Abstract

There is a clear evidence that same psychoactive substance may cause various individual physiological reactions in same environmental conditions. Although there is a general attitude on equal liability to opioid addiction, latest genetic analysis findings imply there are certain quantifiable factors that could lead to elevated individual liability towards development of opioid addiction. The goal of this study was to investigate association of certain personality traits and genetic factors (separately and in combination) with heroin addiction. Total of 200 individuals participated in the study: 100 patients on Metadone Maintenance Treatment (MMT) and 100 age and sex matched healthy volunteers. All were medically examined, interviewed and psychologically evaluated using Eysenck personality questionnaire (EPQ) and genotyped for DRD5 (rs1800497) using PCR-RFLP method. Overrepresentation of certain personality traits (neuroticism, psychoticism and extraversion / introversion), together with environmental risk factors such as: upbringing within incomplete families and familial history of psychotropic substances abuse, are associated with high-risk development of opioid addiction.

KEY WORDS: opioid addiction, heroin, genetics, MMT, DRD5, EPQ, personality traits, PAS-psychoactive substance, genetic association

INTRODUCTION

Opiate addictions is major social and medical problem that impose a significant burden on society. Opioids belong to group of psychoactive substances (PAS), that are commonly abused and produce highly addictive effect. In any of the form of use (natural, semisynthetic or synthetic) – as opium, morphine, kodein or heroin, opioids cause significant health deterioration and its consequences. Although they belong to central nervous system (CNS) sedating agents (sedatives), they cause an euphoria – affective state opposite to depression [1]. According to the International Classification of Diseases, 10th edition (ICD-10) opioid addiction represents a cluster of behavioural, cognitive, and physiological symptoms developed after repeated opioids use. Opioid addiction typically includes a strong desire to take the drug, difficulties in controlling its use and persistance in its use despite harmful consequences [1]. Formal and molecular-genetic studies imply that genetic factors play a significant role in susceptibility and interindividual variability of drug addiction [2]. Although, it has been shown that there is an 8 fold increase in risk for opioid addiction development in first degree relatives, it is not possible to exclude the contribution of environmental effects on particular personality traits linked to this disorder [1]. Moreover, opioid substance abuse is at the most influenced by specific personality characteristics. Neurobiological mechanism of addiction is layed in disturbance of neurophysiological brain functions at reception and transmission of neuronal signals. After opioid intake, i.e. heroin, there is a change in physiologically controlled dopamine release. In longterm opioid addiction, the most important neurochemical mechanisms are prolonged depletion of opioid and dopamine transmission with qualitative and quantitative changes at opioid and dopamine receptors [3] that affects the rewarding system and brain reinforcement [2]. It has been shown that dopamine receptor type 2 (D2) encoded by DRD2 gene (OMIM rs1800497) is involved in liability to different types of addiction: alcohol, nicotine, cocaine and heroin [4]. Several structural changes within DRD2 have been found and explored as potentially significant in the development of opioid addiction.
causative variants in development of opioid addiction [2]. DRD2 TaqI, a SNP also known as the TaqIA (or Taq1A) polymorphism of the dopamine D2 receptor is represented with minor (T) and major (C) allele. Minor allele (Taq IA) is associated with a reduced number of dopamine binding sites in the brain and has been postulated to play a role in alcoholism, smoking, and certain neuropsychiatric disorders [4]. Therefore we explored the variation of DRD2 gene polymorphism and personality traits and their potential association with inherited liability to opioid addiction.

MATERIALS AND METHODS

Patients
This research was prospectively conducted as case-control study and comprised sample of 200 individuals. Case group consisted of 100 patients included in Program of Metadone Substitution Therapy, previously diagnosed with opioid addiction according to ICD-10 and consecutively recruited during the period of one year. Control group contained 100 subjects clinically confirmed as healthy, with no individual history of substance abuse or psychiatric disorders, age and sex matched to case group individuals. Ethical aspects of the study were approved by institutional ethics committee and all participants signed informed consent prior to any study procedure.

Procedures
Psychological evaluation was performed for all individuals using Eysenck personality questionnaire (EPQ). Sociodemography data and family history was collected using study questionnaire followed by blood sampling for genetic analysis. DNA was extracted from blood using salting-out procedure [5] followed by amplification of DRD2 TaqI (rs1800497) flanking region using previously reported method [6]. PCR products were checked for quality on 1% agarose gel and subsequently treated with restriction endonuclease type II under following conditions: 0.5 unit of TaqI per microliter of PCR product was incubated at 37°C overnight. Restricted fragments were electrophoretically separated on 2% agarose gel and photodocumented using KODAK Edas Software.

Statistical analysis
Statistical analysis was performed using IBM Statistics – SPSS v19.0 for Windows i Microsoft Excel 2007.

RESULTS
Total of 200 individuals were recruited to the study under previously defined inclusion criteria. All signed informed consent and after being interviewed, provided blood sample for genetic analysis. DNA was successfully extracted from all samples that all underwent standard PCR-RFLP procedure according to the protocol explained before. All expected genotypes A1A1, A1A2 and A2A2 have been observed in all individuals. Technician blinded to disease status read out and documented genotypes (Figure 1). Frequencies of A1 and A2 alleles in both populations together were 21.7% and 78.25% respectively. Genotypes frequency distribution in whole observed population was 4%, 35.5% and 60.5% for A1A1, A1A2 and A2A2 genotypes respectively. Sociodemographic parameters analysis showed statistically significant differences between two investigated groups in relation to education level and employment status, work efficiency, problems with law, upbringing conditions, parental marital status and intrafamilial relations. Among patients, 15.2% were upbrought by relatives, 2% individuals were abandoned. All control subjects were raised in primary families. Parental marital status differed between groups: 51.5% and 75.8% in case and control group respectively. 30.9% of patients’ parents were widowers and 17.5% were divorced. Family history analysis implies statistically significant differ-
ences between groups according to positive familial history for psychiatric disorders (psychoses and substance abuse) \( p < 0.05 \). Alcohol abuse among first degree relatives of study subjects was more frequent in case (62%) than in control group (Figure 2). Other substances abuse frequency was also increased among first degree relatives of study subjects: 26% and 4% in case and control group respectively. Psychotic and personality disorders of first degree relatives were also overrepresented in case (16%) than in control group (6%) (Figure 3).

Analysis of primary personality traits determined the presence of high correlation between extraversion/intraversion, psychoticism and neuroticism in heroin abusers. Assessment of general distribution of these traits pointed increased occurrence of neuroticism among patients (84%) as compared to control group (26%); similar pattern was shown for psychoticism (68% in cases and 26% in controls), while intraversion was less overrepresented in case (47%) than in control group (36%) (Table 1).

Analysis of investigated DRD2 locus genotypes showed a similar distribution of observed genotypes in both investigated groups. (Chi-square=2.765; \( p > 0.05 \)). Homozygous genotype variants (A1A1 i A2A2) were overrepresented in case groups while heterozygotes were more frequently observed in control group, but no statistically significant difference was found (Table 2). Analysis of genotype A1A1 frequency showed 6% and 2% in case and control groups respectively (Figure 4). Statistical analysis using McNemar and Fisher exact test for binomial samples, pointed statistically significant overrepresentation of A1A1 genotype in case group, as opposed to expected -normal distribution with OR = 1.532 (CI = 1.001-2.344) i \( p < 0.05 \). This implies that A1A1 carriers have 1.5 fold increased risk for development of heroin addiction.
No statistically significant association of DRD2 TaqI genotypes with any of the investigated personality traits in relation to addiction status. Multivariate analysis of parameters of sociodemography, heredity and A1 allele polymorphism, showed that patients - A1 allele carriers – with added factor of “up-bringing in incomplete family” has 2.7 fold increased risk for developing heroin addiction. Furthermore, patients with positive family history of psychosis and A1 allele carriers showed 3.5 fold increase in risk, while patients who had A1 allele and positive family history of drug abuse had even 4.7 times increase in risk for addiction than A2/A2 carriers (Table 3).

**DISCUSSION**

Although current level of knowledge on opioid addiction implies equal liability to this disease, it is clear that certain inherited characteristics of personality play significant role in development of heroin addiction. Results of this study inambiguously showed that there is a clear overrepresentation of basic personality traits (neuroticism, psychoticism, extraversion/intraversion) in group of patients with heroin addiction implying their role in elevation of disease risk as reported previously for different populations [7-9].

A number of studies confirmed an association between DRD2 polymorphism and heroin addiction [10-24]. Our study on DRD2 variation resulted with similar frequency distribution of observed genotypes in both investigated groups (Chi-square=2.765; p=0.05). However, homozygous genotypes (A1A1 and A2/A2) were overrepresented in case group, while heterozygotes (A1A2) were overrepresented in control group with no statistically significant difference observed. Our findings suggest that observation of certain genotype or allele variant (A1) is not necessarily a single predictive factor for liability for opioid addiction, especially when others (i.e. certain personality trait or enrivonmental risk factors) are absent which is consistency with previously published data [14,15, 25]. Considering the abovementioned, it is implicated that augmented values for personality traits (neuroticism, psychoticism, extraversion/intraversion and up-bringing in incomplete families) with factors of heredity (i.e. familial history of substance abuse and psychotic disorders) are associated with increased risk for development of opioid addiction.

In this study we focused the variation in DRD2 gene with small additive effect in overall incidence of PAS abuse disorders, we can conclude that A1A1 genotype associated with other sociodemographic and hereditary factors may increase individual risk towards opioid addiction development up to 1.5 fold as compared to A1A1 non-carriers but with no direct association with heroin addiction.

**CONCLUSION**

Overrepresentation of certain personality traits (neuroticism, psychoticism and extraversion/intraversion), together with environmental risk factors such as: upbringing within incomplete families and familial history of psychotropic substances abuse, are associated with high risk development of opioid addiction. A1A1 genotype associated with other sociodemographic and hereditary factors may increase individual risk towards opioid addiction up to 1.5 fold as compared to A1A1 non-carrier individuals.

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**DECLARATION OF INTEREST**

The authors declare no conflict of interest.

**REFERENCES**