



Prolactin gene polymorphism (–1149 G/T) is associated with hyperprolactinemia in patients with schizophrenia treated with antipsychotics



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ABSTRACT

Background: Antipsychotic drugs can cause hyperprolactinemia. However, hyperprolactinemia was also observed in treatment-naïve patients with a first schizophrenic episode. This phenomenon might be related to the role of prolactin as a cytokine in autoimmune diseases. Extrapituitary prolactin production is regulated by an alternative promoter, which contains the functional single nucleotide polymorphism –1149 G/T (rs1341239). We examined whether this polymorphism was associated with hyperprolactinemia in patients with schizophrenia.

Method: We recruited 443 patients with schizophrenia and 126 healthy controls. The functional polymorphism –1149 G/T (rs1341239) in the prolactin gene was genotyped with multiplexed primer extension, combined with MALDI-TOF mass spectrometry. Genotype and allele frequencies were compared between groups with the χ^2 test and logistic regression models adjusting for covariates.

Results: The frequency of genotypes and alleles in patients with schizophrenia did not differ from those in control subjects. A comparison between patients with schizophrenia with and without hyperprolactinemia revealed significantly higher frequency of the G allele in patients with hyperprolactinemia than in patients without it ($\chi^2 = 7.25$; $p = 0.007$; OR = 1.44 [1.10–1.89]). Accordingly, patients with hyperprolactinemia carried the GG genotype more frequently than patients without hyperprolactinemia ($\chi^2 = 9.49$; $p = 0.009$). This association remained significant after adjusting the estimates for such covariates as sex, age, duration of the diseases and the dose of chlorpromazine equivalents.

Conclusion: This study revealed a significant association between the polymorphic variant rs1341239 and the development of hyperprolactinemia in patients with schizophrenia. The serum prolactin concentration in patients with schizophrenia treated with antipsychotics may provide an indication of the activity of the gene that regulates extrapituitary prolactin production which is believed to play a role in the immune system.

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1. Introduction

Long-term antipsychotic drug use remains the mainstay of treatment for patients with schizophrenia. However, pharmacotherapy with these drugs is complicated by several troublesome side effects,

including metabolic, endocrine, cardiovascular, and movement disorders (Lally and MacCabe, 2015; Staller, 2006). One of these side effects may be hyperprolactinemia (Ajmal et al., 2014; Peuskens et al., 2014). Prolactin secretion is persistently inhibited by dopamine (Fitzgerald and Dinan, 2008; Peuskens et al., 2014), and antipsychotic drugs are believed to increase prolactin release by blocking dopamine receptors.

Prolactin, also called the lactotrophin hormone, is a 199 amino-acid hormone synthesized and secreted in a pulsatile manner (~10 peaks per day in young adults) by the lactotroph cells of the anterior lobe of the

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pituitary gland (i.e., the adenohypophysis) (Fitzgerald and Dinan, 2008; Peuskens et al., 2014). The gene that encodes prolactin (*PRL*) has been mapped to chromosome 6p21 (Evans et al., 1989; Owerbach et al., 1981). The 6p21 region has been identified as a susceptibility locus that harbors genes associated with schizophrenia (Roig et al., 2007; Schwab et al., 2003; Tochigi et al., 2004). A recent genome-wide analysis (Stefansson et al., 2009) also found that this region was significantly associated with schizophrenia. In humans, the *PRL* locus consists of a single gene that contains five coding exons, which is controlled by a pituitary-specific promoter, and a non-coding exon, which is controlled by an alternative promoter. The latter promoter drives expression in non-pituitary tissues (Featherstone et al., 2012). Thus, apart from its role as a pituitary hormone, prolactin is also produced as a cytokine by immune cells; its receptor belongs to the family of cytokine receptors type 1 (Peeva et al., 2003). Stevens et al. (2001) identified a functional polymorphism in the *PRL* gene, –1149 G/T (rs1341239). They showed that the G allele was associated with increased extrapituitary promoter activity and increased levels of lymphocyte prolactin mRNA. This polymorphism was previously associated with autoimmune diseases, such as systemic sclerosis (Fojtíková et al., 2010), rheumatoid arthritis (Lee et al., 2015; Reyes-Castillo et al., 2013), and systemic lupus erythematosus (SLE) (Lee et al., 2015; Stevens et al., 2001; Treadwell et al., 2015).

The immune system is believed to be involved in the pathogenesis of schizophrenia (DeLisi and Crow, 1986; Leboyer et al., 2016). Indeed, SLE was positively associated with schizophrenia (Tiosano et al., 2016). Moreover, stress is an important activator of the immune response (Leonard, 2006), and psychosocial stress has been shown to trigger the outbreak of psychotic symptoms and activate prolactin secretion (Riecher-Rössler et al., 2013). Additionally, Rybakowski et al. (2012) found that the –1149 G allele was associated with schizophrenia, and others showed that the –1149 TT genotype was correlated with high levels of serum prolactin (Treadwell et al., 2015).

In a collaborative Tomsk-Groningen research project, we measured serum prolactin levels (among other things) in patients with schizophrenia treated with antipsychotic drugs (Ivanova et al., 2016). In the present study, we investigated the possible role of the prolactin gene polymorphic variant, rs1341239, in the development of hyperprolactinemia in patients with schizophrenia.

2. Subjects and methods

2.1. 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. None of the participants was compromised in their capacity/ability to consent; thus, consent from the next-of-kin was not necessary, and it was not recommended by the local ethics committee. 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 age 18–75 years old. Exclusion criteria were non-Caucasian physical appearance (e.g., Mongoloid, Buryats, or Khakassians); pregnancy, or any relevant gynecological or endocrine (thyroid) disorder; relevant pharmacological withdrawal symptoms; or organic brain disorders (e.g., epilepsy, Parkinson's disease). A total of 191 patients were treated with conventional antipsychotics in oral and/or long-acting formulations. The most common conventional antipsychotic was haloperidol, which was used in 110 patients, but other treatments included oral chlorpromazine (CPZ), chlorprothixene, trifluoperazin and zuclopenthixol, and/or long-acting formulations of haloperidol-

zuclopenthixol- and flupenthixol-decanoate. A total of 176 patients were treated with atypical antipsychotics: risperidone, clozapine, quetiapine, olanzapine, amisulpride, paliperidone and sertindole. Different combinations of classical and atypical drugs were used by 79 patients. To compare antipsychotic medications, all dosages were converted into CPZ equivalents (CPZeq, Andreasen et al., 2010).

2.2. Control group

The control group consisted of 126 subjects (55 males/71 females), with a mean age of 38.5 ± 13.2 years. These control subjects were recruited from a group of blood donors, hospital staff members, and students, on a voluntary basis. They were mentally and somatically healthy individuals.

2.3. Blood sampling

Blood samples were drawn after an 8-h overnight fast, into tubes containing EDTA, for DNA extraction, or into tubes with a clot activator (CAT) to isolate the serum (BD Vacutainer). Blood samples with EDTA were stored in several aliquots at $-20\text{ }^{\circ}\text{C}$, until the DNA was isolated. Blood samples with CAT were centrifuged for 30 min at $2000 \times g$ at $4\text{ }^{\circ}\text{C}$ to isolate the serum; the serum was stored at $-20\text{ }^{\circ}\text{C}$, until prolactin analysis.

2.4. Hormone analysis

The prolactin concentration was measured in serum with the AccuBind ELISA Microwell kit (Monobind Inc., USA). In this microplate immuno-enzymatic assay, the ELISA had a sensitivity of 0.004 ng/well. This was equivalent to a sample containing 0.150 ng/ml prolactin. Normal prolactin concentrations were defined as ≤ 20 ng/ml for men and ≤ 25 ng/ml for non-pregnant, non-nursing women (Ivanova et al., 2016). These upper limits were consistent with criteria for hyperprolactinemia applied by Kelly et al. (2013) and Peuskens et al. (2014).

2.5. Genotyping

We performed the standard phenol-chloroform method to isolate DNA from leukocytes in whole peripheral blood drawn from patients with mental disorders. The DNA was genotyped for the studied gene in the Laboratory of Genetics of the University of Groningen with the MassARRAY® System (Agena Bioscience™). DNA concentrations were measured with a Thermo Scientific NanoDrop 8000 UV-Vis Spectrophotometer.

2.6. Statistics

Statistical analyses were performed with SPSS software for Windows, release 17. The Hardy-Weinberg equilibrium of genotypic frequencies was tested using chi-square test. Chi-square test and the Fisher's exact test, where necessary, were used for between-group comparisons of genotypes or allele frequencies. In addition, logistic regression models accounting for covariates were also estimated to test for association between the genetic polymorphism and hyperprolactinemia in patients with schizophrenia. Three genetic models were evaluated assuming additive, dominant or recessive effect of rare allele. The best model was chosen using Akaike Information Criteria (AIC). To address multiple testing issue, the significance of the models was estimated using Monte-Carlo permutations. Between-group differences in continuous variables were evaluated with the Student's *t*-test or one-way analysis of variance (ANOVA). Comparisons of prolactin levels in different groups were performed with the Kruskal-Wallis test. *p*-Values < 0.05 were considered significant.

Table 1
Demographics and clinical characteristics of patients with schizophrenia.

Trait	All (446)	Male (221)	Female (225)	p-Value*
Age (mean ± SD)	42.1 ± 12.4	37.8 ± 11.9	45.2 ± 13.9	$p < 0.0001$
Duration of disease, years	13 (6; 22)	11 (5; 18)	15 (7; 26)	$p < 0.0001$
Median (IQR)				
Daily dose of antipsychotics in CPZeq	425 (240; 750)	500 (300; 750)	372 (200; 750)	$p = 0.003$
Median (IQR)				
Prolactin ng/ml	23.32	18.18	34.89	$p < 0.0001$
Median (IQR)	(13.12; 49.96)	(10.61; 32.47)	(15.50; 65.03)	

CPZeq: chlorpromazine equivalents; IQR: interquartile range; *calculated with either the *t*-test or the Mann-Whitney *U* test, as appropriate.

Table 2
Frequencies of genotypes and alleles of the rs1341239 polymorphism in the *PRL* gene in patients with schizophrenia and controls.

Genotypes, alleles	Patients with schizophrenia n (%)	Control n (%)	OR		χ^2	<i>p</i>
			Estimate	95% CI		
GG	154 (34.8%)	50 (39.7%)	0.81	0.54–1.22	1.694	0.429
GT	208 (47.0%)	51 (40.5%)	1.30	0.87–1.95		
TT	81 (18.3%)	25 (19.8%)	0.90	0.55–1.49		
G	516 (58.2%)	151 (59.9%)	0.93	0.70–1.24	0.230	0.630
T	370 (41.8%)	101 (40.1%)	1.07	0.81–1.43		

3. Results

The total sample comprised 446 patients with schizophrenia (Table 1). Of these, 227 patients exhibited hyperprolactinemia (98 males/129 females), according to predefined criteria (Kelly et al., 2013; Peuskens et al., 2014).

The prevalence of genotypes in both the schizophrenic and healthy groups was consistent with Hardy-Weinberg equilibrium. The frequency of genotypes and alleles in patients with schizophrenia did not differ from those in control subjects (Table 2). Table 3 shows the characteristics of patients with schizophrenia, and those with hyperprolactinemia are compared to those with normal prolactin levels.

The frequency of the G allele of the polymorphic variant, rs1341239, was significantly higher in patients with hyperprolactinemia than in patients without it (Table 4; $\chi^2 = 7.25$; $p = 0.007$; OR 1.44; 95%CI: 1.10–1.89). Accordingly, the GG genotype was found significantly more often in patients with hyperprolactinemia than in those without it ($\chi^2 = 9.49$; $p = 0.009$; OR 1.86; 95%CI: 1.25–2.77). As this association can in part be explained by the effects of additional factors, such as sex, age, duration of disease, and the variation in the doses of antipsychotic drugs, we carried out a regression analysis using hyperprolactinemia as the dependent variable and the rs1341239 genotypes as the fixed factor and sex, age, duration of disease, and chlorpromazine equivalents as covariates. The models assuming additive and dominant effects of the rare allele (rs1341239*T) were found statistically significant (OR = 0.698

[0.528–0.921], permutation $p = 0.012$ and OR = 0.567 [0.373–0.856], permutation $p = 0.008$, respectively), and dominant model provided the best fit according to AIC (583.7 for dominant model vs 584.5 for additive model). However, the mean prolactin serum concentration was not significantly different among carriers of the GG (26.38 ng/ml; 95%CI: 14.21–57.03 ng/ml), GT (20.67; 95%CI: 12.5–47.00), and TT (22.41; 95%CI: 12.21–48.89) genotypes (Kruskal-Wallis test, $p = 0.19$; Table 2).

4. Discussion

We studied the association between the –1149 G/T (rs1341239) variant of the *PRL* gene and antipsychotic drug-induced hyperprolactinemia in 443 white patients with schizophrenia from Siberia. We excluded patients with physiological or pathological conditions that might have affected prolactin secretion, and we corrected for variables related to prolactin secretion. The size of our reference group of healthy volunteers was limited; this limitation might explain the lack of significant differences between patients with schizophrenia and control subjects. However, the results presented in Table 2 revealed little difference between the groups; thus, it is unlikely that increasing the reference group would disclose significant differences. We studied both pre- and post-menopausal women with schizophrenia, and we used a fixed criterion for hyperprolactinemia. However, varying this criterion did not significantly alter the results in another study (Ivanova et al., 2016). All patients with schizophrenia had received long-term treatment with a variety of antipsychotic drugs. Therefore, another limitation of this study was the heterogeneity of antipsychotic drugs used and various length of treatment (see Ivanova et al., 2016 for details).

Table 3
Demographics and clinical characteristics of patients with schizophrenia, with or without hyperprolactinemia (HP).

Trait	Without HP (n = 219)	With HP (n = 227)	p-Value*
Age (mean ± S.D.)	42.94 ± 13.56	40.19 ± 13.19	$p = 0.031$
Male/female	123/96	98/129	$p = 0.006$
Duration of disease, years	14.0 (8.0; 22.0)	11.0 (4.0; 22.0)	$p = 0.041$
Median (IQR)			
Daily dose of antipsychotics in CPZeq	400 (225; 750)	400 (280; 750)	$p = 0.074$
Median (IQR)			
Prolactin ng/ml	12.9 (8.14; 16.82)	49.66 (32.5; 76.27)	$p < 0.001$
Median (IQR)			

CPZeq: chlorpromazine equivalents; IQR: interquartile range; *calculated with either the *t*-test or the Mann-Whitney *U* test, as appropriate.

Table 4
Frequency of genotypes and alleles of the rs1341239 polymorphism in the *PRL* gene, among patients with schizophrenia, with and without hyperprolactinemia (HP).

Genotypes, alleles	With HP n (%)	Without HP n (%)	OR		χ^2	<i>p</i>
			Estimate	95% CI		
GG	94 (41.6%)	60 (27.6%)	1.86	1.25–2.77	9.49	0.009
GT	95 (42.0%)	113 (52.1%)	0.67	0.46–0.97		
TT	37 (16.4%)	44 (20.3%)	0.77	0.47–1.25		
G	283 (62.6%)	233 (53.7%)	1.44	1.10–1.89	7.25	0.007
T	169 (37.4%)	201 (46.3%)	0.69	0.53–0.81		

Moreover, the patients received different neuroleptic loads, due to the variable feeding and smoking habits, the use of concomitant drugs, and the poor brain penetration of some antipsychotic drugs that have a high affinity for P-glycoprotein (Moons et al., 2011). All these factors can distort the CPZeq dosage that reaches the pituitary gland, which lies outside the blood-brain-barrier. Moreover, other pharmacological receptor interactions (for example 5-HT_{2C}) may distort the relationship between CPZeq dosage and prolactin release (Ivanova et al., 2016). Therefore, our results can only be considered preliminary.

Our attention was drawn to a finding of the European First Episode Schizophrenia Trial (EUFEST), which showed that about 39% of the 74 patients (11/22 women and 18/52 men) with first schizophrenic episodes that were antipsychotic-naïve exhibited hyperprolactinemia that could not be explained by any reason except schizophrenia (Riecher-Rössler et al., 2013). That finding corresponded to observations in other studies (González-Blanco et al., 2016), but contrasted with several other studies that found that drug-naïve patients with first episodes experienced spontaneous dyskinesia more frequently than healthy controls (Fenton, 2000; Tenback and van Harten, 2011). Hyperprolactinemia is expected to be related to hypodopaminergic states (Fitzgerald and Dinan, 2008; Peuskens et al., 2014) and dyskinesia is related to hyperdopaminergic states (Ivanova and Loonen, 2016; Loonen and Ivanova, 2013). In the present study, the patients chronically used antipsychotic drugs, which were potent dopamine-receptor blockers (Ivanova and Loonen, 2016). Therefore, differences in hyperprolactinemia prevalence could be attributed to differences in the activity of the prolactin gene (provided that the antipsychotic drugs randomly blocked pituitary dopamine receptors to a roughly similar extent in all groups). Extrapituitary prolactin is probably not an important contributor to prolactin serum levels. Accordingly, the –1149 G/T (rs1341239) variant of the *PRL* gene may contribute to a dopamine-independent release of prolactin from the pituitary gland.

The results of this study differed from those of Treadwell et al. (2015), who found that the –1149 TT genotype was correlated with elevated serum prolactin levels. However, they studied patients with SLE that were not using dopamine receptor antagonists. Moreover, their results contrasted with data from the meta-analysis by Lee et al. (2015).

Prolactin is active as a hormone and, probably, also as a cytokine (Peeva et al., 2003). This duality may explain the associations reported between –1149 G/T (rs1341239) variants and certain autoimmune diseases. When pituitary dopamine receptors are inactivated with antipsychotic drugs, prolactin release from the pituitary may be correlated with increased prolactin release from extrapituitary sources, like immune cells within the brain. As a cytokine, the intracerebral release of prolactin may induce neuroplastic changes, which might explain the relationship between –1149 G/T (rs1341239) variants and the pathogenesis of mental disorders, like schizophrenia (see above).

In conclusion, this study showed that, among patients with schizophrenia, the G allele of the polymorphic variant, rs1341239, of the *PRL* gene was observed significantly more frequently in patients with hyperprolactinemia than in patients without it. Because extrapituitary prolactin is unlikely to be an important contributor to serum prolactin, the hyperprolactinemia is probably related to effects of the –1149 G/T (rs1341239) allele on pituitary prolactin release. Therefore, among patients with schizophrenia treated with antipsychotics, the serum concentration of prolactin may provide an indication of the activity of the gene that regulates extrapituitary prolactin release, which is believed to play a role in the immune system.

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Author contributions: SI and AL instigated, designed, coordinated, and supervised the study. MF designed and performed the statistical analysis and contributed to writing the paper. SI wrote the study protocol and selected the SNP. DO, IP, EK, LR, and OF monitored the study, collected clinical data, and isolated DNA. DO and IP genotyped the samples and recorded all data in an Excel database. AB analyzed the prolactin samples. NB and AS supervised the clinical work. SI, AL, and BW supervised the technical work. AL wrote the

manuscript. SI, OF, MF, and BW commented on the manuscript. All authors read the paper and agree with its content.

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