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A polymorphism in the Glutamate Metabotropic Receptor 7 is associated with cognitive deficits in the early phases of psychosis

Boris Chaumette^{1,2,3,4}, Sarojini M. Sengupta^{4,5}, Martin Lepage^{4,5}, Ashok Malla^{4,5},
Srividya N. Iyer^{4,5}, Oussama Kebir^{2,3}, ICAAR study group^a, Patrick A. Dion¹, Guy A. Rouleau¹,
Marie-Odile Krebs^{2,3}, Jai L. Shah^{4,5*}, Ridha Joobar^{4,5*}

1. Montreal Neurological Institute and Hospital, Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada
 2. Université de Paris, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, CNRS, GDR3557-Institut de Psychiatrie, Paris, France
 3. GHU Paris Psychiatrie et Neurosciences, Paris, France
 4. Department of Psychiatry, McGill University, Montreal, Quebec, Canada
 5. Douglas Mental Health University Institute, Montreal, Quebec, Canada
- a. group authorship : ICAAR study group includes Isabelle Amado, Julie Bourgin, Claire Daban Huard, Célia Jantac Mam-Lam-Fook, Marion Plaze, Fabrice Rivollier

* these authors contribute equally to this work

Corresponding author: Dr Boris Chaumette

boris.chaumette@mcgill.ca

Irving Ludmer Building - 1033, Pine av. Room: 327

Montréal, Québec, H3A 1A1 - Canada

Contributors of the ICAAR study group: Isabelle Amado, Julie Bourgin, Claire Daban Huard, Célia Jantac Mam-Lam-Fook, Marion Plaze, Fabrice Rivollier

Abstract

Schizophrenia is an illness characterized by positive symptoms, negative symptoms, and cognitive impairments. Cognitive impairments occur before the onset of psychosis and could reflect glutamatergic dysregulation. Thus, identifying associations between genetic variations in genes coding for glutamatergic receptors and cognitive impairment in schizophrenia may help in understanding the basis of these deficits and in identifying potential drug targets. In a discovery cohort of 144 first-episode of psychosis patients (FEP), we genotyped 58 candidate Single Nucleotide Polymorphisms (SNPs) located in NMDA and metabotropic glutamatergic receptors. These SNPs were selected according to the results from the Psychiatric Genomic Consortium and were tested for association with intellectual quotient (IQ) as assessed with the Wechsler Intelligence Scale. For replication, we used the ICAAR cohort including 121 ultra-high-risk patients (UHR) with the same cognitive assessment. A polymorphism located in *GRM7*, rs1396409, was significantly associated with performance IQ in the discovery cohort of FEP. This association was replicated in the UHR cohort. This polymorphism is also associated with total IQ and verbal IQ in the merged dataset, with a predominant effect on the arithmetic subtest. The rs1396409 polymorphism is significantly associated with cognitive impairment during the onset of psychosis. This genetic association highlights the possible impact of glutamatergic genes in cognitive deficits in the early phases of psychosis and enforce the interest for new therapeutic interventions targeting the glutamatergic pathway.

Keywords: premorbid – IQ – schizophrenia – prodromal – psychosis – genetics

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Introduction

Schizophrenia is a neurodevelopmental disorder typically beginning in adolescence or early adulthood. The main manifestations of schizophrenia and related psychoses are positive symptoms (e.g. hallucination, delusions and disorganized thinking), negative symptoms (e.g. flat affect, lack of socialization), disorganization and cognitive impairments (Owen et al., 2016). Antipsychotics, the first line treatment for schizophrenia, are effective mainly for positive symptoms and their action on the other symptoms is limited (Kahn et al., 2015). Thus, identifying therapeutic targets for negative symptoms and cognitive impairments, both believed to be important for functional recovery, is an important line of investigation (Green and Harvey, 2014).

Variation in cognitive functioning and liability to schizophrenia could share genetic factors as suggested by twin (Toulopoulou et al., 2007), genome-wide association (Smeland et al., 2017) and polygenic risk score studies (Lencz et al., 2014). Cognitive deficits may predate the onset of psychosis (Bora and Murray, 2014): neuropsychological studies have demonstrated that unaffected relatives of patients with schizophrenia (individuals at familial high-risk for schizophrenia, FHR) perform poorly compared to healthy controls in all cognitive domains (Agnew-Blais and Seidman, 2013), and cognitive impairments are present in subjects with sub-threshold psychotic symptoms who are at ultra high-risk (UHR) for psychosis (Fusar-Poli et al., 2012; Mam-Lam-Fook et al., 2017). Patients with a first episode of psychosis (FEP) present global cognitive impairment, particularly in verbal memory and executive function, compared to healthy volunteers (Aas et al., 2014). These early deficits impact general IQ and contribute to deficits in social and occupational functioning (Grau et al., 2016).

Developing new phase-specific interventions targeting cognitive deficits (Millan et al., 2016) may be effective in preventing the onset of cognitive and functional deficits (Nuechterlein et al., 2014). Among the currently-available drugs, modulators of glutamatergic receptors are promising. Since

the pioneering trial about oral glycine on negative symptoms in schizophrenia (Leiderman et al., 1996), several studies have tested modulators of the metabotropic glutamate receptors (Matosin and Newell, 2013) and modulators of the N-methyl-D-aspartate receptor (NMDAR) including D-serine or glycine in add-on in chronic schizophrenia (Kantrowitz et al., 2010). Despite mixed findings of their attenuation of cognitive deficits in later stages (Iwata et al., 2015), these treatments may have efficacy when used earlier, during UHR stages (Kantrowitz et al., 2015). Modulation of N-methyl-D-aspartate receptor has also been reported to improve psychotic symptoms in patients carrying a rare copy-number variant encompassing glutamatergic genes (Bodkin et al., 2019) suggesting efficacy in patients with specific genetic factors. Indeed, rare variants in NMDAR have been associated with schizophrenia (Tarabeux et al., 2011). Common variants associated with schizophrenia pointed towards genes related to synaptic function and expressed in pyramidal glutamatergic neurons (Skene et al., 2018). In addition, N-methyl-D-aspartate-type glutamate receptor (NMDAR) antagonists, such as ketamine, induce cognitive deficits and symptoms closely resembling those of schizophrenia (Anticevic et al., 2012; Vinckier et al., 2016). Consequently, it has been postulated that dysregulation in glutamate neurotransmission may play a significant role in cognitive impairments observed in schizophrenia (Thomas et al., 2017) and may also play a role in the emergence of psychotic symptoms. A meta-analysis of brain spectroscopy studies in patients with UHR revealed that medial frontal glutamate plus glutamine levels are increased compared to healthy controls (Merritt et al., 2016). Recent reports suggest that glutamate level could be higher in FEP compared to controls in the cingular cortex (Chiu et al., 2017; Kim et al., 2017) and striatum (Plitman et al., 2016).

Thus, studying the link between glutamatergic neurotransmission and cognitive impairment during the early phases of psychosis may improve our knowledge about the mechanisms underlying cognitive impairments in schizophrenia and provide clues about new therapeutic

targets. Whereas research on the genetics of neurocognitive domains in schizophrenia has grown rapidly over the last decade, the glutamatergic system remains insufficiently explored (Zai et al., 2017).

The objective of the present study was to explore associations between polymorphisms in glutamatergic receptors and cognition during the onset of psychosis. We first tested the association between cognition and candidate polymorphisms in sixteen glutamatergic receptors (**Supplementary Table 1**) in a discovery cohort of well-phenotyped FEP. Subsequently, we attempted to replicate any significant association in a cohort of UHR subjects.

Methods

Samples

In the FEP cohort, 260 Caucasian individuals were recruited from among patients treated at the Prevention and Early Intervention Program for Psychoses in Montreal (PEPP-Montréal) between 2003-2013 (Iyer et al., 2015). Inclusion criteria were an age between 14 and 35 years, less than 30 cumulative days of antipsychotic treatment, and a FEP diagnosis according to the Structured Clinical Interview for DSM-IV-TR (Diagnostic and Statistical Manual for Mental Disorders, fourth edition, text revised). All diagnoses were confirmed at a consensus meeting attended by a senior research psychiatrist (AM or RJ). All patients gave their written informed consent. The study was approved by the Ethics Review Board at the Douglas Mental Health University Institute and at McGill University.

For the UHR cohort, 173 Caucasian UHR individuals were recruited in the French ICAAR cohort (PHRC AOM-07-118, promoted by Hôpital Sainte-Anne) among the patients (16 to 30 years old) consecutively referred to the Adolescent and Young Adult Assessment Centre (Service Hospitalo-

Universitaire, Hôpital Sainte-Anne, Paris, France) between 2009 and 2014 (Oppetit et al., 2016). The cohort was approved by the institutional ethics committee “Comité de protection des personnes, Ile-de-France III, Paris, France” and written informed consent was obtained from all participants. UHR status was determined based on the CAARMS criteria in its French-translated version (Krebs et al., 2014). Exclusion criteria included current antipsychotic treatment at a chlorpromazine equivalent dose higher than 100 mg for more than twelve weeks, manifest symptoms of established psychiatric diagnoses including psychosis, psychoactive substance dependence or abuse (fulfilling DSM-IV criteria), serious or non-stabilized somatic and neurological disorders, head injury, IQ below 70, and non-French-native speaking (because of the cognitive assessment)

The criteria about dose and duration of the antipsychotic treatments were chosen to select minimally treated patients and to avoid a possible deleterious effect of antipsychotics on cognition. The demographic and baseline clinical characteristics of PEPP and ICAAR cohorts are described in **Table 1**. All procedures at both sites complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration.

Cognitive assessment

In the FEP cohort, full- (FIQ), verbal- (VIQ), and performance (PIQ) were evaluated in 148 individuals using the Wechsler Adult Intelligence Scale (WAIS-III) during a face-to-face interview conducted by trained staff under the supervision of licensed neuropsychologists.

In the UHR cohort, the 9-subtest version of the WAIS-III was administered in approximately ninety minutes in 153 UHR individuals by trained psychologists. This version includes: Vocabulary,

Similarities, Information (constituting the Verbal Comprehension Index, VCI), Arithmetic, Digit Span, Picture Completion, Block Design, Matrix Reasoning (constituting the Perceptive Organization Index, POI) and Digit Symbol-Coding subscale (part of Processing Speed Index, PSI). The scores were age-scaled and normalised as recommended in the WAIS-III manual and Wechsler's instructions as previously reported (Magaud et al., 2014).

SNP selection and genetic assessment

In the FEP cohort, DNA were sampled from whole-blood for each Caucasian participant and extracted following classical protocols. Fifty-eight SNPs located either in NMDA- or metabotropic glutamate receptors (**Supplementary table 1**) were genotyped using Sequenom iPLEX Gold Technology in the Genome Quebec Innovation Centre. The SNPs were selected based on their association with schizophrenia according to the Psychiatric Genomics Consortium (PGC, data freely available online: <http://www.med.unc.edu/pgc>) using the following rationale: (1) We first selected 16 SNPs, each in one of the glutamatergic receptors with the lowest p-value in the PGC dataset. This selection was performed to select at least one SNP by gene. (2) Second, we selected 42 tag-SNPs in glutamatergic receptor genes. Tag-SNPs are supposed to be representative SNPs in a region of the genome with high linkage disequilibrium that represents a group of SNPs. 979 Tag SNPs were identified in the 16 genes according the HapMap CEU database and using the NIH online software <https://snpinfo.nih.gov/snpinfo/snptag.html>. Tag-SNPs were retained if they tag at least 5 SNPs and have a nominal p-value < 0.05 in association with schizophrenia in the PGC database. Six SNPs failed to be genotyped in the cohort due to low intensity (**Supplementary Table 1**).

The SNP found to be associated with cognition in the FEP cohort was subjected to a replication in the UHR cohort including 129 individuals. This cohort has been genotyped using the Illumina Infinium PsychArray BeadChip, specifically designed by the PGC for psychiatric disorders, and

covering half a million SNPs in the whole genome. The significant SNP was directly extracted from the genotyping data. Eight individuals failed to be genotyped in the UHR cohort.

Genetic analyses

The statistical analyses were conducted in Plink v1.07. The FEP cohort was composed of 148 individuals with both cognitive assessment and genetic data. In this cohort 43 SNPs were retained (**Supplementary Table 1**) after quality control using the following criteria: (1) greater than 90% of attempted genotypes were successful, (2) SNPs were in Hardy–Weinberg equilibrium (with a 0.001 threshold), (3) minor allele frequency was greater than 5% (**Supplementary table 1**). The UHR cohort included 121 individuals with non-missing genotype and non-missing phenotype. The extracted SNP had a minor allele frequency of 0.42 in the UHR cohort. Three alternate phenotypes were used in the FEP cohort (VIQ; PIQ; FIQ) and five in the UHR cohort (VIQ; PIQ; FIQ; VCI; POI) as well as subscores for each cohort. Quantitative trait associations were performed using the Wald test. For the FEP cohort, the Wald test asymptotic p-value was corrected for the number of selected SNPs using the Bonferroni method. The alpha-risk was set to 0.05 after correction. Then, we conducted the same analysis in the merged cohort (265 individuals in total) for the three overlapping phenotypes (VIQ; PIQ; FIQ) using 10,000 permutations. The SNP explored in the merged cohort had a minor allele frequency of 0.41.

Results

In the FEP cohort, the association with FIQ, VIQ and PIQ was tested for each of the 43 SNPs, located in one of the following glutamatergic genes: *GRIN2A*, *GRIN2B*, *GRIN3A*, *GRM1*, *GRM3*, *GRM4*, *GRM5*, *GRM7* and *GRM8* (**Supplementary Table 2**). Only one SNP, rs1396409 was significantly associated with performance IQ after multiple-testing correction (non-missing individuals=144; uncorrected p-value= $9.5 \cdot 10^{-4}$; corrected p-value=0.041). This SNP is located in (hg19) chr3:7302907 and encompass the *GRM7* gene. It was not associated with VIQ nor with

total FIQ score. Then, we performed a detailed association between this SNP and each sub-test of the IQ test in the same cohort (**Table 2**). In the UHR cohort, only the SNP rs1396409 was analyzed. This SNP was significantly associated with PIQ, FIQ and POI, but was not associated with VIQ nor VCI (non-missing individuals=121) (**Table 2**).

The two cohorts were merged in a whole dataset (n=265 individuals). The SNP rs1396409 was analyzed and 10,000 permutations were done. This SNP was significantly associated with VIQ, PIQ and FIQ (**Table 2**). The association was significant for the arithmetic subtest of the WAIS and near-significant for the block design and the information subtests. Different genetic models were tested (**Table 3**): the SNP was more significantly associated with FIQ, VIQ and arithmetic subtest in a *T*-allele dominant model whereas it was more significantly associated with PIQ in an additive model. The effect is not due to outliers and we report a real shift of the distribution of IQ depending on the genotypes (**Supplementary Figure 1**).

Discussion

In the present study testing 43 SNPs in 9 glutamatergic genes, only one SNP, located in *GRM7* was associated with cognition in the early phases of psychosis. We found that the *C* allele of rs1396409 was significantly associated with lower PIQ in UHR and FEP cohorts with an additive effect for the *C* allele. Interestingly the association of this SNP with VIQ became significant only in the merged dataset with a recessive effect of the *C* allele. This difference could be explained because the effect on VIQ is less important than on PIQ: loss of 5 VIQ points compared to 10 PIQ points in the *C* allele homozygous carriers. This effect may have required a larger sample size to identify. The effect on full IQ is also significant and could be mediated by the significantly worse performance on the arithmetic subtest in *C*-allele homozygous individuals compared to the *T*-allele carriers.

Association of rs1396409 with two other subtests (information and block design) approached significance in the total data set.

In a previous mega-analysis of the general population (Sniekers et al., 2017), rs1396409 was not found to influence human intelligence ($p=0.429$). Nevertheless, an exploration of the UK Biobank data showed that this SNP has a close to significance association with “age completed full time education” (<http://big.stats.ox.ac.uk/variant/3:7302907-G-A>), a factor correlated with IQ (Plomin and Stumm, 2018). This SNP was not reported to be associated with general cognition in schizophrenia (Smeland et al., 2017). This, combined with results from the current analysis, may indicate that this SNP is specifically associated with cognitive deficits during the onset of psychotic illness. This could be because cognitive deficits in later phases of the illness may stem from multiple other sources such as social deprivation and the effect of medication, which can dilute any genetic association. It is also possible that the genetic underpinnings of cognitive deficits in psychosis may be phase-specific and that cognitive deficits in later stages of the illness may stem from different genetic mechanisms compared with those in early stages. However, the lack of association of this SNP with cognition both in the general population and in chronic schizophrenia could also be due to difference in methodology. For example, large studies investigated the G factor instead of full IQ. G factor refers to the general intelligence factor, a psychometric construct deemed to summarize an individual’s intelligence based on the person’s performance to different cognitive tasks. Whereas G factor may capture the general cognitive ability, it is much less detailed than the WAIS test we used in both of our datasets. Although the WAIS assessment is time-consuming, it provided a detailed cognitive measure with a well-validated face-to-face test.

In summary, we propose that this SNP is associated with cognitive impairment during the onset of psychosis. This association may be masked by other factors in chronic states where etiology of cognition deficits could be more heterogeneous (Cohen and Murante, 2017), under the influence

of long-term medication (Hulkko et al., 2017; Husa et al., 2014) or the “toxic biopsychosocial” impact of the illness progression (Brewer et al., 2006). Investigating the association between genetics variants and cognitive deficits in the early phases of illness may therefore carry the advantage of circumventing several confounding factors that are present in later phases of the illness and could explain why previous genetic associations with cognition in schizophrenia have not identified this SNP.

The effect of rs1396409 on both VIQ and FIQ is large, with an effect-size that should have clinical utility. For example, it has been estimated that every point decrease in IQ significantly increases the risk of schizophrenia by 3.7% , with a similar effect of verbal and nonverbal measures (Khandaker et al., 2011). Here, we reported a shift in the distribution of IQ, as large as 5 points for VIQ and 10 points for PIQ.

Some limitations need to be kept in mind while interpreting the results of this study. First, we could not exclude that the SNP may be indirectly associated with IQ, via other factors like drug use which has been shown to play a role in cognition in early phases of psychosis (Buchy et al., 2015). Second, we restricted our analysis to the glutamatergic receptors, whereas other genes involved in glutamatergic function have shown to influence cognition in schizophrenia, including genes involved in glutamate reuptake, *NEUROG1*, *MAGI2*, *DTNBP1*... (Thomas et al., 2017). For instance, functional polymorphisms of the excitatory amino-acid transporters *EAAT1* and *EAAT2* (also called *SLC1A3* and *SLC1A2* respectively) have been associated with cognitive dysfunction in schizophrenia (Spangaro et al., 2014) but also to a differential response to cognitive remediation therapy in this disorder (Spangaro et al., 2018). Exploring the epistatic interactions between genes involved in the glutamatergic pathway, or more broadly in the excitatory/inhibitory balance, would be an interesting future development. However, testing these interactions would have required larger sample size. Our limited sample size allowed us to identify only one SNP

significantly associated with cognition in the FEP cohort. To improve our statistical power, we merged cohorts recruited in two different centers. Noteworthy, the cognitive assessment was highly comparable as indicated by the standardization of the tests. While merging both UHR and FEP patients may result in a heterogeneous sample, the phenotypes investigated in this study are commonly described in the psychotic field as the early clinical phases of psychosis. A recent study investigated the difference in cognition between FEP and UHR and found no evidence of cognitive decline between these two stages (Carrión et al., 2018). We acknowledge, however, that cognition in UHR may be different between those who later convert to psychosis and those who do not. In our UHR cohort, 37.3% will develop a psychotic disorder after the follow-up. Thus, the heterogeneity of the merged cohort should have (if anything) diminished the statistical significance of our results.

The rs1396409 is a tag SNP for 7 other SNPs. All of them are located in the second intron of the *GRM7* gene in chr3:7239504-7290152 (hg19). Polymorphisms in this gene have previously been associated with schizophrenia (Li et al., 2016, p. 7) and bipolar disorder (Kandaswamy et al., 2014; Wellcome Trust Case Control Consortium, 2007). It is encompassed by Copy Number Variations associated with schizophrenia (Bassett et al., 2017), ADHD (Elia et al., 2011) and ASD (Liu et al., 2015). Rare truncating variants in *GRM7* have been reported in neurodevelopmental disorders with intellectual disabilities (Reuter et al., 2017). *GRM7* has also been implicated in response to antipsychotic treatment in psychosis (Sacchetti et al., 2017; Stevenson et al., 2016) with three intronic SNPs associated with poor response to treatment. One of them, rs2133450, is located in the same intron than rs1396409. Homozygotes for the at-risk allele in the CATIE study respond worse to risperidone in term of positive symptoms but also in the general subscale of the PANSS which include measurement of the cognitive deficits (Sacchetti et al., 2017). Recently, several

SNPs located in *GRM7* have been associated with response to various antipsychotics, suggesting its interesting role in pharmacogenetics (Liang et al., 2020).

Interestingly, rs1396409 is predicted by SCANdatabase (Zhang et al., 2015) to be significantly associated with expression of the transcription factor *CREB2* (with a p-value at 10^{-4} in HapMap Caucasian residents from Utah). *CREB2*, also known as Activating Transcription Factor 2 (*ATF2*), is a CREB repressor, meaning that it decreases the CAMP response element-binding (CREB) proteins. It has been shown that the role of *GRM7* in neurodevelopment is mediated by the CREB pathway (Xia et al., 2015). When signals arrive at glutamate receptors, a proteinic cascade leads to an activation of CREB proteins. In neurons, CREB pathway is involved in the formation of long-term memories and long-term potentiation. Genetic variations in *GRM7* could lead to alteration in the CREB pathway and deficits in learning. *GRM7* undergo a progressive age-dependent decrease of expression in the human prefrontal cortex (Choi et al., 2009), suggesting that this gene could be involved in developmental deregulation, including those that are predisposing to psychiatric disorders. Any disruption in this gene may predispose individuals to cognitive deficits, which, in interaction with other risk factors, can increase the likelihood of the emergence of psychotic disorders.

Conclusion

Exploring the impact of polymorphisms in glutamatergic receptors on cognition in FEP, we detected a significant association between rs1396409 and IQ in this population and replicated this finding in a UHR sample. Cognition is a very important domain in psychosis with a major impact in terms of functioning and functional prognosis; glutamatergic drugs have recently been

proposed to improve cognition. This study could help to provide rationale to address the cognitive deficits in the early phases of psychosis with these new therapeutic drugs.

Table 1: description of the population including the baseline clinical scores

	FEP cohort	UHR cohort
Sample	148 first-episode of psychosis	129 ultra-high risk
Genotyping	Panel of 58 SNPs	Extraction from the PsychArray genotyping data
Phenotypic presentation	77.6% non affective 22.4% affective	37.4% will develop a psychotic disorder
Sex	75.2% male 24.8 % female	59.7% male 40.3% female
Mean age (\pm SD)	22.7 \pm 3.7	21.5 \pm 3.5
Mean SOFAS (\pm SD)	42.7 \pm 13.2	47.3 \pm 10.0
Mean SANS (\pm SD)	31.2 \pm 15.4	30.6 \pm 21.0
Mean SAPS (\pm SD)	35.2 \pm 14.8	16.1 \pm 12.9
Mean PANSS (\pm SD)	83.9 \pm 16.8	69.7 \pm 17.6
Mean VIQ (\pm SD)	94.4 \pm 15.3	104.0 \pm 13.9
Mean PIQ (\pm SD)	91.3 \pm 16.8	98.8 \pm 12.9
Total IQ (\pm SD)	92.8 \pm 15.4	102.0 \pm 13.3

SOFAS=Social and Occupational Functioning Assessment Scale; SANS=Scale for the Assessment of Negative Symptoms; SAPS= Scale for the Assessment of Positive Symptoms; PANSS=Positive And Negative Syndrome Scale; VIQ=verbal intelligence quotient; PIQ=performance intelligence quotient; IQ=intelligence quotient; SD=Standard deviation

Table 2: Association between rs1396409 and cognitive measures.

		FEP cohort (n=144)		UHR cohort (n=121)		Merged dataset (n=265)	
		Beta	Uncorrected p-value	Beta	p-value	Beta	p-value
Verbal IQ		2.94	0.11	3.40	0.07	3.257	0.02
Performance IQ		6.45	9.5.10⁻⁴	3.61	0.04	5.265	2.1.10⁻⁴
Full IQ		7.97	7.10 ⁻³	4.13	0.02	4.558	9.6.10⁻⁴
Verbal comprehension index	Vocabulary	6.25	0.06	0.52	0.20	1.15	0.40
	Similarities	1.06	0.15	0.43	0.31	0.66	0.26
	Information	1.55	0.03	-0.02	0.96	0.80	0.08
Working memory index	Arithmetic	1.00	0.03	0.79	0.04	0.87	8.2.10⁻³
	Digit Span	0.1957	0.67	0.85	0.04	0.42	0.32
Perceptual Organisation Index	Picture completion	1.12	0.02	0.52	0.14	0.75	0.10
	Block Design	1.55	2.6.10⁻⁴	0.90	0.04	3.31	0.06
	Matrix reasoning	NA	NA	0.31	0.39	NA	NA
Processing Speed Index	Digit Symbol Coding	2.25	0.23	0.66	0.10	0.82	0.76

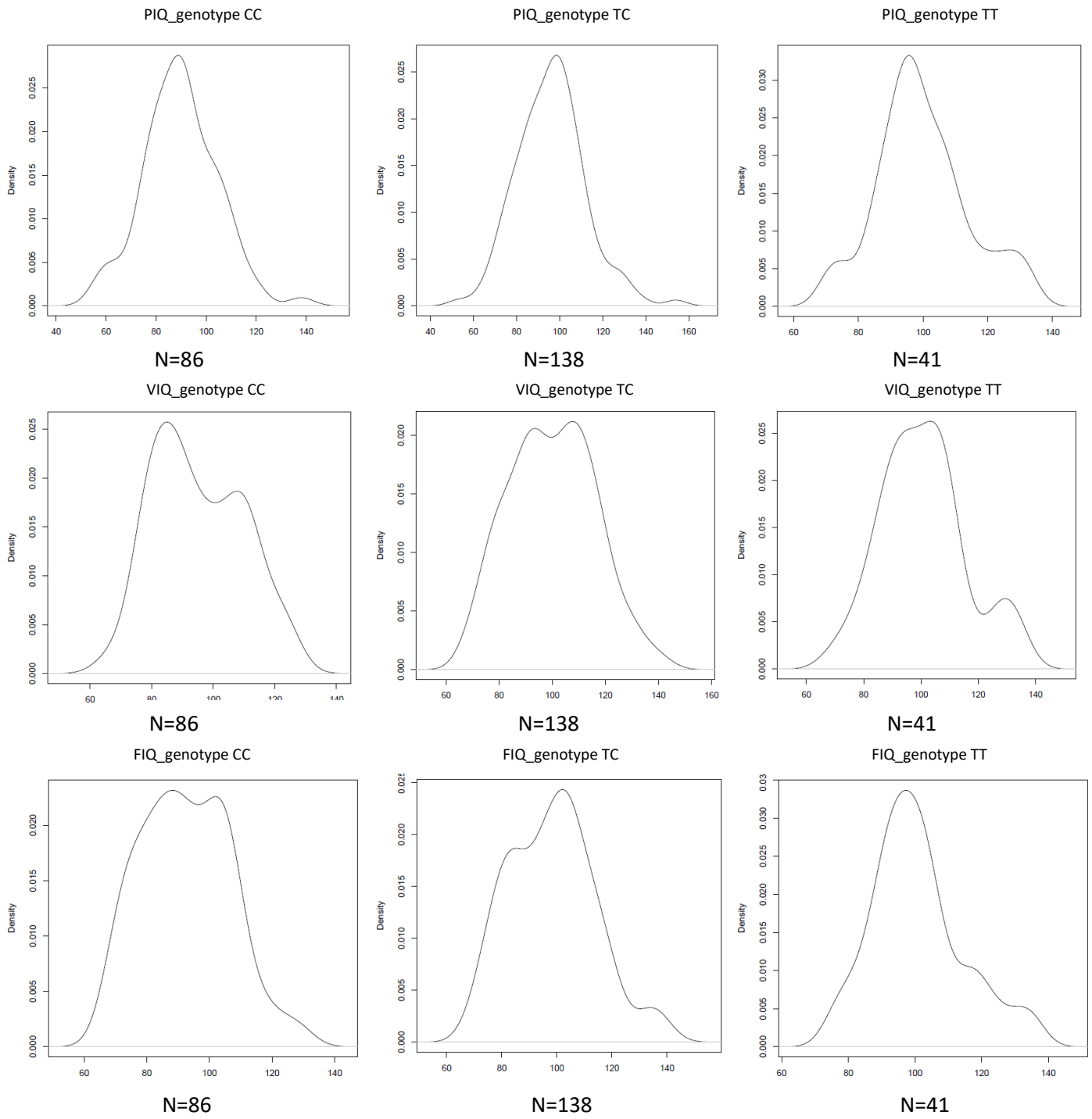
FEP=first-episode of psychosis; UHR=ultra-high risk; IQ=intelligence quotient

Table 3: Genetic models for association between rs1396409 and cognitive domains

Genotype	Number of individuals	frequency	PIQ (means ± SD)	VIQ (means ± SD)	FIQ (means ± SD)	Arithmetic (means ± SD)
TT	41	0.15	99.9 ± 14.3	100.8 ± 14.9	100.8 ± 13.8	11.4 ± 3.4
TC	138	0.52	95.9 ± 15.9	100.3 ± 15.9	98.5 ± 15.7	11.2 ± 3.6
CC	86	0.33	89.8 ± 14.8	95.2 ± 14.5	92.4 ± 14.1	9.9 ± 3.7
p-value in the recessive model (C allele)			5.10 ⁻⁴	0.01	9.0.10 ⁻⁴	4.4.10 ⁻³
p-value in the dominant model (C allele)			0.02	0.34	0.07	0.22
p-value in the additive model			2.1.10 ⁻⁴	0.02	9.6.10 ⁻⁴	0.02

VIQ=verbal intelligence quotient; PIQ=performance intelligence quotient; IQ=intelligence quotient; SD=standard deviation

Supplementary figure 1: Distribution of performance IQ, verbal IQ and full IQ in the merged dataset (FEP+UHR), regarding the genotype for the rs1396409



Supplementary Table 1: selection of candidate SNPs and quality control

NMDA ionotropic glutamate receptors (NMDAR) are composed by different sub-units and one associated-protein coding by 8 genes: GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, GRIN3B, GRINA. Metabotropic glutamate receptor (mGluR) are encoded by 8 genes: GMR1 to GMR8.

Pass: successfully genotyped and remaining after quality control

Excluded after QC: not surviving after quality control

Failed: failed to be genotyped

SNP	Chr	Position_hg19	nominal p-value in PGC	Gene Name	Criteria of selection	Genotyping	minor allele frequency
rs41290007	chr9	140055703	0.01076	GRIN1	Best SNP in PGC	failed	-
rs9922678	chr16	9946319	6.72E-09	GRIN2A	Best SNP in PGC	pass	0.3442
rs2193146	chr12	13732966	1.01E-05	GRIN2B	Best SNP in PGC	excluded after QC	0.02778
rs11575878	chr17	72847899	0.2459	GRIN2C	Best SNP in PGC	excluded after QC	0.05093
rs74192709	chr19	48922695	0.01098	GRIN2D	Best SNP in PGC	excluded after QC	0.02083
rs1337682	chr9	104491984	0.00215	GRIN3A	Best SNP in PGC	pass	0.257
rs35163060	chr19	1003158	0.002879	GRIN3B	Best SNP in PGC	failed	-
rs187720814	chr8	145064304	0.1802	GRINA	Best SNP in PGC	failed	-
rs2206956	chr6	146739228	0.0008147	GRM1	Best SNP in PGC	pass	0.3415
rs113426529	chr3	51746239	0.03932	GRM2	Best SNP in PGC	excluded after QC	0.01852
rs12704290	chr7	86427626	1.04E-10	GRM3	Best SNP in PGC	failed	-
rs3778049	chr6	34000334	0.002248	GRM4	Best SNP in PGC	pass	0.169
rs12364009	chr11	88484625	0.0007805	GRM5	Best SNP in PGC	failed	-
rs79615824	chr5	178411788	0.1188	GRM6	Best SNP in PGC	excluded after QC	0.03505
rs1516570	chr3	7005021	1.21E-05	GRM7	Best SNP in PGC	pass	0.3403
rs34108879	chr7	126533413	0.0006322	GRM8	Best SNP in PGC	failed	-
rs7806785	chr7	86446316	8.69E-05	GRM3	Tag SNP representing 10 SNPs	pass	0.3231
rs10772718	chr12	14042569	0.04944	GRIN2B	Tag SNP representing 11 SNPs	pass	0.4375
rs2173506	chr3	7109343	0.02207	GRM7	Tag SNP representing 11 SNPs	pass	0.4954
rs6943659	chr7	86395926	0.02853	GRM3	Tag SNP representing 12 SNPs	pass	0.338
rs13224108	chr7	126595060	0.00384	GRM8	Tag SNP representing 12 SNPs	pass	0.1651
rs982339	chr7	86399943	0.001183	GRM3	Tag SNP representing 13 SNPs	pass	0.2269
rs9924590	chr16	10198160	0.004941	GRIN2A	Tag SNP representing 17 SNPs	excluded after QC	0.4179
rs10236114	chr7	126211706	0.02832	GRM8	Tag SNP representing 17 SNPs	pass	0.2256
rs10274631	chr7	86376791	0.0425	GRM3	Tag SNP representing 18 SNPs	excluded after QC	0.3291
rs950789	chr7	126459894	0.04188	GRM8	Tag SNP representing 19 SNPs	pass	0.3167
rs9390385	chr6	146732956	0.001393	GRM1	Tag SNP representing 20 SNPs	pass	0.3373
rs17047063	chr3	7343584	0.02344	GRM7	Tag SNP representing 21 SNPs	pass	0.4907
rs12489402	chr3	7346663	0.01915	GRM7	Tag SNP representing 22 SNPs	pass	0.4352
rs2067052	chr7	126576100	0.0146	GRM8	Tag SNP representing 27 SNPs	pass	0.3542
rs3808138	chr7	126615249	0.03532	GRM8	Tag SNP representing 28 SNPs	pass	0.346
rs17717959	chr3	7481854	0.02896	GRM7	Tag SNP representing 33 SNPs	pass	0.412
rs7196095	chr16	9885832	2.94E-06	GRIN2A	Tag SNP representing 34 SNPs	pass	0.3495
rs11640274	chr16	9986993	0.0005092	GRIN2A	Tag SNP representing 39 SNPs	pass	0.2245
rs8052950	chr16	9910348	9.68E-06	GRIN2A	Tag SNP representing 41 SNPs	pass	0.3056
rs7205180	chr16	10195584	0.02053	GRIN2A	Tag SNP representing 5 SNPs	pass	0.5
rs2300253	chr12	13861951	0.001193	GRIN2B	Tag SNP representing 5 SNPs	pass	0.4769
rs12208577	chr6	146730405	0.004148	GRM1	Tag SNP representing 5 SNPs	pass	0.2977
rs17126	chr7	86471913	0.0007028	GRM3	Tag SNP representing 5 SNPs	pass	0.2986
rs308893	chr11	88270912	0.01301	GRM5	Tag SNP representing 5 SNPs	pass	0.375
rs8049651	chr16	9943666	1.95E-06	GRIN2A	Tag SNP representing 50 SNPs	pass	0.2685
rs1805543	chr12	13784313	0.004763	GRIN2B	Tag SNP representing 7 SNPs	excluded after QC	0.2598
rs10234440	chr7	86420377	4.39E-07	GRM3	Tag SNP representing 7 SNPs	pass	0.1667
rs9469690	chr6	34012911	0.01449	GRM4	Tag SNP representing 7 SNPs	pass	0.2847
rs9879127	chr3	7371887	0.00616	GRM7	Tag SNP representing 7 SNPs	pass	0.4953
rs17863212	chr7	126739666	0.02346	GRM8	Tag SNP representing 7 SNPs	pass	0.1852
rs1375075	chr16	10175729	0.03155	GRIN2A	Tag SNP representing 79 SNPs	pass	0.1455
rs2499677	chr6	34007054	0.04234	GRM4	Tag SNP representing 8 SNPs	excluded after QC	0.3471
rs1396409	chr3	7302907	0.02254	GRM7	Tag SNP representing 8 SNPs	pass	0.4019
rs9812897	chr3	7277163	0.008734	GRM7	Tag SNP representing 8 SNPs	pass	0.3981
rs12447502	chr16	10149278	0.01992	GRIN2A	Tag SNP representing 9 SNPs	pass	0.481
rs2315272	chr16	9969102	0.0002387	GRIN2A	Tag SNP representing 9 SNPs	pass	0.3152
rs7196797	chr16	9864569	0.002781	GRIN2A	Tag SNP representing 9 SNPs	pass	0.4112
rs2300256	chr12	13868410	0.003367	GRIN2B	Tag SNP representing 9 SNPs	pass	0.3843
rs2282958	chr7	86280851	0.002104	GRM3	Tag SNP representing 9 SNPs	pass	0.09091
rs802432	chr7	86284433	0.0002564	GRM3	Tag SNP representing 9 SNPs	pass	0.2083
rs973716	chr11	88258182	0.004673	GRM5	Tag SNP representing 9 SNPs	pass	0.1366
rs12706761	chr7	126740946	0.04958	GRM8	Tag SNP representing 9 SNPs	pass	0.2605

Supplementary Table 2: Quantitative association study with full IQ, verbal IQ and performance Q in the PEPP cohort

SNP	Gene	Full IQ					Verbal IQ					Performance IQ				
		Sample size	Beta value	Standard error	Uncorrected P value	Corrected P value	Sample	Beta	Standard error	Uncorrected P value	Corrected P value	Sample	Beta	Standard error	Uncorrected P value	Corrected P value
rs1396409	GRM7	144	7.974	2.916	0.007062	0.303666	144	2.936	1.83	0.1108	1	144	5.142	1.523	0.0009535	0.0410005
rs10236114	GRM8	146	-10.46	3.6	0.004257	0.183051	146	-5.321	2.231	0.01839	0.79077	146	-4.61	1.928	0.0181	0.7783
rs17126	GRM3	147	-4.001	2.983	0.182	1	147	-0.1074	1.841	0.9536	1	147	-3.642	1.562	0.02111	0.90773
rs973716	GRM5	147	7.805	4.081	0.05781	1	147	6.331	2.479	0.01168	0.50224	147	1.19	2.189	0.5876	1
rs10234440	GRM3	147	2.805	3.613	0.4387	1	147	3.157	2.205	0.1543	1	147	0.202	1.919	0.9163	1
rs10772718	GRIN2B	147	1.906	2.99	0.5249	1	147	0.8637	1.835	0.6385	1	147	1.086	1.585	0.4942	1
rs11640274	GRIN2A	147	-0.9883	3.314	0.7659	1	147	-0.5456	2.032	0.7887	1	147	-0.04287	1.757	0.9806	1
rs12208577	GRM1	147	2.573	3.156	0.4163	1	147	0.5813	1.939	0.7648	1	147	2.922	1.659	0.08031	1
rs12447502	GRIN2A	143	0.5652	2.913	0.8464	1	143	-0.05426	1.77	0.9756	1	143	1.21	1.546	0.4353	1
rs12489402	GRM7	147	3.059	2.886	0.2909	1	147	2.455	1.765	0.1663	1	147	0.6757	1.535	0.6604	1
rs12706761	GRM8	146	1.613	3.243	0.6197	1	146	1.004	1.994	0.6154	1	146	0.2554	1.717	0.882	1
rs13224108	GRM8	146	-1.181	3.946	0.7651	1	146	-0.1919	2.413	0.9367	1	146	-1.338	2.102	0.5254	1
rs1337682	GRIN3A	146	-0.6483	3.155	0.8375	1	146	-1.279	1.934	0.5096	1	146	1.576	1.665	0.3453	1
rs1375075	GRIN2A	144	1.424	3.878	0.7141	1	144	2.836	2.377	0.2348	1	144	-1.713	2.044	0.4034	1
rs1516570	GRM7	147	1.293	3.151	0.6821	1	147	-0.4072	1.933	0.8335	1	147	1.937	1.663	0.2461	1
rs17047063	GRM7	146	-1.542	2.833	0.5872	1	146	-0.9583	1.737	0.5821	1	146	-0.5833	1.503	0.6985	1
rs1717959	GRM7	147	-1.61	2.552	0.5291	1	147	-0.9472	1.565	0.546	1	147	-0.161	1.355	0.9055	1
rs17863212	GRM8	147	4.234	3.641	0.2468	1	147	2.05	2.237	0.3609	1	147	1.883	1.933	0.3315	1
rs2067052	GRM8	147	-1.417	2.941	0.6306	1	147	-1.628	1.8	0.3671	1	147	0.9504	1.558	0.5428	1
rs2173506	GRM7	147	-0.1854	2.534	0.9418	1	147	-0.07975	1.554	0.9591	1	147	-0.08256	1.344	0.9511	1
rs2206956	GRM1	139	6.236	3.023	0.041	1	139	2.476	1.866	0.1866	1	139	3.335	1.606	0.03976	1
rs2282958	GRM3	143	-3.619	5.419	0.5054	1	143	0.03406	3.316	0.9918	1	143	-3.933	2.859	0.1711	1
rs2300253	GRIN2B	147	-1.207	2.571	0.6395	1	147	-0.9958	1.575	0.5283	1	147	-0.2197	1.364	0.8722	1
rs2300256	GRIN2B	147	3.799	2.932	0.1971	1	147	1.263	1.805	0.4853	1	147	2.684	1.547	0.08487	1
rs2315272	GRIN2A	146	-3.259	2.911	0.2647	1	146	-1.496	1.789	0.4044	1	146	-1.56	1.544	0.3142	1
rs308893	GRM5	147	-2.891	3.061	0.3466	1	147	-0.5992	1.882	0.7507	1	147	-1.533	1.623	0.3463	1
rs3778049	GRM4	147	6.304	3.28	0.05654	1	147	2.755	2.024	0.1755	1	147	3.281	1.739	0.06122	1
rs3808138	GRM8	143	4.165	3.389	0.2211	1	143	3.12	2.088	0.1374	1	143	0.5395	1.795	0.7642	1
rs6943659	GRM3	147	-2.456	2.902	0.3988	1	147	0.5191	1.784	0.7714	1	147	-2.796	1.525	0.0687	1
rs7196095	GRIN2A	147	-1.176	2.908	0.6865	1	147	-1.541	1.779	0.3881	1	147	0.5433	1.542	0.725	1
rs7196797	GRIN2A	146	0.05662	2.937	0.9846	1	146	-0.8771	1.779	0.6228	1	146	1.627	1.56	0.2985	1
rs7205180	GRIN2A	143	2.952	2.823	0.2975	1	143	1.598	1.729	0.3569	1	143	1.365	1.484	0.3594	1
rs7806785	GRM3	144	-1.895	2.753	0.4923	1	144	0.4733	1.683	0.7789	1	144	-2.199	1.448	0.131	1
rs802432	GRM3	147	0.8661	3.183	0.7859	1	147	1.153	1.95	0.5553	1	147	0.05023	1.688	0.9763	1
rs8049651	GRIN2A	147	0.1917	3.13	0.9513	1	147	-0.2579	1.92	0.8933	1	147	0.7622	1.658	0.6465	1
rs8052950	GRIN2A	147	-1.323	2.993	0.6592	1	147	-1.047	1.835	0.5691	1	147	-0.01803	1.588	0.991	1
rs9390385	GRM1	141	5.047	3.072	0.1026	1	141	1.961	1.924	0.3098	1	141	2.653	1.615	0.1028	1
rs9469690	GRM4	147	1.965	2.809	0.4854	1	147	1.376	1.722	0.4254	1	147	0.2647	1.491	0.8594	1
rs950789	GRM8	142	0.4559	3.192	0.8866	1	142	-1.275	1.955	0.5154	1	142	1.325	1.685	0.4328	1
rs9812897	GRM7	147	-1.359	2.959	0.6468	1	147	0.004356	1.816	0.9981	1	147	-1.233	1.567	0.4325	1
rs982339	GRM3	147	2.934	3.298	0.3752	1	147	2.658	2.016	0.1893	1	147	0.6587	1.752	0.7075	1
rs9879127	GRM7	146	1.299	2.929	0.658	1	146	-1.838	1.771	0.301	1	146	3.165	1.54	0.0417	1
rs9922678	GRIN2A	147	-1.788	2.849	0.5314	1	147	-0.6792	1.749	0.6983	1	147	-0.9292	1.511	0.5394	1

Author contribution

BC, SMS, MOK, JLS and RJ designed the study. GAR, MOK, JLS and RJ obtained funding and supervised the study. BC, SMS, ML, AM, SNI, OK and contributors of the ICAAR study group collected the data. BC analyzed the data. BC, SMS, and PAD interpreted the data. BC, SMS, PAD, JLS and RJ drafted the report. All authors and contributors of the ICAAR study group read and approved the final manuscript.

Conflicts of interest

Dr. Joober reports to be a speaker and/or consulting committee member for Pfizer, Janssen, BMS, Sunovian, Myelin, Otsuka, Lundbeck, shire and Perdue, and to have received grants from Janssen, BMS, Otsuka, Lundbeck, Astra Zeneca and HLS, and to have royalties from Henry Stewart talks, all outside the submitted work.

Dr. Malla served as a research consultant to and gave lectures at conferences supported by Lundbeck and Otsuka and was on an advisory board meeting for the same two companies for which he received honoraria.

Pr. Krebs has received honoraria from and participated in advisory boards or did educational conference for F. Hoffmann-La Roche, Janssen Cilag and Otsuka-Lundbeck. She received financial support for investigator-driven educational initiative from Eisai, Janssen Cilag and Otsuka-Lundbeck.

Dr. Lepage reports grants from Otsuka Lundbeck Alliance, personal fees from Otsuka Canada, personal fees from Lundbeck Canada, grants and personal fees from Janssen, personal fees from MedAvante-Prophase, personal fees from Amplexor, outside the submitted work.

Dr. Chaumette has received speaking fees from Janssen Cilag, outside the submitted work.

All authors declare they have no conflict of interest related to this article. The contributing Group members (ICAAR study group) declare no conflict of interest.

Role of the sponsors

The sponsors had no role in the design and conduct of the study, in the collection, management, analysis or interpretation of the data, in the preparation, review or approval of the manuscript, or in the decision to submit the manuscript for publication.

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