).

Genotyping

Genetic analysis for patient samples was conducted on DNA extracted from whole blood. SNP data for these samples was available from a recent genome-wide association study using the Affymetrix SNP Array 6.0 as previously described (Bellenguez et al. 2012).

Calculating risk allele load

Polygenic scores for variants located within the CAM pathway were calculated in four steps. Firstly, all available SNPs within 20Kb of genes in the CAM pathway were identified. CAM pathway genes were identified based on data from the KEGG database as previously described by us (O'Dushlaine et al. 2011). A total of 132 genes were identified (see Table S1); five of these could not be tagged with genotyped SNPs using the above criteria. Secondly, alleles within these SNPs were identified as risk or non-risk using data from the PGC SZ GWAS analysis according to three different thresholds: $p < 10^{-5}$, $p < 0.05$, $p < 0.5$. Using a variety of threshold cut-off points for determining risk is in line with procedures used in previous polygenic analysis (Purcell et al. 2009). Regarding the three thresholds we selected, these are arbitrary and were pragmatically selected to reflect a distribution including strong ($10e-5$), nominal (.05) and non-significant baseline (.5) associations. The SNPs were all coded so that the “target” allele was the one positively associated with schizophrenia; hence, the directionality (increased risk) is the same for all SNPs. Thirdly, to account for differences between variants in the effect size of the association with illness, each risk allele was weighted as the $\log_{10}$ of the effect size described in the PGC dataset ($W_{\text{SNP}} = \log_{10}(\text{OR}_{\text{PGC}})$). Included variants were not LD pruned; inclusion of all variants has previously been recommended to capture all variation associated with risk (ISC, 2009). Finally, a risk score for each individual was calculated based on the number of weighted risk alleles they carried at each of the three p-value thresholds using the equation: $\text{Score}(p < \text{threshold}) = \sum_j (S_{\text{SNP}}) / (j - m)$, where j = number of SNPs at $P < \text{threshold}$ and m = number of SNPs with missing genotypes. A risk score for each of the CAM SNPs was

calculated as ($S_{\text{SNP}} = W_{\text{SNP}} * \text{Risk Allele Count}$). The number of missing genotypes was consistently low within each p-value threshold (for $p < 10^{-5}$ it was 6 (2.5%), for $p < 0.05$ it was 44 (0.85%), and for $p < 0.5$ it was 254 (0.49%)).

Single gene variant selection

As we hypothesized that polygene risk scores would better explain variance in neuropsychological function than would be explained by single SNP analyses, we planned to follow up any significant neurocognitive findings from the CAM polygene analysis by characterising the effects of single SNPs within CAM on neurocognition. To do this, we selected the most strongly associated single SNPs from each of the four CAM genes most strongly associated with SZ risk in the PGC analysis. These were: *HLA-DQA1* (rs9272105; OR = 0.87; $p = 9.97 \times 10^{-9}$), *CDH4* (rs2427104; OR = 0.90; $p = 0.00006$), *NRXN1* (rs1819972; OR = 1.1; $p = 0.0004$), and *CNTNAP2* (rs1548743; OR = 0.92; $p = 0.0005$). Selecting these 4 variants for analysis was based on an arbitrary cut-off point for statistical association with SZ of $p = 0.0005$. Furthermore, while 11 other HLA genes exceeded this cut-off threshold we only included the most strongly associated given the high LD in this region.

Statistical Analysis

Associations between CAM pathway polygenic risk allele scores and the phenotypes of IQ, episodic memory, working memory and attention were tested in a series of multiple regression analyses implemented in SPSS 17 (SPSS 2008). In each case, scores for each neuropsychological subtest were entered as dependent variables, and where appropriate age and gender were entered on the first step of the analysis as effects of no interest, followed by CAM pathway risk allele score on the second step. Exactly the same approach was taken in the analysis of the single variants, with the risk genotype score (0, 1, or 2 alleles) in each case replacing the polygenic score as the independent variable. The R^2 value, or variance explained, was calculated between these nested models; namely, a model containing the intercept plus sex and age (when appropriate) and the model containing these same terms plus the pathway score. We report this pathway score-specific R^2 plus the corresponding F -test p-value. Finally, effects sizes for all significant effects were calculated using Cohen's d in ClinTools (ClinTools 2005) to enable comparison between the polygenic scores analysis and analysis of the individual SNPs considered.

Results

Demographic and clinical characteristics for all patients appear in Table 1. No differences were observed between the narrow psychosis group (SZ and SZA only) and broad psychosis group (all patients with psychosis) in terms of age, gender, age at onset, or general cognitive ability as indexed by full-scale IQ. Based on factor scores previously calculated for symptom severity based on OPCRIT (Cummings et al. 2013), no differences were observed between the two groups in severity of symptoms of depression, positive symptoms, negative symptoms or disorganisation. Differences were however observed for on the 'mania' factor, with the broad psychosis group scoring significantly higher on the manic scale than the narrow psychosis group. No between group differences were observed in medication dosage as measured by chlorpromazine equivalents.

The effects of CAM pathway risk allele load on cognition

R^2 change and p-values from the regression analyses for each of the 3 cognitive domains of IQ, memory and attention by CAM pathway risk allele load are presented in Figure 1 and Table 2. Across both narrow sense and broad sense psychosis groups, *higher* polygenic risk scores within the CAM pathway was significantly associated with *deficits* in both memory function (as measured by the CANTAB paired associate learning test) and sustained attention (as measured by the SART). For the broad diagnoses groups, CAM pathway risk allele load was also associated with poorer verbal episodic memory function as measured by WMS-III logical memory task. In the narrow psychosis group, this effect was observed at trend level only. By contrast, the narrow psychosis group showed a nominal association between preserved premorbid IQ and higher CAM pathway risk polygene scores (but only for SNPs thresholded at $p=10 \times 10^{-5}$), whereas this association was only observed at trend level in the broad psychosis group. The amount of variance in cognitive performance explained by CAM pathway polygenic risk scores ranged between 1–3% in regression models that were significant, with the highest percentage of variance explained on the SART attentional control task. Calculated effect sizes (Cohen's d) for this variance explained ranged from 0.23 to 0.37 with a mean effect size of 0.29.

Cognitive analysis of SZ-associated individual SNPs within the CAM pathway genes

HLA-DQA1, CDH4, NRXN1 and CNTNAP2—We next tested whether variance in neurocognitive function explained by CAM pathway scores was comparable to that explained by individual SNPs within the CAM pathway. As described above, this was based on the analysis of SNPs within each of the four genes most strongly associated with SZ risk in the PGC analysis - rs9272105 within *HLA-DQA1*, rs2427104 within *CDH4*, rs1819972 within *NRXN1* and rs1548743 within *CNTNAP2* (See Table 3). Only the *HLA-DQA1* SNP (the most strongly associated CAM pathway SNP from the PGC analysis and the only variant achieving genome wide associated significance) was observed to be associated with variation in neurocognitive performance – specifically attentional control in both the narrow and broad diagnosis groups, and pre-morbid IQ in the narrow diagnosis group only. No association with memory function was observed. None of the other variants within *CDH4*, *NRXN1* or *CNTNAP2* were associated with variation on any of these three neurocognitive measures. Similarly, a combined regression analysis that included all four SNPs failed to explain a significant amount of variation on any of these three neurocognitive measures.

Given the significant contribution of rs9272105 to explaining variation in neuropsychological functioning, we re-ran our CAM pathway polygenic regression analysis to exclude all variants at this gene locus (resulting in the exclusion of 3 SNPs). When we re-calculated CAM pathway polygenic risk allele load scores minus these three *HLA-DQA1* variants, the association between the CAM polygene score and memory largely remained significant (see Table 4). By comparison the association with attentional control was no longer significant. The nominal association with pre-morbid IQ seen in the narrow diagnosis group using the $p=10 \times 10^{-5}$ threshold also became non-significant.

Discussion

This study used polygenic risk allele scores derived from the PGC schizophrenia GWAS case-control analysis to investigate whether risk variants within the CAM pathway were associated with poorer neuropsychological function amongst 424 patients with either narrow sense or broad sense psychosis. We further compared the variation in neuropsychological performance explained by CAM pathway polygenic risk allele scores to the individual CAM pathway variants identified by the PGC as most strongly associated with SZ risk (*CDH4*, *NRXN1*, *HLA-DQA1*, and *CNTNAP2*). Based on these analyses we found that (1) polygenic scores for the CAM pathway explained a statistically significant proportion of variance in neuropsychological function; (2) one risk SNP – *HLA-DQA1* was also individually associated with variation in neuropsychological function, and (3) after removal of this gene from the polygene analysis, polygenic risk scores continued to explain variants in memory, but not attentional control. To our knowledge this is the first study to characterise the effects on neurocognition of risk variants within the CAM pathway – or any other pathway – in patients with SZ.

A specific criticism of the single variant approach in studying both illness phenotypes and intermediate phenotypes (including cognition) is that as illness risk is polygenically determined¹³ the function of single variants cannot be understood in isolation from either other risk variants or from the biological pathways in which they function. In this context, we investigated both whether pathway based risk estimates significantly accounts for variation in neuropsychological deficits and if so, how the amount of variance explained compared to that explained by individual SNP genotypes. When compared to results from single SNP analysis from the four most strongly associated CAM pathway genes, CAM pathway polygene scores explained a greater percentage of variance in memory function than the *HLA-DQA1* SNP most strongly associated with risk in the PGC analysis, and this variance explained was undiminished after the *HLA-DQA1* SNP was removed from the polygene score analysis. For attentional control, however, variation on this variable was better explained by the SNP than the pathway.

The CAM pathway has previously been implicated in a variety of neurocognitive processes, including memory. Consistent with this, an association with variation on a neurocognitively-associated phenotype has been reported for three of the four individual genes characterised: *CDH4* has been associated with total brain volume (Seshadri et al. 2007), *NRXN1* with white matter volume (Voineskos et al. 2011), and *CNTNAP2* with language processing (Kos et al. 2012). This is the first study to our knowledge that specifically implicates the *HLA-DQA1* gene in neuropsychological performance in humans. Beyond these single variant analyses, this is the first study to our knowledge that demonstrates the relevance of CAM genes to cognition at the pathway level. Specifically, it highlights the role of previously identified SZ risk variants within the CAM pathway on cognition in a manner that goes beyond the effects of individual variants. While making this point, two caveats regarding the involvement of *HLA-DQA1* are relevant. First, while the *HLA-DQA1* gene is located within the KEGG cell adhesion pathway, its demonstrated roles in cell adhesion have been confined to the immune system. This is noteworthy because a role for immune related MHC class 1 molecules in neuronal plasticity (which is strongly linked to learning and memory) has long

been speculated (Shatz 2009). It should, of course also be noted that the *HLA-DQA1* resides in an area of strong linkage disequilibrium encompassing many genes, many of which are not involved in cell adhesion. In summary, therefore, while this study highlights the role of CAM genes in cognition, the observed cognitive effects of *HLA-DQA1* may occur independently of this pathway.

This finding that pathway based polygenic risk scores for SZ explain variance in cognition is relevant to the recent debate regarding the genetic overlap between cognitive performance and schizophrenia in particular and psychosis in general may also be important. While a high degree of overlap between cognitive deficits and schizophrenia have previously been inferred from twin studies (Toulopoulou et al. 2007), recent evidence by Fowler and colleagues (Fowler et al. 2012) has suggested that this may not be quite as high when based on non-biased epidemiological samples. In a polygenic analysis of age related changes in cognition in healthy adults over time, McIntosh and colleagues (2013) found that polygene scores (again based on the PGC SZ dataset) significant predicted ~1% variance in cognitive change. In the present study we extend these findings by demonstrated that polygenic risk scores also predict variance in SZ related cognitive deficits in patients (~3%). Furthermore by focusing on a previously implicated biological pathway our data highlights the relevance of polygenic risk in the CAM pathway in particular to cognitive deficits in this group. The CAM pathway is unlikely to be unique in this regard - polygenic risk scores analysis based on other pathways is likely to also be informative about cognitive deficits in this group. For example, a recent study by Greenwood et al. (2011) of 94 candidate SZ genes suggests that glutamate pathway genes are also likely to be important. The approach taken in our study is equally applicable to the study of these other pathways, and may well be informative not just for explaining cognitive deficits in patients, but also for explaining the genetics architecture of cognition in the healthy population.

Conclusion

In conclusion this study, building on previous literature adopting either pathway based or polygenic based approaches to psychosis risk and cognitive dysfunction, investigated the role of pathway-specific risk variants in the cognitive deficits associated with psychosis. The data supports a role for the CAM pathway in memory formation and attention related reaction time. It also provided evidence that a single SNP – in *HLA-DQA1* – was also associated with variation in attentional control, and to a lesser extent pre-morbid IQ, in psychotic patients. In doing so, this study demonstrates the feasibility of pathway specific polygenic risk analysis to studying an intermediate phenotype for psychosis, while at the same time suggesting that single gene analysis nonetheless continues to be informative about the effects of gene effects on cognition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Plot of regression analyses of neuropsychological variables showing r^2 values and associated significance for each polygenic risk threshold.

Table 1:

Patient demographic characteristics.

	Narrow Psychosis Dx	Broad Psychosis Dx
Total	N=340	N=424
<i>Psychosis subtype:</i>		
Schizophrenia	N = 282	N = 282
Schizoaffective disorder	N = 58	N = 58
Bipolar disorder I	NA	N = 61
Major depressive disorder	NA	N = 11
Psychosis not otherwise specified	NA	N = 12
<i>Gender</i> (ratio; M:F)	2.6:1	2.2:1
<i>Age</i> (years; mean (SD))	41.3 (12.2)	41.3 (12.4)
<i>Age at onset</i> (years; mean(SD))	22.8 (7.2)	23.2 (7.5)
<i>Medication</i> (Chlorpromazine equiv. mg/day; mean(SD))	589.8 (562.4)	555.5 (540.7)
<i>SAPS/SANS factor scores:</i>		
Manic (mean (SD))	-0.18 (0.95)	0.04(1.09)
Depression (mean (SD))	0.16 (1.07)	0.23(1.06)
Positive (mean (SD))	-0.02 (0.99)	-0.12(0.95)
Disorganised (mean (SD))	-0.22 (0.76)	-0.31(0.78)
Negative (mean (SD))	0.39 (0.90)	0.32(0.87)
Full scale IQ (mean (SD))	89.6 (17.8)	90.3(18.3)

Table 2:

CAM pathway polygenic score regression analysis for each neuropsychological variable. CAM risk alleles included were thresholded at (a) $p=10 \times 10^{-5}$ (b) $p=.05$ (c) $p=.5$

Neuropsych variable		All patients with psychosis			Patients with SZ or SZA		
		10×10^{-5}	0.05	0.5	10×10^{-5}	0.05	0.5
		r ² (p)	r ² (p)	r ² (p)	r ² (p)	r ² (p)	r ² (p)
IQ	Premorbid IQ	.008(.07)	.005(.17)	.005(.168)	.013(.045)	.006(.178)	.004(.239)
	Verbal IQ	.000(.854)	.000(.675)	.001(.63)	.000(.944)	.001(.633)	.000(.693)
	Performance IQ	.000(.954)	.000(.807)	.003(.309)	.000(.776)	.000(.777)	.005(.201)
	Full scale IQ	.000(.985)	.000(.713)	.002(.419)	.000(.791)	.000(.715)	.002(.403)
Memory	Logical memory 1	.002(.407)	.004(.206)	.005(.176)	.000(.768)	.005(.24)	.006(.181)
	Logical memory 2	.008(.079)	.013(.023)	.014(.021)	.003(.36)	.011(.063)	.013(.051)
	PAL total errors	.011(.044)	.021(.005)	.032(.001)	.004(.27)	.01(.083)	.021(.013)
Attention	SART reaction time	.006(.201)	.026(.005)	.024(.008)	.009(.141)	.029(.009)	.027(.011)
	CPT d'Prime 2 digit	.004(.304)	.000(.957)	.000(.94)	.012(.103)	.002(.549)	.001(.57)
	CPT d'Prime 3 digit	.000(.798)	.007(.16)	.004(.296)	.004(.346)	.001(.69)	.000(.76)

Table 3:Regression analysis for SNPs within *HLA-DQA1*, *NRXN1*, *CNTNAP2* and *CDH4*.

	Neuropsych variable	r square	Adjusted r square	F	p
<i>HLA-DQA1</i> rs9272105	<u>All patients with psychosis</u>				
	Premorbid IQ	0.01	0.007	3.7	0.055
	Logical memory 2	0.035	−0.002	0.44	0.508
	SART Reaction time	0.028	0.021	4.0	0.019
	PAL Total errors	0.003	0.001	0.898	0.344
	<u>Patients with SZ + SZA only</u>				
	Premorbid IQ	0.021	0.017	6.25	0.013
	Logical memory 2	.009	.005	2.38	0.123
	SART Reaction time	0.036	0.027	3.98	0.02
	PAL Total errors	0	−0.003	0.083	0.773
<i>NRXN1</i> rs1819972	<u>All patients with psychosis</u>				
	Premorbid IQ	0	−0.002	0	0.996
	Logical memory 2	0.032	−0.002	0.386	0.535
	SART Reaction time	0.012	0.008	3.538	0.061
	PAL Total	0.008	0.005	2.819	0.094
	<u>Patients with SZ + SZA only</u>				
	Premorbid IQ	0	−0.003	0	0.983
	Logical memory 2	.003	−0.001	.831	0.363
	SART RT	0.012	0.008	2.81	0.095
	PAL Total errors	0.011	0.007	3.1	0.079
<i>CNTNAP2</i> rs1548743	<u>All patients with psychosis</u>				
	Premorbid IQ	0	−0.002	0.188	0.664
	Logical memory 2	0.01	−0.003	0.038	0.845
	SART Reaction time	0	−0.003	0.066	0.797
	PAL Total errors	0.006	0.004	2.43	0.119
	<u>Patients with SZ + SZA only</u>				
	Premorbid IQ	0.001	−0.002	0.271	0.603
	Logical memory 2	0.03	0.001	0.324	0.57
	SART Reaction time	0	−0.004	0.005	0.946
	PAL Total	0.008	0.005	2.4	0.122
<i>CDH4</i> rs2427104	<u>All patients with psychosis</u>				
	Premorbid IQ	0	−0.002	0.154	0.695
	Logical memory 2	0.042	0.002	0.656	0.419
	SART Reaction time	0.001	−0.002	0.311	0.577
	PAL Total errors	0	−0.002	0.113	0.737
	<u>Patients with SZ + SZA only</u>				
	Premorbid IQ	0.001	−0.002	0.411	0.522
	Logical memory 2	0.085	0.007	2.19	0.14

Neuropsych variable	r square	Adjusted r square	F	p
SART Reaction time	0.003	−0.001	0.785	0.377
PAL Total errors	0	−0.003	0.055	0.815

Table 4:

Recomputation of the regression analyses for the CAM pathway polygenic risk scores without 3 SNPs mapped to the *HLA-DQAI* gene.

Neuropsych variable		All patients with psychosis			Patients with SZ or SZA		
		10×10^{-5}	0.05	0.5	10×10^{-5}	0.05	0.5
		r ² (p)	r ² (p)	r ² (p)	r ² (p)	r ² (p)	r ² (p)
IQ	Premorbid IQ	.006(.123)	.004(.236)	.003(.259)	.005(.192)	.003(.296)	.002(.414)
Memory	Logical memory 2	.006(.128)	.012(.029)	.010(.049)	.002(.389)	.010(.077)	.007(.151)
	PAL total errors	.008(.079)	.012(.031)	.015(.017)	.003(.357)	.006(.166)	.008(.114)
Attention	SART reaction time	.001(.53)	.002(.416)	.002(.393)	.000(.883)	.000(.755)	.001(.702)