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Effects of *GRASP* variation on memory in psychiatrically healthy individuals and cognitive dysfunction in schizophrenics

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ABSTRACT

Mechanistic studies indicate general receptor for phosphoinositides-1-associated scaffold protein (GRASP, also referred to as Tamalin) is involved in neurite development, proliferation, and branching in hippocampal neurons, but its physiological effects on cognitive function is mostly unknown. Cognitive impairment is a core feature of schizophrenia, and recent reports indicate increased abundance of GRASP proteins in postmortem schizophrenia cortex and hippocampus, both of these structures being highly relevant to cognitive processes. We therefore assessed the effects of a single nucleotide polymorphism (SNP) rs10876227 [G > A] in *GRASP* on eight different domains of cognitive function in a well-established Caucasian case-control cohort for schizophrenia. In 261 control individuals (166 males), strong effects of rs10876227 were observed on immediate memory, delayed memory, and working memory, with the major G allele associated with worse memory performance on each test. Additional analyses including 249 patients with schizophrenia (174 males) indicated that the G allele of rs10876227 was also able to distinguish male schizophrenia participants with severe cognitive deficits (CD; 81 males) from male schizophrenia participants with relatively spared cognitive function (CS; 91 males). However analyses of the effects of *GRASP* variation on individual cognitive domains in the combined sample showed no interactive effects of clinical status and rs10876227 variation. These findings converge with prior mechanistic and postmortem studies to strongly support contribution of *GRASP* variation to memory function, and general cognitive ability in men with schizophrenia, likely via GRASP-directed plasticity. The implications of these findings extend to other disorders where cognitive function is a core component, such as dementia, autism and mental retardation.

1. Introduction

The General Receptor for phosphoinositides 1-Associated Scaffold Protein (GRASP; also referred to as the alias Tamalin) is a putative regulator of cognitive function by modulation of neuronal plasticity (Yanpallewar et al., 2012). The main function of GRASP is to form macromolecular complexes in the postsynaptic density (PSD) by binding multiple signaling partners *via* its protein-interacting domains (Kitano et al., 2003). Importantly, GRASP clusters the major scaffold proteins PSD-95 and GKAP proteins (Kitano et al., 2003), which facilitate widespread protein-protein interactions in the PSD (Kitano et al., 2003). GRASP also facilitates cell surface expression and intracellular movement of inhibitory and excitatory G-protein coupled neurotransmitter receptors, such as the gamma aminobutyric acid (GABA) receptor and mGluR1/5 (Kitano et al., 2002).

Organization of GABA and glutamate receptors in time and space is critical for modulation of inhibitory:excitatory neurotransmission and plasticity (Lewis, 2014), suggesting an important role for *GRASP* in the modulation of cognitive function. This hypothesis is supported in mice, with a deficiency in *GRASP* expression blocking electroconvulsive shock therapy (ECS)-induced neurite proliferation, development and

Abbreviations: GRASP, general receptor for phosphoinositides-1-associated scaffold protein; SNP, single nucleotide polymorphism; CD, cognitive deficits; CS, cognitively spared; PSD, postsynaptic density; NMDARs, *N*-methyl-D-aspartate receptors; AMPARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; GABA, gamma aminobutyric acid; mGluR1/5, metabotropic glutamate receptors 1 and 5; ECS, electroconvulsive shock therapy; 5′ UTR, 5′ untranslated region; DIP, diagnostic interview for psychosis; WASI, Wechsler Abbreviated Scale of Intelligence Test; WTAR, Wechsler Test for Adult Reading; LNS, Letter Number Sequencing Test; RBANS, Repeatable Battery of Neuropsychological Status; GoM, Grade of Membership; MALDI-TOF MS, Matrix-assisted laser desorption and ionisation time-of-flight mass spectrometry; HWE, Hardy-Weinberg Equilibrium.

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dendritic arborization in adult progenitor cells from the dentate gyrus (Yanpallewar et al., 2012). Knockout of *GRASP* in rat hippocampal cultures was also shown to reduce dendritic outgrowth and arborization (Mo et al., 2012), together supporting that *GRASP* critically contributes to the modulation of dendritic development and consequently may influence activity-dependent plasticity. *GRASP*$^{-/-}$ knockout mice showed no difference in neurodevelopment or behaviors involving sensorimotor functions (including prepulse inhibition) or emotion (light/dark transition, elevated plus maze, social interactions or forced swim tests); however, the effects of *GRASP* knockout on cognitive functions was limited (Ogawa et al., 2007).

Cognitive dysfunction is a core symptom of the severe neuropsychiatric disorder, schizophrenia. Cognition is moderately to severely impacted in the disorder across several domains, including learning and memory (Green, 2006). This cognitive decline is arguably the most debilitating and least well-treated aspect of schizophrenia, considering the severity of impairment is closely linked with the level of disability and long-term functional outcomes (Green, 2006; Heinrichs, 2005; Jablensky, 2006a, 2006b; Keefe and Harvey, 2012). However cognitive impairments are not uniformly severe among schizophrenia patients, as demonstrated by several recent studies that have delineated two subtypes of schizophrenia on the basis of cognitive profile. The existence of these two subtypes of schizophrenia have been replicated in large case-control cohorts and their family members, representing cases with severe cognitive deficits (CD) as distinct from those with relatively spared cognitive function (CS) (CS; Green et al., 2013; Hallmayer et al., 2005; A. Jablensky, 2006a, 2006b). Further study of genetic variants specific to cognitive subtypes may assist in understanding how genetic variation contributes to cognitive impairment in schizophrenia.

Despite converging findings indicating a role for *GRASP* in human cognition, this remains unconfirmed. The present study therefore aimed to explore the role of genetic variation in *GRASP* in human cognition, and its potential contribution to cognitive dysfunctions observed in schizophrenia. To our knowledge, there have been no studies examining single nucleotide polymorphisms (SNP) in *GRASP* within human cohorts. We therefore selected a variant, rs10876227, on the basis of its location near the 5′ untranslated region (5′ UTR) of the gene (Fig. 1), which is a genomic region critical for the regulation of protein translation (Chorev and Carmel, 2012; Hughes, 2006), and relevant in light of recent postmortem reports indicating increased GRASP protein levels in schizophrenia (Matosin et al., 2015a, 2015b). Rs10876227 was tested for its association with eight measures of cognitive function in a Caucasian cohort, consisting of 268 healthy control participants and 268 matched schizophrenia cases. A separate postmortem human brain cohort was also genotyped to assess the possible impact of the chosen variants on GRASP protein levels. It was hypothesized that the examined genetic variant in *GRASP* would be associated with cognitive function in healthy controls and participants with schizophrenia. Considering the position of rs10876227 near the 5′ UTR, we also hypothesized this variant would be associated with the levels of GRASP protein levels in the brains of individuals with schizophrenia.

2. Materials and methods

2.1. Participants

Samples were obtained from the Australian Schizophrenia Research Bank (ASRB), a national bank of biological specimens. Subjects were selected from the bio bank using strict criteria:

(1) Schizophrenia patients diagnosed with schizophrenia according to the DSM-IV;

(2) Control subjects were required to have no personal or family history of mental disorder;

(3) Control subjects were selected to match schizophrenia cases according to sex and age (Table 1);

(4) All participants were required to be of Caucasian ethnicity, fluent in English and have no history of an organic brain disorder, post-traumatic amnesia, mental retardation, movement disorder, or substance dependence;

(5) Participants who received electroconvulsive therapy in the six months prior to testing were excluded from selection.

Trained researchers performed the Diagnostic Interview for Psychosis (DIP) for all participants. Extensive details regarding the clinical and demographic characterization, sampling frameworks and consent procedures for samples from the ASRB are published elsewhere (Loughland et al., 2010). This study was approved by and conducted according to the guidelines of the University of Wollongong Human Research Ethics Committee (HE10/161) and the University of New South Wales Human Ethics Committee (HC12658).

2.2. Neuropsychological measures and cognitive subtyping

Standardized measures of premorbid and current intelligence quotient (IQ) were obtained using the Wechsler Abbreviated Scale of Intelligence test (WASI) and the Wechsler Test for Adult Reading (WTAR) (Wechsler, 1997, 2001). The Letter Number Sequencing test (LNS) was used to assess working function (Spreen, 1998; Wechsler, 1997). Indices of attention, delayed memory, immediate memory, visuospatial construction and language construction were derived using the Repeatable Battery of Neuropsychological Status (RBANS) (Randolph, 1998). A large subgroup of 247 schizophrenia patients were classified as either displaying a general cognitive deficit (CD) or displaying relatively spared cognitive function (CS), based on previous Grade of Membership (GoM) analyses of the ASRB sample previously described in detail (Green et al., 2013). Briefly, continuous indices for individual cognitive performance domains were converted to categorical performance measures (poor, moderate or good), and entered into the GoM analysis along with descriptive and demographic information including (but not limited to) sex, age of onset, mode of onset, psychosocial stressors, drug abuse, illness course, and family history of schizophrenia (Green et al., 2013). Breakdowns of the demographics for this sample are provided within Tables 1 and 4.

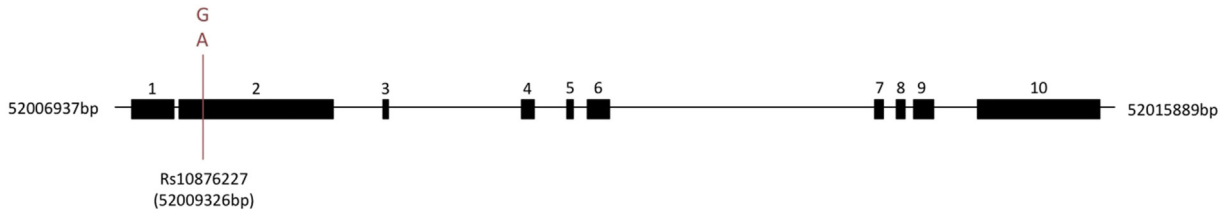

Fig. 1. Schematization of *GRASP* and rs10876227 (located in exon 2). Abbreviations: bp, base pair; SNP, single nucleotide polymorphism; rs, reference SNP.