Synaptosomal-Associated Protein 25 Gene Polymorphisms and Antisocial Personality Disorder: Association With Temperament and Psychopathy

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Objective: The molecular genetic of personality disorders has been investigated in several studies; however, the association of antisocial behaviours with synaptosomal-associated protein 25 (SNAP25) gene polymorphisms has not. This association is of interest as SNAP25 gene polymorphism has been associated with attention-deficit hyperactivity disorder and personality.

Methods: We compared the distribution of DdeI and MnlI polymorphisms in 91 young male offenders and in 38 sex-matched healthy control subjects. We also investigated the association of SNAP25 gene polymorphisms with severity of psychopathy and with temperament traits: novelty seeking, harm avoidance, and reward dependence.

Results: The MnlI T/T and DdeI T/T genotypes were more frequently present in male subjects with antisocial personality disorder (APD) than in sex-matched healthy control subjects. The association was stronger when the frequency of both DdeI and MnlI T/T were taken into account. In the APD group, the genotype was not significantly associated with the Psychopathy Checklist–Revised scores, measuring the severity of psychopathy. However, the APD subjects with the MnlI T/T genotype had higher novelty seeking scores; whereas, subjects with the DdeI T/T genotype had lower reward dependence scores. Again, the association between genotype and novelty seeking was stronger when both DdeI and MnlI genotypes were taken into account.

Conclusion: DdeI and MnlI T/T genotypes may be a risk factor for antisocial behaviours. The association of the SNAP25 DdeI T/T and MnlI T/T genotypes with lower reward dependence and higher novelty seeking suggested that SNAP25 genotype might influence other personality disorders, as well.

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Clinical Implications

- SNAP25 DdeI and MnlI T/T genotypes may be a risk factor for antisocial behaviours.
- Other psychiatric disorders may be sharing SNAP25 gene polymorphisms as a common risk factor.

Limitations

- Small sample size of the study and control groups.
- Interpretation of the findings is limited to males.

Key Words: *antisocial personality disorder, gene polymorphism, synaptosomal-associated protein 25 gene, temperament, psychopathy, personality disorder*

APD is characterized by the hallmark features of the pervasive violation of others' rights, irresponsibility, impulsiveness, aggressiveness, deceitfulness, and lack of remorse.[1] The TCI temperament traits (novelty seeking, harm avoidance, reward dependence, and persistence) represent stable, inheritable, and neurobiological dispositions in the learning of automatic behavioural reactions in response to specific environmental stimuli.[2] Among these traits, APD has been reported to reflect high novelty seeking, low harm avoidance, and low reward dependence, while impulsive borderline personality disorder reflects high novelty seeking, high harm avoidance, and low reward dependence.[2] Psychopathy is a closely related but somewhat different concept. The Hare PCL-R is the most frequently used instrument in the measurement of psychopathy.[3]

The genetics of antisocial behaviours have been investigated extensively in recent years. It has been shown that there might be a genetic risk factor for the general vulnerability to personality disorder and negative emotionality. Conversely, there are 2 more specific genetic factors that might reflect high impulsivity and introversion.[4] Molecular genetic studies indicated that dopamine receptor 4 gene C-521T polymorphism might be associated with novelty seeking and impulsivity.[5] Meta-analysis results did not support a significant association between dopamine receptor 4 variable number tandem repeat polymorphism and novelty seeking, nor did they associate the serotonin transporter promoter region short allele with neuroticism or harm avoidance.[5]

SNAP25 is a presynaptic plasma membrane protein that plays an important role in the docking and fusion of the synaptic vesicle membrane.[6] SNAP25 constitutes complexes with synaptobrevin on the synaptic vesicles and with syntaxin on the plasma membrane that are related to the neuronal exocytosis triggered by calcium.[7] Simply stated, SNAP25 protein is important for fusion of synaptic vesicles and plasma membranes, which is critical for neurotransmission. The transmission of SNAP25 alleles in ADHD has been investigated, and these studies reported an increased transmission of the DdeI allele of a haplotype (made of allele 1 [T] of MnlI and allele 2 [G] of the DdeI) and of microsatellites in ADHD subjects.[8–12] Meta-analysis of these studies showed a significant association between MnlI and ADHD[13] (OR 1.19; 95% CI 1.03 to 1.38). In another meta-analysis, the SNAP25 gene was revealed to indicate the subject to be a strong candidate for schizophrenia.[14] A recent study[15] investigating the association between MnlI polymorphism, verbal memory and executive functions reported that carriers of the TT genotype (people homozygous for allele 1) showed lower performance. Conversely, another study reported a significant association of DdeI TT homozygosity with better cognitive performance in schizophrenia patients.[16] A significant association between a polymorphic marker (an area within gene DNA sequence in which a nucleotide is replaced with another) (rs363050, which is a SNAP25 gene variant) and performance IQ was also reported in which the subjects with the A allele produced higher IQ scores.[17] Therefore, the association between SNAP25 gene polymorphisms and cognitive performance is currently unclear.

The association between SNAP25 gene DdeI and MnlI polymorphisms and APD has not been investigated. The SNAP25 gene is an interesting candidate for several reasons. First, SNAP25 is associated with ADHD, which, aside from modifying the behavioural symptoms in APD, may increase the risk of the latter disorder.[18] Second, as the SNAP25 protein is related to vesicle membrane docking and fusion, it may be associated with the functioning of several different neurotransmitters. This point is important, given that the TCI temperament traits have been claimed to be associated with several neurotransmitter systems.[2] Third, the SNAP25 gene has been reported to be associated with personality in a genome-wide association study.[19] In our study, we compared the distribution of DdeI I and MnlI polymorphisms in young male offenders and in sex-matched healthy control subjects. We also investigated the association of SNAP25 gene polymorphisms with PCL-R factor scores and with the TCI temperament traits novelty seeking, harm avoidance, and reward dependence.

Abbreviations

ADHD	attention-deficit hyperactivity disorder
APD	antisocial personality disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
PCL-R	Psychopathy Checklist—Revised
PCR	polymerase chain reaction
SCID	Structured Clinical Interview for DSM-IV
SNAP25	synaptosomal-associated protein 25
TCI	Temperament and Character Inventory

Methods

Study Sample

We included 91 adult male offenders (aged 20 to 27 years, mean 21.8, SD 1.9) and 38 healthy male control subjects (aged 19 to 24 years, mean 20.7, SD 1.3) in our study. All patients were evaluated during their mandatory military service and were consecutive referrals to the tertiary military health centre for the assessment of antisocial behaviour. Their APD diagnosis was confirmed by using the SCID-II, using DSM-IV criteria. Psychopathy of all participants was evaluated with the PCL-R. It is a 20-itemed, reliable, and valid instrument to assess psychopathy, both in categorical and dimensional natures. All patients had a total score of 29 (of possible 40) or higher from the PCL-R, indicating a high degree of psychopathy.[20] The total PCL-R score

includes 2 factor scores: Factor 1, which consisted of interpersonal and affective problems, callousness, and domination seeking, and Factor 2, which consisted of social deviance. It has been argued that Factor 1 reflects a core psychopathology. The PCL-R was administered by a single psychiatrist who personally examined all of the subjects. Haydarpasa Gulhane Military Medical Academy (Haydarpasa GMMA) instutional review board approved the research and informed consent was obtained from the participants. The control subjects were recruited from other military conscripts in terms of voluntary participation to the study.

We also screened all patients and control subjects for current and lifetime psychosis, schizophrenia, major depression, substance abuse (other than smoking), and bipolar affective disorder by the corresponding modules of the SCID-I. SCID-I is a semi-structured interview for DSM-IV Axis I diagnoses, which is completed by trained interviewers. It consists of 6 modules, and usually takes 25 to 50 minutes to complete. It has been translated into Turkish by Ozkurkcugil et al,[21] and has been found to be reliable. The control subjects with any current DSM-IV Axis I or II diagnosis were excluded from our study.

TCI was used to assess temperament and character dimensions. TCI is a self-administered questionnaire, which consists of 240 true or false items. Novelty seeking and harm avoidance are each measured by 4 subscales, reward dependence by 3 subscales, and persistence by 1. The Turkish version of the TCI[22] has been approved by Cloninger and has been found to be valid and reliable.

Data on the frequency, time of onset, duration, severity, and methods of self-injurious behaviours, substance abuse, criminal behaviours (as evaluated by a combination of self-report and criminal records), and suicide attempts were collected with a semi-structured interview.

DNA Extraction and Analysis

A blood sample was drawn from each person after we had been provided written, informed consent. Venous blood samples were collected in ethylene diamine tetra acetic acid-containing tubes. DNA was extracted from the whole blood by a salting-out procedure.[23]

PCR-restriction fragment length polymorphism assays were used to determine SNAP25 gene (GenBank Accession Number D21267), DdeI (rs1051312), and MnlI (rs3746544) (the numbers show SNAP25 gene variants) polymorphisms.

The oligonucleotide primers used to determine DdeI and MnlI polymorphisms within the SNAP25 gene have been described in previous studies.[10] The primers forward 5'-TTCTCCTCCAAATGCTGTCG-3' and reverse 5'-CCACCGAGGAGAGAAAATG-3' were used to amplify the SNAP25 gene. PCR was performed in a 25 μL volume with 100 ng DNA, 100 μm dNTPs, 20 pmol of each primer, 1.5 mM $MgCl_2$, 1× PCR buffer with $(NH_4)SO_4$ (Fermentas, Vilnius, LT) and 1U Taq DNA polymerase (Fermentas, Vilnius, LT). Amplification was performed on an automated thermal cycler (Techne Flexigene, Cambridge, GB). PCR conditions were established at 2 minutes for initial denaturation at 95 °C, 35 cycles at 95 °C for 45 seconds for denaturation, 1 minute at 58 °C for annealing, 2 minutes at 72 °C for extension, and 7 minutes at 72 °C for final extension. After amplification, PCR products were digested by restriction endonuclease 10 U DdeI (Fermentas, Vilnius, LT) or 10 U MnlI (Fermentas, Vilnius, LT) for 14 hours at 37 °C. The genotyping of the SNAP25 gene DdeI or MnlI polymorphisms was determined by fragment separation at 120 V for 40 to 50 minutes on a 3.5 % agarose gel containing 0.5μg/mL ethidium bromide. A 100 bp marker (50 bp DNA Ladder, Fermentas, Vilnius, LT) was used as a size standard for each gel lane. The gel was visualized under ultraviolet light using a gel electrophoresis visualizing system (Vilber Lourmat, France). The 261 bp fragment in allele 1 (T) of DdeI was not cut, and for allele 2 (C), the fragment was cut into 2 fragments of 228 bp and 33 bp. For allele 1 (T) of the MnlI digest, the 261 bp fragment was cut into 2 fragments of 256 bp and 5 bp but was not cut at the polymorphic restriction site. For allele 2 (G), the 261 bp fragment was cut into 210 bp, 46 bp, and 5 bp fragments. The 5 bp, 33 bp, and 46 bp fragments were difficult to visualize because of their small size and their comigration with the similarly sized primer residue. However, detection of this fragment was not critical in determining the genotypes. Genotyping was based on independent scoring of the results by 2 reviewers who were unaware of the case–control status.

Data Analysis

We compared the PCL-R and TCI scores of the groups with 1-way ANOVA. A chi-square test (and a Fisher exact test for any 2 × 2 matrix) was used to compare the frequency of SNAP25 polymorphisms between the groups. We investigated the association of genotypes with PCL-R and TCI scores only within the APD group. We did not investigate these associations in the control group as the variation was very small for the PCL-R scores in this group. PCL-R was available for every subject. TCI was performed for every control subject but only in 70 subjects with APD. $P < 0.05$ was accepted as statistically significance level, and all of the tests were 2-tailed.

Results

PCL-R and TCI Scores

The PCL-R total score and the TCI novelty seeking and harm avoidance scores were significantly higher, and the TCI reward dependence score was significantly lower in the APD group (Table 1).

Table 1 Comparison of mean PCL-R total score and TCI novelty seeking, harm avoidance, and reward dependence scores between patients with APD and control subjects

PCL-R and TCI scores	APD mean (SD)	Control subjects mean (SD)	F^a	*P*
PCL-R	31.5 (3.1)	2.7 (3.7)	2077.7	<0.001
Novelty seeking	21.9 (3.6)	16.8 (3.1)	52.6	<0.001
Harm avoidance	22.3 (5.3)	17.4 (5.4)	20.0	<0.001
Reward dependence	10.1 (3.3)	13.0 (3.1)	19.4	<0.001

[a] *df* = 1,70

Table 2 The frequency of SNAP25 MnlI and DdeI polymorphisms in the APD and control groups

	SNAP25 MnlI polymorphism[a]			SNAP25 DdeI polymorphism[b]		
Groups	T/T	T/G	G/G	T/T	T/C	C/C
APD	52 (57.1%)	32 (35.2%)	7 (7.7%)	62 (68.1%)	25 (27.5%)	4 (4.4%)
Control subjects	15 (39.5%)	22 (57.9%)	1 (2.6%)	17 (44.7%)	17 (44.7%)	4 (10.5%)

[a] χ^2 = 6.03, *df* = 1, *P* = 0.049, φ = 0.22
[b] χ^2 = 6.47, *df* = 1, *P* = 0.04, φ = 0.22

Table 3 The frequency (%) of combined SNAP25 MnlI and DdeI T/T homozygosity in the APD and control groups

Groups	MnlI and DdeI T/T homozygosity	Others	χ^2 (*df* = 1)	*P*	φ
ASPD	34 (37.4%)	57 (62.6%)	5.8	0.02	0.28
Control subjects	6 (15.8%)	32 (84.2%)			

SNAP25 DdeI and MnlI Polymorphisms in APD Subjects and Control Subjects

DdeI T/T homozygosity and MnlI T/T homozygosity were more common in the APD group. When the MnlI T/T was compared with MnlI T/G and G/G combined there was no significant difference between the groups (APD: 57.1% T/T, compared with control subjects: 39.5%; χ^2 = 3.4, *df* = 1, *P* = 0.08). Conversely, when DdeI T/T was compared with DdeI T/C and C/C combined, DdeI T/T was significantly more common in the APD group (APD: 68.1% T/T, compared with control subjects : 44.7%; χ^2 = 6.2, *df* = 1, *P* = 0.02) (Table 2).

When both DdeI and MnlI polymorphisms were taken into account, the DdeI T/T, MnlI T/T haplotype was more common in the APD group (APD: 37.4% T/T, compared with control subjects: 15.8%; χ^2 = 5.8, *df* = 1, *P* = 0.02) (Table 3). Phi values reflecting the effect sizes are given in the corresponding tables.

SNAP25 DdeI and MnlI Polymorphisms and PCL-R Scores

There were no significant differences between SNAP25 DdeI and MnlI polymorphisms and PCL-R total scores.

SNAP25 DdeI and MnlI Polymorphisms and TCI Scores

As there were too few subjects who were homozygous for DdeI C/C or MnlI G/G, we compared subjects with DdeI T/T or MnlI T/T with other combined polymorphisms. APD subjects with the MnlI T/T genotype had significantly higher novelty seeking scores (F = 6.46, *df* = 1,70, *P* = 0.01, η^2 = 0.09), while subjects with the DdeI T/T genotype had significantly lower reward dependence scores (F = 4.76, *df* = 1,70, *P* = 0.03, η^2 = 0.07). The subjects with the DdeI T/T-MnlI T/T haplotype also had significantly higher novelty seeking scores (F = 7.5, *df* = 1,70, *P* = 0.01, η^2 = 0.10) (Table 4).

Discussion

In our study, we found that the MnlI T/T and DdeI T/T genotypes were more frequently present in male subjects with APD than in sex-matched healthy control subjects. The association was stronger when the frequency of both DdeI and MnlI T/T were taken into account. In the APD group, genotypes were not significantly associated with the PCL-R scores, which measure the severity of psychopathy. However, APD subjects with the MnlI T/T genotype had higher novelty seeking scores, whereas subjects with the DdeI T/T genotype had lower reward dependence scores.

Table 4 The association of PCL-R total score and TCI novelty seeking, harm avoidance, and reward dependence scores with SNAP25 MnlI and DdeI genotype within the APD group

PCL-R and TCI scores	MnlI and DdeI combined			MnlI			DdeI		
	T/T	Others	F^a	T/T	T/G, G/G	F^a	T/T	T/C, C/C	F^a
PCL-R	31.4 (3.1)	31.6 (3.1)	0.13	31.7 (3.1)	31.3 (3.1)	0.28	31.3 (3.0)	31.9 (3.2)	0.80
Novelty seeking	23.3 (3.1)	21.0 (3.3)	7.5[b]	22.8 (3.6)	20.7 (3.4)	6.46[c]	21.9 (4.0)	21.9 (2.8)	0.01
Harm avoidance	23.4 (5.7)	21.5 (5.1)	2.2	22.7 (5.9)	21.7 (4.6)	0.72	22.7 (5.4)	21.2 (5.1)	1.2
Reward dependence	9.4 (3.0)	10.6 (3.5)	2.2	9.9 (3.0)	10.4 (3.7)	0.29	9.6 (3.2)	11.4 (3.3)	4.7[c]

[a] *df* = 1,70; [b] $P < 0.01$; [c] $P < 0.05$

All other *P* values are >0.05

Again, the association between genotype and novelty seeking was stronger when both DdeI and MnlI genotypes were present. This was also reflected in the phi values indicating the effect sizes. It must be mentioned that the effect sizes were relatively small.

It has been shown previously that SNAP25 gene polymorphisms may be related to ADHD and schizophrenia[14] and to various dimensions of personality.[19] In our study, we found that SNAP25 DdeI and MnlI T/T genotypes may also be a risk factor for antisocial behaviours.

It has been suggested that the TCI temperament traits (novelty seeking, harm avoidance, reward dependence, and persistence) are inheritable and associated with different neurotransmitter systems.[2] SNAP25 protein is part of a complex, which has an important role in exocytosis. Therefore, alterations in SNAP25 function may lead to changes in several neurotransmitter systems. Because we found that SNAP25 DdeI T/T and MnlI T/T were associated with lower reward dependence and higher novelty seeking, we can suggest that the SNAP25 genotype might influence other personality disorders as well. For example, borderline personality, antisocial personality, and histrionic personality disorders have in common higher novelty seeking scores, making it possible to hypothesize that people with DdeI and MnlI T/T genotype might be at risk for all cluster B personality disorders. In fact, together with the lack of significant association between PCL-R scores and the SNAP25 genotype, our findings may suggest that the effect of the SNAP25 genotype may not be specific to psychopathy. Alternatively, by leading to high levels of novelty seeking together with low levels of reward dependence, the SNAP25 DdeI and MnlI T/T genotypes may be risk factors for both borderline and antisocial personality disorders, but not for narcissistic personality, in which reward dependence is high rather than low. Low scorers in reward dependence were described as detached, reserved, cold, and independent, and these are more typical of cluster A personality disorders.[24] It may be interesting to investigate the association of SNAP25 MnlI and DdeI genotypes with cluster A personality disorders. All these possibilities suggest that it may be very promising to study SNAP25 polymorphisms in a large sample consisting of subjects with several different personality disorders. In fact, although the effect size was small and failed to replicate in an independent sample, a recent genome-wide scan study[19] showed that the SNAP25 gene was associated with neuroticism, a condition related to the tendency to experience negative emotions.

There were several limitations in our study. First of all, the sample consisted only of males. Therefore, our results do not provide evidence for female subjects. Second, the sample size was small, and this may lead to false-negative results. However, our finding of an association between the high-risk T/T allele with the TCI temperament traits, which were different in the APD group, provided support to our results. Additionally, small sample size of the control group did not allow us to investigate the possible associations between the SNAP25 genotype and the TCI temperament traits. It must also be kept in mind that the effect sizes were rather small, suggesting that there are other numerous factors, other than SNAP25 polymorphisms, moderating the association between APD diagnosis and TCI scores.

Conclusions

Besides its previously shown associations with ADHD, schizophrenia and various dimensions of personality SNAP25 DdeI and MnlI T/T genotypes may be a risk factor for antisocial behaviours. The SNAP25 gene polymorphism was also shown to be associated with lower reward dependence and higher novelty seeking temperament traits measured by TCI in patients with APD. Our findings also suggest a possible association of the SNAP25 genotype with other personality disorders, which remains a critical unanswered question of future studies.

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Résumé : Polymorphismes génétiques de la protéine 25 associée au synaptosome et trouble de la personnalité antisociale : association avec tempérament et psychopathie

Objectif : La génétique moléculaire des troubles de la personnalité a fait l'objet de plusieurs études, mais pas l'association des comportements antisociaux avec les polymorphismes génétiques de la protéine 25 (SNAP25) associée au synaptosome. Cette association est intéressante car le polymorphisme génétique de la SNAP25 est associé avec le trouble d'hyperactivité avec déficit de l'attention et la personnalité.

Méthodes : Nous avons comparé la distribution des polymorphismes DdeI et MnlI chez 91 jeunes délinquants masculins et 38 sujets témoins en santé du même sexe. Nous avons également investigué l'association des polymorphismes génétiques de la SNAP25 avec la gravité de la psychopathie et avec les traits du tempérament: recherche de nouveauté, évitement du danger et dépendance à la récompense.

Résultats : Les génotypes MnlI T/T et DdeI T/T étaient plus fréquemment présents chez les sujets masculins souffrant du trouble de la personnalité antisociale (TPA) que chez les sujets témoins en santé du même sexe. L'association était plus forte lorsque la fréquence des deux DdeI et MnlI T/T était prise en compte. Dans le groupe du TPA, le génotype n'était pas significativement associé aux scores de l'échelle de psychopathie révisée qui mesurent la gravité de la psychopathie. Toutefois, les sujets du TPA ayant le génotype MnlI T/T avaient des scores supérieurs pour la recherche de nouveauté; alors que les sujets ayant le génotype DdeI T/T avaient des scores inférieurs pour la dépendance à la récompense. Encore une fois, l'association entre génotype et recherche de nouveauté était plus forte lorsque les deux génotypes DdeI et MnlI étaient pris en compte.

Conclusion : Les génotypes DdeI et MnlI T/T peuvent être un facteur de risque des comportements antisociaux. L'association des génotypes DdeI T/T et MnlI T/T de la SNAP25 avec une faible dépendance à la récompense et une recherche de nouveauté élevée suggérait que le génotype de la SNAP25 pourrait influencer d'autres troubles de la personnalité également.