Coll. Antropol. **34** (2010) 4: 1427–1432
Original scientific paper

Comparative Study on Gene Tags of the Neurotransmission System in Schizophrenic and Suicidal Subjects

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A B S T R A C T

Schizophrenia and suicidal behaviour are sever and complex mental disorders, largely determined by factors of inheritance. Both disorders present pathological changes in the catecholamine neurotransmitter system. The study was conducted on three groups; a group of subjects suffering from schizophrenia, a second compounded by individuals who attempted suicide and a third group of phenotypically healthy examinees. The blood samples of schizophrenic patients as of those who attempted suicide were obtained at the Psychiatric Hospital »Sveti Ivan« in Zagreb in the year 2004. Tests were conducted on the statistic relation between a total of 18 SNPs within three candidate-genes of the dopamine and adrenergic system (DRD4, SLC6A3 and ADRA2B) and the manifestation of schzophrenia and suicidal behaviour. Cases were genotyped by use of SNPlex system. Statistically significant differences were determined in the allelic frequency between the mentioned groups. Findings show a siginficant connection between 4 SNPs (ADRA2B rs749457, SLC6A3 rs464094, DRD4 rs11246226 and rs4331145) and schizophrenia, and 2 SNPs with suicidal attempt (ADRA2B rs1018351 i SLC6A3 rs403636). In addition, this is the first study that highlights the potential role/effect of polymorphisms in ADRA2B on the manifestation of schizophrenia, as on suicidal behaviour.

Key words: *association, candidate-genes, Croatia, polymorphisms, schizophrenia*

Introduction

Schizophrenia is a mental disorder whose main characteristics are alteration of thought, perception, speech, behaviour, emotion, volition and self perception. The everage life time risk of schizophrenia is 1% of the overall population, and in the majority of cases it manifests itself between 20 and 39 years of age. Around 10% of schizophrenia cases commit suicide, most frequently in the starting period of the disorder[1].

The course of the disorder can be continuous or with intervals of partial remission and with progressive and permanent damage of personality. Most cases, around 50–75% report psychological and social consequences from the chronic course of the disorder, which most frequently appear within the first year up to two years after the beginning of the disorder. However, in some cases, the course of the disorder is discontinuous with oscillations from psychotic relapsis to remission. A complete remission of symptoms is rare and, depending on studies, is between 7% and 41% of schizophrenic patients. Both, Classification of Mental and Behavioural Disorders – Clinical Descriptions and Diagnostic Guidelines (10th edition) of the World Health Organization (MKB-10)[3] and the 4th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV), differentiate, in consideration of clinical characteristics, five major subtypes of schizophrenia.

Mathematical models taken from former studies on the inheritance of schizophrenia within families have estimated that the genetic influence is 80–85%[5].

It is estimated that suicide is the cause of 2% of all deaths (data of the WHO). Statistics show that in Croa-

Received for publication September 30, 2010

tia, the incidence of suicides is 34.6 in men and 11.7 in women on 100,000[6]. Suicidal behaviour assumes suicidal attempt but also the existance of suicidal thoughts. There is no particular classification of suicidal disorders according to the MKB-10 or DSM-IV classification systems.

Over 90% of subjects who have attempted suicide present some psychiatric disorder. The most common disorders which are related to suicidal behaviour are mood disorders, anxiety disorder, PTSD, schizophrenia and addiction (alcoholism).

It is estimated that, in suicidal behaviour and suicide, the genetic component is responsible for 43% while the environmental components are responsible for 57% of the cases.

Former studies are not unison, but they indicate changes in the monoaminie transmission in both disorders.

The aims of this study are: a) to determin and compare the allelic frequency in the examined groups of schizophrenia cases and subjects who have attemtped suicide in relation to a control group of phenotipically healthy subjects; b) to estimate the (un)balance in the relation between the mentioned polyphormisms within ADRA2B, DRD4 and SLC6A3 genes; and c) on grounds of the findings, to assume the effect of disorders in neurochemical mechanisms on schizophrenia and suicidal attempts.

Subjects and Methods

Subjects

Cases of the study were divided in three groups; a first group consisting of schizophrenic patients, a second of subjects who attemtped suicide and a third group of phenotypically healthy subjects. The blood samples of schizophrenic patients as of those who attempted suicide were obtained at the »Sveti Ivan« Psychiatric Hospital in Zagreb in the year 2004. Diagnoses of all patients were coded according to the MKB-10 Classification of Mental and Behavioural Disorders. The shizophrenia cases did not attempt suicide and do not have suicidal thoughts (verified during a structured interview and after objective psychological questionnaires). The first group consisted of 103 subjects between 23 and 74 years of age (mean age 43.5±10.55). The subjects classification according to MKB--10 types of schizophrenia and the characteristics of the cases according to sex are presented in Table 1.

TABLE 1
CLASSIFICATION OF THE SCHIZOPHRENIA CASES GROUP ACCORDING TO MKB-10 CLINICAL TYPES OF SCHIZOPHRENIA

Diagnosis	Males	Females	Total
F20.0 (paranoid schizophrenia)	35	26	61
F20.1 (hebephrenic schizophrenia)	3	0	3
F20.5 (residual schizophrenia)	23	13	36
F20.6 (simple schizophrenia)	0	3	3
Total	61	42	103

The group of subjects who attempted suicide consisted of 125 individuals aged between 19 and 94 years (mean age 43.6±17.58) who were treated at the »Sveti Ivan« Psychiatric Hospital during the year 2004 and who did not suffer from schizophrenia. Diagnostic categories according to the MKB-10 cassification and according to sex are presented in Table 2. Considering the heterogeneity of the group that comprises a wide range of psychiatric disorders, the subjects were classified in major diagnostic groups.

The control group of phenotypically healthy individuals, who had not received psychiatric treatment, consisted of 131 unrelated subjects, recruited during the project »Population structure of Croatia – anthropogenic approach« supported by the Croatian Ministry of Science. The subjects were aged between 30 and 74 years (mean age 50.3±7.51), and were sampled from 9 Croatian cities (Zagreb, Zadar, Dubrovnik, Pazin, Zabok, Hvar, Krk, Donji Miholjac and Delnice).

DNA analysis

Cases DNA was isolated from whole blood (7 mL) either by the method given by Muller et al.[9], or by Nucleon Genomic DNA Extraction kit (Tepnel Life Sciences PLC) standard protocols.

The study was conducted on the following genes: DRD4, SLC6A3 and ADRA2B. Potentially informative SNPs were selected using SNPbrowser softwer (Applied Biosystems), which uses databases of 160,000 integrated SNPs, given by the company itself by use of the TaqMan SNP Genotyping techology, as well as of over one million SNPs proved at the International HapMap project (HapMap Consortium 2004).

Examined genes and the chromosomal location, precise position (bp), reciprocal distance of the chosen SNPs as well as the changes of the nucleotides are presented in Table 3.

Cases SNPs were detected using the SNPIex Genotyping System (Applied Biosystems). The genotyping system is based on the oligonucleotide ligitation assay (OLA) (Applied Biosystems), followed by multiplexed PCR (with polymerase chain reaction).

TABLE 2
DIAGNOSTIC GROUPS AND CHARACTERISTICS OF SUICIDAL CASES

Diagnosis	Males	Females	Total
F03–F07 (organic disorders)	4	7	11
F22–F25 (without F20) (delusional disorders)	8	12	20
F31–F33 (mood disorders)	11	21	32
F43–F42 (anxiety disorders)	8	11	19
F60–F61 (personality disorders)	11	18	29
F10–F19 (addictions)	5	9	14
Total	47	78	125

TABLE 3
TAGS, LOCATION AND RECIPRICAL DISTANCE OF THE ANALYSED POLYMORPHISMS

SNP #rs	Allele	Tag	SNP location	Reciprocal distance	Chromosome	Gene
rs3758653	C/T	DRD4_1	626399		11	DRD4
rs11246226	A/C	DRD4_2	631191	4792	11	DRD4
rs936465	C/G	DRD4_3	633568	2377	11	DRD4
rs4331145	A/G	DRD4_4	633683	115	11	DRD4
rs40184	A/G	SLC6A3_1	1448077		5	SLC6A3
rs11133767	A/G	SLC6A3_2	1454580	6503	5	SLC6A3
rs6869645	C/T	SLC6A3_3	1457548	2968	5	SLC6A3
rs6347	A/G	SLC6A3_4	1464412	6864	5	SLC6A3
rs37022	A/T	SLC6A3_5	1468629	4217	5	SLC6A3
rs464049	C/T	SLC6A3_6	1476905	8276	5	SLC6A3
rs460000	A/C	SLC6A3_7	1485825	8920	5	SLC6A3
rs403636	G/T	SLC6A3_8	1491354	5529	5	SLC6A3
rs3756450	C/T	SLC6A3_9	1501148	9794	5	SLC6A3
rs10183151	G/T	ADRA2B_1	96196660		2	ADRA2B
rs3813662	G/T	ADRA2B_2	96201569	4909	2	ADRA2B
rs1168965	C/G	ADRA2B_3	96209773	8204	2	ADRA2B
rs749457	C/T	ADRA2B_4	96217818	8045	2	ADRA2B

After the multiplexed PCR, with a specific probe detector (ZipChute), the allelic SNPs were detected by capillar electrophoresis on Applied Biosystems 3130 DNA Analyzer. All steps in the genotyping process were performed by producer's protocol.

Data analysis

The allelic frequency in the examined polymorphic locus in the case-control groups were determined by counting, while the allelic association with schizophrenic and suicidal phenotypes was statistically determined by χ^2--test[10]. Adjustment for multiple testing was performed by permuting association results 10,000 times in order to determine the lowest possible significance level. Statistics programme SPSS for Windows v7.5 was used to perform the mentioned computation.

The HW balance was verified by Exact SNP test of the PEDSTATS programme.

TABLE 4
PROBABILITY OF HW EXPECTATIONS BETWEEN EXAMINED ALLELES AND THEIR FREQUENCY IN THE CASE-CONTROL POPULATON (SCHIZOPHRENIA)

SNP	SNP rs	Alleles	Location	p (HWE)	Control group	Cases (sch)	χ^2	p_{sch}
ADRA2B_1	rs1018351	G/T	96196660	1	0.18	0.247	2.697	0.101
ADRA2B_2	rs3813662	T/G	96201569	1	0.043	0.015	3.026	0.082
ADRA2B_3	rs1168965	C/G	96209773	0.78	0.207	0.209	0.003	0.957
ADRA2B_4	rs749457	T/C	96217818	0.802	0.49	0.337	9.867	0.002
SLC6A3_1	rs40184	G/A	1448077	0.009	0.452	0.39	1.138	0.286
SLC6A3_2	rs11133767	A/G	1454580	0.149	0.239	0.196	0.787	0.375
SLC6A3_3	rs6869645	C/T	1457548	0.643	0.098	0.064	1.283	0.257
SLC6A3_4	rs37022	A/T	1468629	0.532	0.25	0.275	0.244	0.622
SLC6A3_5	rs464049	C/T	1476905	0.725	0.355	0.465	4.015	0.045
SLC6A3_6	rs460000	A/C	1485825	0.112	0.283	0.256	0.169	0.681
SLC6A3_7	rs403636	G/T	1491354	1	0.05	0.018	2.547	0.111
SLC6A3_8	rs3756450	C/T	1501148	0.969	0.212	0.195	0.151	0.698
DRD4_1	rs3758653	C/T	626399	0.019	0.395	0.450	0.421	0.517
DRD4_2	rs11246226	A/C	631191	0.736	0.183	0.078	6.100	0.014
DRD4_3	rs936465	C/G	633568	0.417	0.395	0.352	0.267	0.606
DRD4_4	rs4331145	A/G	633683	0.039	0.327	0.202	4.298	0.038

TABLE 5
ANALYSIS OF THE RELATION OF THE POLYMORPHISMS IN ADRA2B, SLC6A3 AND DRD4 WITHIN CASE-CONTROL GROUPS (SUICIDAL ATTEMPT)

SNP	Control group	Suicidal subjects (N=125)	χ^2	P_{sui}
ADRA2B_1	0.18	0.286	0.009	0.009
ADRA2B_2	0.043	0.024	0.249	0.249
ADRA2B_3	0.207	0.268	0.158	0.158
ADRA2B_4	0.49	0.476	0.758	0.758
SLC6A3_1	0.452	0.643	3.042	0.081
SLC6A3_2	0.239	0.825	1.971	0.160
SLC6A3_3	0.098	0.111	0.182	0.670
SLC6A3_4	0.25	0.297	0.919	0.338
SLC6A3_5	0.355	0.402	0.805	0.370
SLC6A3_6	0.283	0.815	2.663	0.103
SLC6A3_7	0.05	0.986	4.152	0.042
SLC6A3_8	0.212	0.292	2.962	0.085
DRD4_1	0.395	0.430	0.115	0.896
DRD4_2	0.183	0.104	3.236	0.072
DRD4_3	0.395	0.284	2.195	0.138
DRD4_4	0.327	0.242	2.117	0.145

By using the data of the genotype it was possible to determine the belonging of each individual to one potential subpopulation, and consequently to possible population substructures. Cases were tested on a value of K=2.3 and 4, using the linkage model, which assumes a mixed population, and a sensitive model of correlated allelic frequencies. Possible substructures of population were tested in the described fashion by the STRUCTURE programme[12].

Results

The data on the examined polymorphisms are presented in the tables that follow. Table 4 shows the results of the analysis on the relation between polymorphysims in ADRA2B, SLC6A3 and DRD4 and the manifestation of schizophrenia in relation to the control group, while Table 5 refers to examined polymorphisms in suicidal subjects.

Results show a significant allelic association between 4 SNPs and schizophrenia and between 2 SNPs and suicidal attempt. The allele in rs749457 SNP in ADRA2B shows a strong relation ($p<0.01$) with suicidal attempt. Schizophrenia has relation with ($p<0.01$) both SNPs in SLC6A3 (rs464094) and in DRD4 (rs11246226, rs4331145), while suicidal attempt is related with the SNP of the SLC6A3 gene (rs403636).

D values are used to define haplotype (LD) blocks by HaploView programme. No significant unbalance in examined polymorphisms was detected in DRD4. In ADRA2B there are significant unbalances between the SNPs 2 and 3 (2 kB block) and between 7 ad 8 (5 kB block), but none of the examined poymorphisms shows a connection with the manifestation of the disorder.

Discussion and Conclusions

The inheritance component plays a very significant role in etiopathogenesis of schizophrenia and suicidal behaviour. We assume that a better knowledge of the pathophysiological mechanisms of schizophrenia and suicidal behaviour, along with the discovery of the genes responsible for their development, may enable early diagnosis and better treatment[13]. The structure of the Croatian population, in particular that of its islands, has been studied for several years and started as part of anthropological projects back in 1971 by Rudan et al.[14].

Disorders of the mesolimbic dopamine pathway may lead to the manifestation of a positive group of psychopathological symptoms of schizophrenia, while the reduced activity of mesocortical dopamine pathway causes negative symptoms and cognitive disorders[15]. Noradrenaline, through its receptors, can affect the variability and reactivity of dopamine neurons.

Subjects who attempted suicide present a reduced level of noradrenaline in the limbic regions of the brain, but a higher level in the PFC (prefrontal cortex). In addition, there is evidence of reduced dopamine transmission.

This study focuses on two genes of the dopamine system, DRD4 and SLC6A3, and the gene of the noradrenergic system ADRA2B. According to available data, there are no associative studies on these genes on the Croatian population (search of Croatian Scientific Literature).

The SLC6A3 gene codes for the dopanime pathway which transfers dopamine from the extracellular area into the neuron. An extensive study conducted by Talkowski et al.[16] showed the relation between 3 SNPs of SLC6A3 gene, among which is rs46409 and schizophrenia, and that matches with our results. The frequency of a rare allele in SPN rs46409 (f=0.48) in patients is comparable to the frequency of the same allele in the part of the Croatian population affected by schizophrenia (f=0.465). This SNP is situated in the third intron of SLC6A3, therefore we can assume its possible influence on the expression of the functional proteine.

A change of expression of the transporter may cause an increased quantity of dopamine, and may consequently increase the effects of dopamine transmission. The expression of SLC6A3 is highest in the striatum, and is almost absent in PFC[17]. A non-functional dopamine transporter could lead to a hyperactivity of the dopamine system in the subcortical regions of the brain and, at the same time, due to the regulation of the feedback, it could cause the reduction of the activity of the dopamine system in PFC[17].

We assume that the dopamine pathway is reduced in suicidal subjects. Hypothetical changes in the functioning of the dopamine transporter connected with SNP rs403636 could contribute to the deficits of the dopamine system in subjects who attempted suicide. Considering that there exists a mutual regulation of the serotonin and dopamine systems, a reduced serotonin transmission

could be the cause of changes in the transmission of dopamine[18].

A high number of genetic studies indicate influence of polymorphysms in DRD4 on the schizophrenic phenotype. A meta-analysis (SzGene database) shows a higher incidence of S alleles 120pb ins/del polymorphisms in DRD4 in subjects suffering from schizophrenia (OR (95% CI)=0.81 (0.7, 0.94)). Studies on the relation between 40pb VNTR polymorphisms and schizophrenia are mainly negative as regards the Caucasion population. Talkowski et al.[16] did not find any connection between the SNPs of the DRD4 gene and schizophrenia. However, the results of this study indicate a connection betwen the alleles of two SNPs (rs11246226, rs4331145) in the 3rd region of the DRD4 gene and schizophrenia.

This study shows that there exists a connection between SNPs in ADRA2B and schizophrenia and suicidal attempt. The SNP rs749457 is situated in the 3rd region of the ADRA2B gene and is connected with schizophrenia, while rs10181251 is situated in the 5th region of the gene and is connected with suicidal attempt.

According to our knowledge, this is the first study that points out a potential role of polymorphisms within a region of the ADRA2B gene in the manifestation of psychiatric disorders.

Evidence of the importance of the ADRA2 receptors in schizophrenia is the efficiency of clozapine, which is also the antagonist of the ADRA2 receptors. Clozapine reduces suicidal behaviour regardless of its antipsychotic effect[19], as the ADRA2 receptors can modulate the transmission of serotonin. We can assume that polymorphisms alone or the neighbouring genetic regions related to the examined SNPs are functional in relation to a more intense activity of ADRA2B receptors. An intense activity of the examined receptor would increase the risk of a manifestation of schizophrenia and/or suicidal attempt.

The antagonists of ADRA2 receptors also reduce the variability of dopamine transmission in the ventral tegmental area (VTA). Besides the influence on the mesolimbic system, the antagonists of ADRA2 also increase the availability of dopamine in PFC, hence milding cognitive disfunction[20].

Yamamoto et al.[21] suggested a theory according to which positive symptoms of schizophrenia would be the consequence of hyperactivity of the noradrenergic system, while negative symptoms a consequence of its hypoactivity[22].

At the origin of impulsivity lies a reduced serotonin transmission, while the cause of feelings of helplessness is a reduced noradrenergic transmission. Both phenomena may eventually lead a subject to suicidal attempt[23].

In conclusion, the results of the study have hypothetical biological grounds in the pathological changes of catecholamine systems in schizophrenia and suicidal behaviour[24]. Further studies on the subject are needed in order to determin a possible significance of the examined SNPs in SLC6A3, DRD4 and ADRA2B in the functionality of their protein products[25].

A limitation of this study lies in the small sample. Positive results give way to future studies which would be conducted on a much wider range of subjects of Croatian origin and their detailed stratification

Acknowledgements

This work was supported by the Croatian Ministry of Science, Education, and Sports grant »Population structure of Croatia – anthropogenic approach« (No. 196-1962766-2751 to P.R.).

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POREDBENO ISTRAŽIVANJE GENSKIH BILJEGA NEUROTRANSMITORSKIH SUSTAVA U SHIZOFRENIH I SUICIDALNIH OSOBA

S A Ž E T A K

Shizofrenija i suicidalno ponašanje su teški i kompleksni te velikim dijelom nasljednim faktorima determinirani psihički poremećaji. U oba poremećaja postoje patološke promjene u katekolaminergičkim neurotransmitorskim sustavima. U istraživanje su bile uključene tri skupine ispitanika; skupina oboljelih od shizofrenije, skupina osoba koje su pokušale samoubojstvo i skupina fenotipski zdravih ispitanika. Uzorci krvi shizofrenih bolesnika kao i osoba koje su pokušale samoubojstvo prikupljeni su u Psihijatrijskoj bolnici »Sveti Ivan« u Zagrebu tijekom 2004. godine. Ispitana je statistička povezanost ukupno 18 SNP-ova unutar tri gena dopaminskog odnosno adrenergičkog sustava (DRD4, SLC6A3 i ADRA2B) s pojavom shizofrenije odnosno suicidalnog ponašanja. Ispitanici su genotipizirani korištenjem SNPlex sustava obzirom na navedenih 18 polimorfizama. Utvrđene su statistički značajne razlike u učestalosti ispitivanih alela između navedenih skupina. Rezultati pokazuju značajnu povezanost 4 SNP-a (ADRA2B rs749457, SLC6A3 rs464094 te DRD4 rs11246226 i rs4331145) sa shizofrenijom i 2 SNP-a s pokušajem samoubojstva (ADRA2B rs1018351 i SLC6A3 rs403636). Uz to, ovo istraživanje je prvo koje ukazuje na potencijalnu ulogu/učinak polimorfizama unutar ADRA2B gena u nastanku shizofrenije, kao i u podlozi suicidalnog ponašanja.