Association between a Synaptosomal Protein (SNAP-25) Gene Polymorphism and Verbal Memory and Attention in Patients with Endogenous Psychoses and Mentally Healthy Subjects


Synaptosomal protein SNAP-25 is involved in the process of transmitting nerve spikes in the CNS and in the consolidation of memory traces in the hippocampus. Two independent studies have demonstrated associations between SNAP-25 gene polymorphisms and intellectual functions in a group of mentally healthy subjects and patients with schizophrenia. The aim of the present work was to perform a comparative study of the association between the MnlI polymorphism of SNAP-25 and cognitive functions (verbal memory, attention/executive functions) in 66 patients with endogenous psychoses, 75 of their mentally healthy relatives, and 136 healthy control subjects. Statistical analysis showed that the effectiveness of performing cognitive tests was significantly affected by group assignment (p = 0.00001) and genotype (p = 0.012). The interaction between genotype and group assignment also had an influence (p = 0.02). In all groups, carriers of the TT genotype had worse measures than carriers of other genotypes. The similar nature of the influences of the MnlI polymorphism on variations in measures in all groups indicates that this gene is related to overall intellect.

KEY WORDS: attention, memory, SNAP-25 gene, schizophrenia, general intellect.

Impairments to cognitive processes are regarded as among the key characteristics of the pathogenesis of schizophrenia. Studies of families have shown that relatives of patients have a whole series of neuropsychological impairments, similar to those noted in the patients themselves but less marked [1]. Quantitative assessments of the contribution of the genetic component vary from 35% to 50% depending on the cognitive measure being investigated [5, 15]. The search for genetic variants contributing to differences in neurocognitive measures was initiated relatively recently, and the number of candidates is as yet quite small. As a rule, these are genes involved in the functioning of the monoaminergic systems, as well as the processes of neuron growth, proliferation, and plasticity [2]. Thus, detection of new candidate genes contributing to variability in cognitive measures is a very relevant task.

One of the genes recently addressed by investigators is the SNAP-25 gene (synaptosomal-associated protein), which is located at chromosomal site 20p12-12p11.2. This gene encodes a synaptosomal protein with a molecular weight of 25 kDa, which is involved in nerve spike transmission, where it plays a key role in the release of neurotransmitter from synaptic vesicles, as well as in the processes of axon growth and dendrite formation. It is therefore very likely that changes in the structure of the SNAP-25 protein may influence the functioning of neurotransmitter systems associated with cognitive functions. Thus, experiments on laboratory animals showed that SNAP-25 is relat-
ed to the processes of memory trace consolidation (i.e., the transfer of information from short-term memory to long-term memory) because of its influences on long-term poten-
tiation in the hippocampus [8]. In the human brain, this pro-
tein’s activity has been detected in the neocortex, hip-
campus, anterior thalamic nuclei, substantia nigra, and
cerebellum. Studies of different parts of the brain in patients
with schizophrenia [9] demonstrated low levels of SNAP-25
in the cerebellum, which the authors felt could affect the
transmission of signals from this structure to the anterior
lobes of the brain. SNAP-25 immunoreactivity was also
lower in the hippocampus [14]. Increased levels of this pro-
tein were seen in the cerebrospinal fluid of schizophrenia
patients, and correlations were found between the level of
this protein and the severity of psychotic symptoms and the
occurrence of thought disorders [14]. Decreases in the
mRNA level were also found in various parts of the brains
in post mortem studies of patients with bipolar affective dis-
order [10].

Molecular genetic studies using a number of SNAP-25
polymorphic markers1 were first performed in children with
attention deficit hyperactivity disorder [13]. The search for
associations between gene polymorphisms and schizophrenia
did not yield any positive results [12, 16]. Further results
were reported [6] in which three polymorphic markers of
the SNAP-25 gene were used in mentally healthy subjects
and tests were performed to assess intellectual capacities.
These experiments demonstrated that one of the markers
(rs363050), located in intron 1 on a fragment of length
13.8 kb, showed a statistically significant association with
verbal intellect (Performance IQ, PIQ), and the authors
evaluated the contribution of the polymorphism to the phe-
notypic variability of PIQ as 3.4%.

In schizophrenia patients, the association between
SNAP-25 gene polymorphisms and cognitive characteris-
tics was first studied by Lezheiko [3]. This study used two
markers (MnlI and DdeI, or T1065G and T1069C, respec-
tively). An association between the T1065G polymorphism
of the SNAP-25 gene with the effectiveness of performing
neurocognitive tests was seen not only in schizophrenia
patients, but also in mentally healthy subjects. A recent
report [11], whose authors used these same markers, as well
as the TaI gene marker, to seek associations between
SNAP-25 and cognitive functions in patients with
schizophrenia and schizoaffective disorders, revealed an
association between one of them (DdeI) and the overall
level of cognitive functioning in patients and measures of
executive functions and verbal memory.

The aim of the present work was to continue studies of
the association between the T1065G polymorphism of the
SNAP-25 gene and measures of attention and verbal mem-
ory in an enlarged cohort of patients with endogenous psy-
choes and mentally healthy subjects.

MATERIALS AND METHODS

A total of 227 people took part in the study and were
assigned to three groups. Group 1 included 66 patients (21
men and 45 women) with a mean age of 34.7 ± 12.9 years;
mean age at onset of illness was 24.7 ± 9.4 years. Among
these patients, 37 had diagnoses of schizophrenia (ICD-10
F20), 26 had schizoaffective disorder (F25), and four had
bipolar disorder (F31).

Group 2 included 75 mentally healthy subjects (36 men
and 39 women) with a mean age 46.3 ± 12.9 years. All had
first-degree relatives with endogenous psychosis.

Group 3 (control group) included 136 mentally healthy
subjects (59 men and 77 women), with a mean age of 31.8 ±
13.0 years. In these cases there was no inherited tenden-
cy to mental diseases.

All study participants provided informed consent.

Psychological investigations included methods assess-
ing short-term and long-term verbal memory and atten-
tion/executive functions. Short-term memory was assessed
by asking subjects to remember and repeat, as quickly as
possible, words from a series read by the experimenter.
Each subject was presented two series each of 10 words.
The mean number of words reproduced was recorded.
Long-term memory was assessed using the pictogram
method – subjects were read 16 words with instructions to
link each word to a picture allowing the words to be remem-
bered after 40–60 min. Verbal fluency was assessed by ask-
ing the subject of name as many words of a specified
semantic category as possible for one minute. Two catego-
ries were presented in sequence. The total number of
words named by the subject in both tests was recorded.
Concentration of attention was assessed by serial counting
from 2 to 200 and adding fives to reach 100. The number of
correctly performed operations per minute was recorded.
This method allows attention and working memory to be
evaluated. Selectivity of attention was assessed by the
Munsterberg method, in which the subjects were presented
with a form with rows of letters, among which there were
some words, and asked to look at the form and name the
words. This assessed voluntary visual attention.

Molecular genetic methods included extraction of DNA
from venous blood using the phenol-chloroform method
and genotyping using the polymerase chain reaction. Genotyping
was performed using two markers, G1065T and C1069T,
located in the immediate vicinity of each other. SNAP-25
(T1065G, T1069C) genotyping was performed using
oligonucleotide primers TTTCTCCTCCAAATGCTGTCG
and CCACCCAGGAGAGAAATAATG, with denaturation
for 5 min at 95°C followed by 35 amplification cycles (94°C

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1 Polymorphic markers (polymorphisms) are used in seeking asso-
ciations between genes and any trait; these are areas within gene
DNA sequences in which one nucleotide is substituted by anoth-
er nucleotide, as well as other structural changes.