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BRIEF REPORT

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Pharmacogenetics of tardive dyskinesia in schizophrenia: The role of *CHRM1* and *CHRM2* muscarinic receptors

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ABSTRACT

Objectives: Acetylcholine M (muscarinic) receptors are possibly involved in tardive dyskinesia (TD). The authors tried to verify this hypothesis by testing for possible associations between two muscarinic receptor genes (*CHRM1* and *CHRM2*) polymorphisms and TD in patients with schizophrenia.

Methods: A total of 472 patients with schizophrenia were recruited. TD was assessed cross-sectionally using the Abnormal Involuntary Movement Scale. Fourteen allelic variants of *CHRM1* and *CHRM2* were genotyped using Applied Biosystems amplifiers (USA) and the MassARRAY System by Agena Bioscience.

Results: The prevalence of the rs1824024*GG genotype of the *CHRM2* gene was lower in TD patients compared to the group without it ($\chi 2 = 6.035$, $p = 0.049$). This suggested that this genotype has a protective effect for the development of TD (OR = 0.4, 95% CI: 0.19–0.88). When age, gender, duration of schizophrenia and dosage of antipsychotic treatment were added as covariates in regression analysis, the results did not reach statistical significance.

Conclusions: This study did identify associations between *CHRM2* variations and TD; the results of logistic regression analysis with covariates suggest that the association is, however, likely to be secondary to other concomitant factors.

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Introduction

The extrapyramidal side effects (EPSs) of antipsychotic drugs (akathisia, parkinsonism, dystonia and tardive dyskinesia (TD)) are caused by dysfunctions of the cortico-–striato–[.]–thalamo–cortical regulatory circuits (Loonen and Ivanova 2013). The vast majority of the neurons of the corpus striatum (caudate, putamen, and accumbens) belong to gamma-amino butyric acid (GABA)-ergic medium-sized spiny projection neurons (MSNs) (∼95%), or to three types of GABA-ergic interneurons (∼ 4%). Only 1–2% (approximately) of the striatal nerve cells are cholinergic interneurons, but still these giant, aspiny neurons make the striatum the largest cholinergic nucleus of the central nervous system as they ramify extensively and send projections widely throughout this ganglion (Lim et al. 2014; Gonzales and Smith 2015). Almost all striatal cholinergic synapses belong to one of these cholinergic interneurons, which are believed to be the analogues of tonically active neurons identified by in vivo recordings in the putamen of primates (Deffains and Bergman 2015). This means that these neurons show spontaneous activity, in which this basal activity can be modulated up- and downward by synaptic input. Acetylcholine stimulates both striatal nicotinic and

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muscarinic receptors. Muscarinic receptors are more widely spread and can be divided into excitatory M1 class (M1, M3, M5) and inhibitory M2 class (M2, M4) receptors (Goldberg et al. 2012; Lim et al. 2014). Blocking these muscarinic receptors non-selectively with anticholinergic drugs such as trihexyphenidyl (Cyclodol) (Bolden et al. 1992) is common procedure in the treatment of antipsychotic drug-induced parkinsonism and dystonia. Concomitant (prophylactic) anticholinergic treatment of EPSs is, however, considered to be one of the risk factors for TD (Jankelowitz 2013), although Altamura et al. (1990) did not find a significant association between anticholinergic drug use and the prevalence of TD. On the other hand, some studies suggest an improvement in TD with the cessation of anticholinergics (Desmarais et al. 2012).

Muscarinic receptor inhibition has been associated with a variety of neuropsychiatric disorders, including delirium (Hshieh et al. 2008; Campbell et al. 2009), dementia (Campbell et al. 2009; Jiang et al. 2014), depression (Drevets et al. 2013; Jeon et al. 2015), bipolar disorder (Jeon et al. 2015; Van Enkhuizen et al. 2015) and schizophrenia (McKinzie and Bymaster 2012). In particular, gene polymorphisms in the M1 receptor (*CHRM1*) have been found to be associated with psychiatric symptoms and cognitive function in schizophrenic patients (Liao et al. 2003), in the M4 receptor (*CHRM4*) with schizophrenia (Scarr et al. 2013), and in the M2 receptor (*CHRM2*) with autonomic nervous system activity in patients with schizophrenia on high-dose antipsychotics (Miyauchi et al. 2016).

The present study aims to test for associations between the muscarinic receptor (*CHRM1* and *CHRM2*) gene polymorphisms and the prevalence of TD in 472 ethnic Russian patients with schizophrenia.

Methods

Patients

This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki 1975, revised in Fortaleza, Brazil, 2013), established for experiments involving humans. We recruited patients from three psychiatric hospitals located in the Tomsk, Kemerovo, and Chita oblasts (regions) of Siberia, Russia. Each patient provided written informed consent after the study was approved (protocol N63/7.2014) by the Local Bioethics Committee of the Mental Health Research Institute. The inclusion criteria were a clinical diagnosis of schizophrenia, according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10: F20), and being aged between 18 and 75 years old. Exclusion criteria were non-Caucasian physical appearance (e.g., Mongoloid, Buryats, or Khakassians), pregnancy, any relevant physical disorder, including organic brain disorders (e.g., epilepsy or Parkinson's disease), or any relevant pharmacological withdrawal symptoms. To compare antipsychotic medications, all drug doses taken at the time of investigation were converted into chlorpromazine equivalents (CPZeq; Andreasen et al. 2010).

A total of 194 patients received typical antipsychotics (of which haloperidol was the most often used: 115 patients; chlorpromazine, 44 patients (as well as chlorprothixene, zuclopenthixol, thioridazine and periciazine)). A total of 172 patients received atypical antipsychotics (mainly risperidone, clozapine and quetiapine, and to a lesser extent olanzapine, sertindole, paliperidone, and amisulpride), and 83 patients received combined therapy. Patients were assessed once for the presence or absence of dyskinesia according to the abnormal involuntary movement scale (AIMS) (Loonen and Van Praag 2007; Loonen et al. 2000, 2001). The AIMS scores were transformed into a binary form (presence or absence of dyskinesia) with Schooler and Kane's criteria (1982). Schooler–Kane criteria require: (i) at least 3 months of cumulative exposure to neuroleptics; (ii) the absence of other conditions that might cause involuntary movements and (iii) at least moderate dyskinetic movements in one body area ($\geq$3 on AIMS) or mild dyskinetic movements in two body areas ($\geq$2 on AIMS).

DNA analysis

Blood samples were obtained from each participant and used for DNA isolation by a standard phenol-chloroform method. Genotyping was performed without any knowledge of the patient's clinical status. Genotyping was carried out on six polymorphic variants of gene CHRM1 (rs2075748, rs544978, rs2067477, rs2067479, rs2186410 and rs542269) and eight polymorphic variants of gene CHRM2 (rs2061174, rs324650, rs2350780, rs1824024, rs7810473, rs2350786, rs324640 and rs1378650) by real-time PCR using Applied Biosystems amplifiers (USA) in the Laboratory of Molecular Genetics and Biochemistry of Mental Health Research Institute (Tomsk), and with the use of The MassARRAY System by Agena Bioscience in the Laboratory of Genetics of the University of Groningen. DNA concentrations were measured with a Thermo Scientific NanoDrop 8000 UV-Vis Spectrophotometer. Possibly relevant SNPs were selected according to the literature data on associations with schizophrenia and

other mental disorders (Cohen-Woods et al. 2009; Jagannathan et al. 2010; Michel and Teitsma 2012; Miyauchi et al. 2016) and programme LD TAG SNP Selection (TagSNP).

Statistical analysis

Statistical analyses were performed using SPSS for Windows, v. 17. The Mann–Whitney test was used to compare qualitative traits and the $\chi 2$ test was used for categorical traits. Genotype prevalence was checked for concordance with the expectation under Hardy–Weinberg equilibrium using the χ^2-test. Allele and genotype frequencies were compared using the χ^2-test and Fisher's exact test, if necessary. The differences were considered statistically significant at $P < 0.05$. The size of the effect of genetic polymorphism on the risk of TD was estimated using odds ratio (OR) and 95% confidence intervals (CIs). Also, logistic regression with adjustment for covariates was applied to test for association between the SNPs and TD. Age, gender, duration of schizophrenia and dosage of antipsychotic treatment were used as covariates since they have been shown to have statistically significant effects on the risk of TD. No essential multicollinearity was observed between the covariates (variance inflation factors ranged from 1.2 to 2.3). Experiment-wise permutations were used to address the multiple testing issue as described in the paper Churchill and Doerge (2011).

Results

A total of 472 patients with schizophrenia was recruited after obtaining informed consent, of whom 449 patients were included for subsequent study due to their fulfilling the criterion of receiving the antipsychotic treatment for more than 3 months. According to the other predefined criteria, 121 patients suffered from TD (Table 1).

The mean age of patients with dyskinesia was significantly higher than the age of the comparison group and the duration of schizophrenia was significantly longer than in patients without TD.

The prevalence of genotypes of studied genes did not deviate from expectation under the Hardy–Weinberg equilibrium, except for rs544978, rs2067477 and rs2186410 in the *CHRM1* gene. These SNPs were therefore excluded from analysis.

Table 2 presents the genotype and allele prevalence in patients with and without TD; a statistically significant lower frequency of the rs2061174*C allele of the *CHRM2* gene was found in patients with TD in comparison to the group without TD ($\chi^2 = 3.84$, $P = 0.05$).

The frequency of the rs1824024*GG genotype of the *CHRM2* gene was marginally significantly lower in TD patients compared to the group without it ($\chi^2 = 6.035$, $P = 0.049$) suggesting its protective effect on the development of TD (OR = 0.40, 95% CI: 0.19–0.88).

When age, gender, duration of schizophrenia and dosage of antipsychotic treatment in CPZeq were added as covariate in logistic regression analysis, however, the results did not reach statistical significance (permutation $p > 0.05$).

Discussion

In this study we found a borderline statistical significant association between two variants of the muscarinic M2 receptor (*CHRM2*) gene and the risk of developing TD: rs2061174 and rs1824024. However, logistic regression analysis showed that this observation may also be related to well-known risk factors of TD, such as sex, age, duration of the disease and the dosages of antipsychotics (Solmi et al. 2018). All these factors were associated with TD in our study.

SNPs rs2061174 and rs1824024 are located in the intron; their functional role is not fully understood, but they have been demonstrated to be significantly associated with risk for major depression, alcoholism and cognitive abilities (Wang et al. 2004; Luo et al. 2005, 2007; Thongket et al. 2016).

CHRM2 has a relative low abundancy within the striatum in comparison to CHRM1 and CHRM4 (Lim et al. 2014). CHRM2 is a primarily inhibitory autoreceptor of cholinergic interneurons and moreover inhibits glutamatergic thalamostriatal and corticostriatal terminals on direct and indirect pathway MSNs (Goldberg et al. 2012; Lim et al. 2014). As cholinergic interneurons show spontaneous activity, inactivity of CHRM2 can, in theory, lead to TD. Inactivity of M2 receptors would increase cholinergic stimulation of M1 and M4

Table 1. Characteristics of the studied patient groups.

	Patients without TD ($n = 328$)	Patients with TD ($n = 121$)	P value
Gender: Male, *n* (%)	152 (46.3%)	71 (58.7%)	0.027
Female, *n* (%)	176 (53.7%)	50 (41.3%)	
Age, years	37 [31; 48]	48 [37.5; 58]	<0.001
Age of onset, years	24 [20; 30]	25 [20; 32]	0.974
Duration of disease, years	11 [5; 18]	20 [12; 29.5]	<0.001
CPZeq	396 [200; 750]	500 [286.2; 750]	0.021

Table 2. Genotype distribution in patients with TD.

Gene	Polymorphic variant	Genotypes/Alleles	With TD	Without TD	OR		χ^2	*P*
					value	95% CI		
CHRM1	rs2075748	GG	80 (66.7%)	223 (68.4%)	0.92	0.59–1.44	0.179	0.915
		GA	36 (30.0%)	94 (28.8%)	1.06	0.67–1.67		
		AA	4 (3.3%)	9 (2.8%)	1.21	0.37–4.02		
		G	0.817	0.828	0.92	0.63–1.36	0.16	0.69
		A	0.183	0.172	1.08	0.74–1.59		
	rs2067479	TT	0 (0.0%)	0 (0.0%)	2.7	0.05–136.61	1.311	0.252
		TC	7 (5.8%)	32 (9.8%)	0.57	0.24–1.32		
		CC	114 (94.2%)	295 (90.2%)	1.77	0.76–4.12		
		T	0.029	0.049	0.58	0.25–1.33	1.7	0.19
		C	0.971	0.951	1.73	0.75–3.97		
	rs542269	CC	5 (4.5%)	14 (4.6%)	0.97	0.34–2.77	1.07	0.586
		CT	39 (35.1%)	123 (40.6%)	0.79	0.50–1.25		
		TT	67 (60.4%)	166 (54.8%)	1.26	0.81–1.96		
		C	0.221	0.249	0.85	0.59–1.23	0.72	0.4
		T	0.779	0.751	1.17	0.81–1.69		
CHRM2	rs2061174	TT	60 (49.6%)	144 (44.0%)	1.25	0.82–1.90	5.633	0.06
		TC	53 (43.8%)	134 (41.0%)	1.12	0.74–1.71		
		CC	8 (6.6%)	49 (15.0%)	0.4	0.18–0.88		
		T	0.715	0.645	1.38	1.00–1.90	3.84	**0.05**
		C	0.285	0.355	0.73	0.53–1.00		
	rs324650	AA	27 (22.5%)	79 (24.2%)	0.91	0.55–1.49	0.171	0.918
		AT	59 (49.2%)	159 (48.8%)	1.02	0.67–1.54		
		TT	34 (28.3%)	88 (27.0%)	1.07	0.67–1.70		
		A	0.471	0.486	0.94	0.70–1.26	0.17	0.68
		T	0.529	0.514	1.06	0.79–1.43		
	rs2350780	AA	53 (43.8%)	142 (43.4%)	1.02	0.67–1.55	1.467	0.48
		AG	56 (46.3%)	139 (42.5%)	1.17	0.77–1.77		
		GG	12 (9.9%)	46 (14.1%)	0.67	0.34–1.32		
		A	0.669	0.647	1.11	0.81–1.51	0.4	0.53
		G	0.331	0.353	0.9	0.66–1.24		
	rs1824024	GG	8 (6.7%)	49 (15.0%)	0.4	0.19–0.88	6.035	**0.049**
		GT	55 (45.8%)	125 (38.3%)	1.36	0.89–2.08		
		TT	57 (47.5%)	152 (46.6%)	1.04	0.68–1.58		
		G	0.296	0.342	0.81	0.59–1.11	1.69	0.19
		T	0.704	0.658	1.24	0.90–1.71		
	rs7810473	AA	44 (37.6%)	99 (35.0%)	1.12	0.72–1.75	0.292	0.864
		AG	51 (43.6%)	131 (46.3%)	0.9	0.58–1.38		
		GG	22 (18.8%)	53 (18.7%)	1	0.58–1.74		
		A	0.594	0.581	1.05	0.77–1.44	0.11	0.74
		G	0.406	0.419	0.95	0.70–1.29		
	rs2350786	GG	60 (54.5%)	155 (51.2%)	1.15	0.74–1.78	1.198	0.549
		GA	44 (40.0%)	122 (40.3%)	0.99	0.63–1.54		
		AA	6 (5.5%)	26 (8.6%)	0.61	0.25–1.54		
		G	0.745	0.713	1.18	0.83–1.68	0.85	0.36
		A	0.255	0.287	0.85	0.60–1.20		
	rs324640	GG	37 (30.8%)	103 (31.5%)	0.97	0.62–1.52	0.038	0.981
		GA	56 (46.7%)	153 (46.8%)	1	0.65–1.51		
		AA	27 (22.5%)	71 (21.7%)	1.05	0.63–1.73		
		G	0.542	0.549	0.97	0.72–1.31	0.04	0.85
		A	0.458	0.451	1.03	0.77–1.39		
	rs1378650	CC	33 (29.5%)	76 (25.0%)	1.25	0.77–2.03	1.933	0.38
		CT	50 (44.6%)	159 (52.3%)	0.74	0.48–1.14		
		TT	29 (25.9%)	69 (22.7%)	1.19	0.72–1.96		
		C	0.518	0.512	1.03	0.75–1.39	0.03	0.87
		T	0.482	0.488	0.97	0.72–1.32		

receptors on MSNs and excitatory nicotinergic receptors at glutamatergic and dopaminergic terminals. Less-active CHRM2 would increase the release of glutamate from thalamostriatal and corticostriatal terminals on MSNs. As inhibitory CHRM4 are less abundant on indirect pathway MSNs, these neurons would be more vulnerable to glutamatergic (over)stimulation than direct pathway MSNs. We have previously suggested that neurotoxicity of indirect pathway MSN could explain the development of TD (Loonen and Ivanova 2013). Increased glutamatergic activity and/or augmented sensitivity to glutamatergic activation could result in greater likelihood of reaching neurotoxic effects. However, this would be unrelated to the usage of anticholinergic drugs, since these non-selectively block all subtypes of muscarinic receptors (Bolden et al. 1992).

The CHRM4 is particularly interesting in this respect as this inhibitory muscarinic receptor is unevenly distributed between direct and indirect pathway MSN.

The *CHRM4* rs2067482 polymorphism was associated with an increased risk of schizophrenia identified by sequencing this gene from the brains of 76 people with the disorder, and from 74 people with no history of psychiatric disorders (Scarr et al. 2013).

The study of gene–gene interaction between muscarinic receptors and glutamate receptors and the relationship between *CHRM4* gene and TD, possibly through the pathogenesis of schizophrenia, therefore, merits further investigation.

A limitation of our study might be the usage of anticholinergic drug (trihexyphenidyl) and drugs with anticholinergic effects, including certain antipsychotics (Bolden et al. 1992) and that of atypicals, affecting the prevalence of TD through other types of receptor interactions. Patients receiving monotherapy or combination therapy with different typical and atypical antipsychotics may have a higher risk of developing TD (like typical antipsychotics) or be associated with lower TD risk (like clozapine).

Two advantages of our study are the large patient numbers and the careful diagnosis of TD according to Schooler and Kane's criteria (1982).

It can be concluded that, in our patient population, a rather weak association between the prevalence of TD and two variants of the *CHRM2* gene were found, which lost significance when other possibly contributing factors accounted for.

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Disclosure of interest

The authors report no conflict of interest.

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