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CLINICAL RESEARCH

The MAOA and COMT Gene Polymorphisms in Patients with Schizophrenia Committed Homicide

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Abstract

Numerous studies have indicated that aggression and homicide are more frequent among people with schizophrenia than in the general population. There is considerable evidence that schizophrenia involves a dysbalance between subcortical and cortical dopaminergic systems. The major pathways for catecholamine degradation are oxidative deamination through the action of monoamine oxidase A (MAOA) and by methylation through the action of catechol-O-methyltransferase (COMT). Activity of both enzymes is encoded by the corresponding genes—MAOA and COMT. ***The aim*** of our study was to analyze the association between the COMT-Val158Met and MAOA-uVNTR polymorphisms and the risk of committing homicide by patients with schizophrenia.

Methods: The study included 50 Caucasian male patients with paranoid schizophrenia (PS). All patients were divided into two groups: Group 1 consisted of 26 PS patients who have committed homicide; Group 2 consisted of 24 PS patients who did not have a history of socially violent behavior. The control group comprised 23 apparently healthy Caucasian men of the same age. All patients underwent clinical-psychopathological and clinical-anamnestic examinations. Molecular genetic studies were performed in the Shared Research Facility Center "High Technologies" at SFedU.

Results: Our study revealed no direct correlation between the COMT-Val158Met and MAOA-uVNTR polymorphisms and risk of committing homicide by patients with schizophrenia. At the same time, we detected an association between high-activity gene variants, viz., the MAOA-4R allele and the COMT-158Met/158Met genotype, and the schizoid and unstable premorbid accentuation in patients who had committed murder, whereas the schizoid and unstable accentuation correlated with homicide behavior in patients with schizophrenia.

Conclusion: The obtained findings suggest that genetic variation affects the homicidal behavior indirectly, through the various types of premorbid accentuation and confirm the validity of the well-known concept of "syndrome-person-situation," traced back to the mid-20th century, which explains the commission of serious offenses by patients with schizophrenia.

Keywords: *schizophrenia; homicide; COMT-Val158Met and MAOA-uVNTR polymorphisms.*

Introduction

Numerous studies have indicated that aggression and homicide are more frequent among people with schizophrenia than in the general population [1-4].

Understanding the mechanisms of socially dangerous acts committed by patients with schizophrenia, and the formation of an effective prevention system for these actions, are far from complete [3,5].

Many findings indicate that a more or less pronounced brain function disorder and, above all, a neuronal developmental disorder underlie schizophrenia. On the neuropharmacological level, the so-called dopamine hypothesis of schizophrenia continues to be of paramount importance. There is considerable evidence that schizophrenia involves

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a dysbalance between subcortical and cortical dopaminergic systems. Subcortical mesolimbic dopaminergic projections appear to be hyperactive, while the mesocortical dopamine system, which connects to the prefrontal cortex, is hypoactive. The former could be associated with positive symptoms and the latter with disturbances of cognitive function [6-9].

The major pathways for catecholamine degradation are oxidative deamination through the action of monoamine oxidase A (MAOA) [6] and by methylation through the action of catechol-O-methyltransferase (COMT) [10]. Activity of both enzymes is encoded by the corresponding genes—MAOA and COMT [2,6].

MAOA gene, located on the X chromosome, encodes the monoamine oxidase A enzyme, which plays a major role in the metabolism of biogenic amines, including dopamine, noradrenalin, and serotonin. MAOA has been shown repeatedly to be relevant for treating aggressive behavior [11,12], and MAO-A promoter uVNTR polymorphism in particular appears to be involved. This MAOA uVNTR consists of a 30-bp repeated sequence present in 2, 3, 3.5, 4, or 5 copies. The two most common alleles are those with 4 and 3 repeats [13,14]. The 3 and 4 repeat alleles were the most frequent ones in the different ethnic groups evaluated throughout the studies, corresponding to more than 95% of the variance.

Enzyme expression is known to be 2–10 times higher for the 3.5 and 4 repeats than for the 3 repeat [13]. Therefore, the 3.5-repeat and 4-repeat alleles (3.5R and 4R) were classified as high-activity whereas the 3-repeat alleles (3R) were classified as low-activity.

In general, the studies associated the low activity alleles with impulsivity and aggressive behavior ("hyperactive behaviors"), and the high activity alleles of the gene with "hypoactive behaviors", such as depression and anxiety, which demonstrates a modulation of the MAOA enzyme in "hyperactive" and "hypoactive" disorders [15]. At the same time, according to 27, a higher frequency of the allele with 3.5 and 4 repeats ("high-activity" variants) of the promoter polymorphism was found in schizophrenia patients with aggression [16]. Two further studies also found no association of MAO-A and MAO-B with aggressiveness in schizophrenia patients [17,18]. In addition, Strous et al found negative results for the MAO-A gene [19].

A.Caspi and colleagues provided the first evidence that a large sample of maltreated male children carrying low-activity alleles of MAOA were more likely to develop antisocial problems in adulthood as compared to abused children with the highactivity MAOA variant [20]. Two meta-analyses, published in 2006 and 2007, strongly supported the original hypothesis [21,22], while two very recent studies published in 2013 and conducted in very large samples did not replicate these previous findings [23,24].

COMT is one of the enzymes responsible for the catabolism of dopamine and noradrenaline in the brain. A common biallelic single nucleotide polymorphism, involving Val(valine) to Met(methionine) substitution at codon 158 of the COMT gene has been identified and localized to chromosome 22q11.1-11.2 [25]. The Val allele at this locus is associated with high enzymatic activity, whereas the Met allele is associated with low enzymatic activity. There is evidence of the Met allele association with behavioral traits such as emotionality, impulsivity, hostility, anger, violence, aggression, and the risk of committing homicides and suicides by violent means [26,27]. Conversely, some studies did not find the association between the Met allele and violence in schizophrenics [28,29] but found an association with verbal aggression [30] and violence and physical aggression against objects in epistasis with two other SNPs in the COMT gene [31]. JP Singh et al conducted a meta-analysis of 15 studies comprising 2,370 individuals with schizophrenia. Authors concluded that male schizophrenia patients who carry the low activity Met allele in the COMT gene were at a modestly elevated risk of violence [32].

The aim of our study was to analyze the association between the COMT-Val158Met and MAOA-uVNTR polymorphisms and the risk of committing homicide by patients with schizophrenia.

Methods

The study included 50 Caucasian male patients (mean age: 36.1±10.7 years) with paranoid schizophrenia (PS). Written informed consent was obtained from each patient. All patients were divided into two groups: Group 1 consisted of 26 PS patients who have committed homicide; Group 2 consisted of 24 PS patients who did not have a history of socially violent behavior. The control group comprised 23 apparently healthy Caucasian men of the same age (30.3±8.9 years). All patients underwent clinical-psychopathological and clinical-anamnestic examinations. All data (age, family history, premorbid accentuation, and the diagnosis, the main positive and negative symptoms based on the PANSS scale) were entered into a specially designed research card. The ratio of patients with continuous and episodic types of PS was equal in both groups.

Molecular genetic studies were performed in the Shared Research Facility Center "High Technologies" at SFedU. Genomic DNA was extracted from peripheral blood leucocytes using "DNA-Express-Blood" kits according to the manufacturer's protocol. The COMT Val158Met and MAOA-uVNTR polymorphisms were analyzed by *PCR*/*RFLP*. Deviation from Hardy-Weinberg equilibrium and differences in allele distributions between the two groups were assessed by $\chi 2$- test with 1 degree of freedom (df), whereas differences in genotype distributions between cases and controls were assessed by the $\chi 2$- test with 2 df. The odds ratio (OR) and their 95 % confidence intervals (CI) were calculated to estimate the strength of the association. Allele frequencies (for название аллелей) within pairs were compared using Wilcoxon signed rank test. P values of<0.05 were considered statistically significant.

Results and Discussion

The MAOA allele frequencies of 3R and 4R were 0.25:0.75 in the control group, 0.5:0.5 in Group 1, and 0.45:0.55 in Group 2. There were no significant differences

between the patient groups and control group (P>0.05). The 2, 3.5 and 5 repeat alleles (2R, 3.5R and 5R) were not found in any group.

Overall, the results are consistent with data in the literature [6,13,14]. The predominance of MAOA low-activity alleles in PS patients indicates the involvement of the dopamine system in the formation of clinical disorders. The absence of differences in allele frequencies between the law-abiding patients and patients with homicidal tendencies indicates a nontrivial mechanism for formation of such a behavioral act as murder. According to the literature, a low-activity variant of the MAOA gene is associated with aggressive behavior, but not with murder; "aggressive face" of the low activity MAOA gene is manifested in the favored environment, namely with child abuse in childhood [8,20].

All genotype variants of COMT-Val158Met polymorphism were present in the groups of patients and the control group. The following genotypes were observed in the control group: Met/Met–0.2, Met/Val–0.55, Val/Val–0.25 and in the PS patients: Met/Met–0.286, Met/Val–0.476, and Val/Val–0.524. Data of the PS patients and control group were in Hardy-Weinberg equilibrium. The frequencies of Met and Val alleles were 0.524:0.476 in patients and 0.474:0.526 in the control group ($\chi 2$= 0.32, P=0.57; OR=1.22; 95% CI: 0.61-2.46). The differences between the expected and observed frequencies of heterozygosity (D=(hobs–hexp)/hexp) were +0.098 and -0.046 in control group and group of patients, respectively. Comparative analysis showed no significant association between the Met/Met genotype and schizophrenia, according to a general model of inheritance ($\chi 2$= 0.63, P=0.73; OR=1.60; 95% CI: 0.49-5.28).

The lack of statistical differences in the frequencies of the COMT-Val158Met genotypes and alleles in patients with schizophrenia and healthy individuals indicates a low association between the studied gene and the tendency of patients with schizophrenia to commit a homicide. The data obtained are partially consistent with data of M.Soyka [6]: in 4 out of 11 samples of patients, an association of aggressive behavior with the low-activity Met/Met-genotype was not detected; only one sample of patients was related to homicidal behavior; in other cases, an aggression was studied parameter.

Spearman's rank correlation analysis showed a lack of significant direct correlation between 6 genotypes (Met/Met, 3; Met/Val, 3; Val/Val, 3; Met/Met, 4; Met/Val, 4; Val/al, 4) and the likelihood committing homicide by patients with schizophrenia. Obviously, in addition to the biochemical characteristics, anomalies must be present in the reticular formation, amygdala, cingulate gyrus, and orbitofrontal cortex for the formation of aggressive behavior [8].

We performed rank correlation analysis between the gene polymorphisms and the accentuation types in patients with schizophrenia. This analysis revealed no correlation between polymorphic markers and the individual radicals of premorbid accentuation in patients, possibly due to the small sample size. By combining frequency of the unstable and schizoid accentuation (these personal radicals were revealed most frequently in Group 1 patients), we found a significant correlation. Spearman's correlation coefficient was R=0.83 (p=0.011) for the frequencies of the unstable and schizoid accentuation and genotype options. Correlation between the frequency of the unstable and schizoid accentuation and frequencies of genotypes in patients with schizophrenia who committed homicides was R=0.81 (P=0.013) (Fig.1), which was especially noticeable in the area of high-activity genotypes. This result is interesting because there was no direct correlation between gene polymorphisms and homicidal behavior of patients.

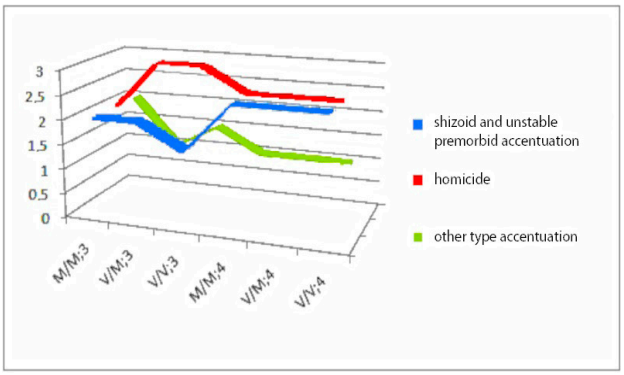

Figure 1. *Distribution of the premorbid radicals and homicides and the genotype frequencies of the COMT Val158Met and MAOA-uVNTR polymorphisms in PS patients*

The obtained findings suggest that genetic variation affects the homicidal behavior indirectly, through the various types of premorbid accentuation. Finally, it has been recently proposed that these genetic variants may actually increase the individual susceptibility not merely to the negative environmental factors, but to the positive ones as well. In this view, such alleles would play a wider modulatory role, by acting as "plasticity" rather than "vulnerability" genes [33].

Correlation analysis revealed no statistically significant associations between the low-activity and high-activity genotypes and the main psychiatric symptoms in patients of Groups 1 and 2. In Group 1 patients, the negative psychopathological symptoms were dominant in the general picture of the disease at the time of the study; in Group 2 patients, the positive symptoms were dominant. This discrepancy may be due not only to the main differences between these groups, but also to a different duration of the disease, a different ratio of patients with continuous and episodic type of schizophrenia, or the features of the pharmacological therapy of patients undergoing compulsory treatment in Group 1 compared to Group 2. The complex of psychopathological phenomena for disease is a movable and a relatively rapidly changing parameter, so its comparison with the genotype has some difficulties. Further studies on the genetics of antisocial behavior, including a more objective evaluation of the environmental influence, more selective scales to evaluate different behavioral traits, and, last but not least, the analysis of multi-allelic genetic profiles, will allow scientists to achieve a more comprehensive understanding of the role of genetics on violence [33].

Conclusion

Our study revealed no direct correlation between the COMT-Val158Met and MAOA-uVNTR polymorphisms and risk of committing homicide by patients with schizophrenia. At the same time, we detected an association between high-activity gene variants, viz., the MAOA-4R allele and the COMT-158Met/158Met genotype, and the schizoid and unstable premorbid accentuation in patients who had committed murder, whereas the schizoid and unstable accentuation correlated with homicide behavior in patients with schizophrenia.

In our opinion, the characteristic degradation of monoamines is unlikely to fully define such common property as a premorbid radical, but in the schizoid and unstable accentuation there are similarities that may be due to the influence of the genotype. In particular, the lack of concern for the opinion of society in patients with schizophrenia can be formed due to a sufficiently high activity of the degradative enzyme monoamine (the first phase of stress mediators), which reduces situational anxiety and the ability to predict the consequences of anti-social actions leading to the opinion of society having a less significant position in forming one's individual standards and sense of the public interest [5]. Our results confirm the validity of the well-known concept of "syndrome-person-situation", traced back to the mid-20th century, which explains the commission of serious offenses by patients with schizophrenia [3].

Competing interests

The authors declare that they have no competing interests.

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