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Abstract. **Hyperprolactinemia (HPRL) is considered to be a frequent and typical adverse drug reaction caused by antipsychotic medications first and foremost due to excessive dopamine D2 receptors blockade. The aim is to study the set of polymorphisms of genes encoding neurotransmitter synthesis and metabolism enzymes *COMT, TPH1* and *TPH2* in schizophrenia inpatients. A comprehensive examination of 446 schizophrenia inpatients, aged 18-75 years, was conducted. Genotyping of DNA samples in patients with or without HPRL was carried out for 14 polymorphisms of *COMT, TPH1,* and *TPH2* genes. We revealed an association between carriership of the *COMT* rs165774* G allele and HPRL. As a result of the study, a regression model was designed to predict the risk of developing HPRL in schizophrenia inpatients, taking into account age, gender, and treatment duration, the dosage of drugs in chlorpromazine equivalents as independent covariates and genotypes of the studied polymorphisms.**

Keywords — schizophrenia; hyperprolactinemia; gene polymorphism; COMT.

I. MOTIVATION AND AIM

A. Motivation

Therapy with antipsychotic drugs is currently the main method of treating patients with schizophrenia; these medications both improve the clinical outcome by facilitating the disease coming in remission [1, 2], and sadly have a variety of adverse drug reactions [1, 3-5]. Such endocrinopathy as hyperprolactinemia (HPRL) represents one of those frequently seen in schizophrenia patients conditions [1, 6], and primarily attributed to dopamine D2 receptors blockade on mammatrophic cells of the adenohypophysis. A relatively new scientific field, pharmacogenetics, aims to identify the genetic factors determining the person's drugs response, and the risk of adverse drug reactions [7-9]. A large number of pharmacogenetic studies of dopamine receptor genes are presented in the scientific literature [7, 10, 11]. At the same time, polymorphism of genes encoding for enzymes for the synthesis and metabolism of dopamine and serotonin also have functional importance contributing to the HPRL development [12].

B. Aim

The purpose of this work was to analyze the polymorphisms set of genes encoding for enzymes of neurotransmitter synthesis and metabolism in patients with schizophrenia: catechol-O-methyl transferase (*COMT*), tryptophan hydroxylases 1 (*TPH1*) and 2 (*TPH2*).

II. MATERIALS AND METHODS

A. Patients and control groups

A comprehensive examination of 446 patients with schizophrenia, aged 18-75 years, who were classified for schizophrenia in accordance with the International Classification of Diseases 10 (ICD-10, F20) resulted in their clinical characterization. Clinical symptoms were assessed using the standart scales: Positive and Negative Syndrome Scale (PANSS), the Udvalg for Kliniske Undersogelser Scale

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(UKU), and the Clinical Global Impression scale (CGI). Based on the assessment of the serum prolactin concentration and in accordance with international criteria for the HPRL (normal PRL levels were agreed at ≤20 ng/ml for men and ≤25 ng/ml for women) [6], patients were divided into two groups: those suffering from HPRL and those who not.

B. Blood sampling and genotyping

Blood samples were drawn by antecubital venipuncture in BD Vacutainer tubes with clot activator (CAT) for prolactin serum level measurement with an empty stomach and following 8 h fasting overnight and in EDTA tubes for genomic DNA extraction. Several aliquots of the EDTA blood samples were stored at -20 °C until analysis. Serum was obtained by centrifuging blood samples collected at 1500 rpm for 30 min at 4 °C followed by storage at -80 °C [12, 13]. DNA was isolated using a standard phenol-chloroform method. Genotyping of DNA samples of patients with and without HPRL was carried out for 14 polymorphic variants of genes encoding neurotransmitter synthesis and metabolism enzymes *COMT* (rs6269, rs4680, rs4818, rs4633, rs165774, rs769224, rs174696), *TPH1* (rs7933505, rs1800532, rs684302), and *TPH2* (rs4290270, rs7305115, rs1487278, rs1386494) (Table 1) at The Core Facility "Medical Genomics", Tomsk NRMC by Applied Biosystems ™ QuantStudio ™ 5 Real-Time PCR System (USA) and with use of multiplex genotyping by Agena Bioscience ™, SEQUENOM Consumables iPLEX Gold 384 using matrix-activated laser desorption/ionization. The level of serum prolactin was detected applying immunoenzyme method (AccuBind ELISA Microwells kit, USA).).

Table 1 - List of studied single nucleotide polymorphisms in genes encoding neurotransmitter synthesis and metabolism enzymes

Gene	SNP	Chromosome position	Alleles	MAF*
COMT	rs4680	22:19963748	A/G	0.461
	rs6269	22:19962429	A/G	0.381
	rs4633	22:19962712	C/T	0.463
	rs4818	22:19963684	C/G	0.337
	rs769224	22:19964281	A/G	0.047
	rs165774	22:19965038	A/G	0.263
	rs174696	22:19965653	C/T	0.382
TPH1	rs1800532	11:18026269	G/T	0.344
	rs7933505	11:18024440	A/G	0.304
	rs684302	11:18038806	C/T	0.353
TPH2	rs7305115	12:71979082	A/G	0.420
	rs4290270	12:72022455	A/T	0.428
	rs1386494	12:71958763	A/G	0.168
	rs1487278	12:72007071	C/T	0.190

* MAF – minor allele frequency

C. Statistics

Statistical analysis was done by operating SPSS 20.0 package for Windows. The sample was checked for normal distribution according to the Shapiro-Wilk test. For the analysis of quantitative traits when comparing two independent samples, the U-test of Mann-Whitney was applied. Genotypes distribution of the studied samples was tested in accordance with Hardy-Weinberg equilibrium. Genotype and allele frequencies were compared using $\chi 2$ test and Fisher's exact test. Risk assessment was performed using indicator odds ratio (OR) with 95% confidence intervals (95% CI). The critical p-value of significance was 0.05. To develop a prognostic model for predicting the risk of HPRL, a regression and discriminant analysis was done in the software environment R applying its key options.

III. RESULTS

A. Description

First, we studied the clinical and demographic characteristics of schizophrenia inpatients depending on the presence (n=227) or absence (n=219) of HPRL. The description of the studied patient population has previously been published by Osmanova et al. [12] and Ivanova et al. [14]. The group of patients with HPRL was found to be female-dominated (129 women versus 98 men), which was statistically different (p=0.006) from the group of patients without HPRL (96 women versus 123 men). Schizophrenia inpatients suffering from HPRL had a significantly (p=0.031) older age (49.19±13.19 years) compared with those without HPRL (42.94±13.56 years). The dose of antipsychotics taken by schizophrenia inpatients was converted into chlorpromazine equivalent and did not differ in two studied groups (p=0.074). Treatment duration was significantly shorter (p=0.041) for schizophrenia inpatients with HPRL (11.0 (4.0;22.0)) compared to those without HPRL (14.0 (8.0; 22.0)). We have shown the strong difference (p=0.001) in PANSS total scores between two studied groups with predominance in the group of patients suffering from HPRL (96,1±22,8 versus 80,6±15,5).

As a result of our study, the socio-demographic, gender and age, clinical and pharmacological risk factors for drug-induced HPRL development in schizophrenia inpatients could be identified, which included the female sex, a younger age, a shorter duration of the disease and a lesser severity of negative symptoms.

We have specified our statistical analysis of the frequency of HPRL in our sample of patients with schizophrenia addressing the identity of the antipsychotics as used by them. In general, the prevalence of HPRL in the total group of studied patients was 51%. In a comparative analysis of specific antipsychotic drugs, the highest frequency of HPRL was found in patients taking the atypical antipsychotic

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risperidone (80%). In the study sample, the prevalence of risperidone-induced HPRL among women is very high and amounts to 86.6%, among men this figure was 64.5%. The lowest frequency of HPRL was found for another atypical antipsychotic - quetiapine (38%). The frequency of HPRL was detected in 58% for haloperidol; 60.3% - for chlorpromazine; 50% - for trifluoperazine; and 57.1% - for olanzapine.

We revealed a significant association of *COMT* rs165774 with HPRL development ($\chi2 = 3.97$; $p = 0.046$) (Table 2).

Table 2 – Genotypes and alleles frequencies of polymorphic variant rs165774 in patients with and without HPRL

SNP			With HPRL,%	Without HPRL,%	χ^2	*p*
rs165774	genotypes	AA	16 (7.1)	26 (11.9)	4.12	0.127
		AG	89 (39.4)	92 (42.0)		
		GG	121 (53.5)	101 (46.1)		
	alleles	A	121 (26.8)	144 (32.9)	3.97	**0.046**
		G	331 (73.2)	294 (67.1)		

Allele G is significantly more frequent in schizophrenia inpatients with drug-induced HPRL (73.2 %) and is risky for the development of the studied side effect (OR 1.34; 95% CI: 1.00 – 1.79).

This association was also obtained in the group of patients taking risperidone/paliperidone (n = 76) ($\chi2 = 4.02$; $p = 0.045$) (Table 3).

Table 3 – Frequencies of *COMT* rs165774 genotypes and alleles in patients taking risperidone/paliperidone depending on the presence of HPRL

SNP			With HPRL,%	Without HPRL,%	χ^2	*p*
rs165774	genotypes	AA	3 (5.1)	4 (23.5)	5.55	0.062
		AG	22 (37.3)	6 (35.3)		
		GG	34 (57.6)	7 (23.5)		
	alleles	A	28 (23.7)	14 (41.2)	4.02	**0.045**
		G	90 (76.3)	20 (58.8)		

Schizophrenia inpatients who were carriers of *COMT* rs165774* G allele demonstrated an increased level of prolactin and were at higher risk of HPRL development under antipsychotic therapy (OR 2.25; 95% CI: 1.01 - 5.03).

Allele A frequency is higher in the group of patients with normal prolactin level (41.2 %), which may indicate its protective effect in relation to the development of HPRL (OR 0.44; 95% CI: 0.20 - 0.99). We can also speak of a tendency toward a decrease in the frequency of occurrence of the AA genotype in the group of patients with increased prolactin (5.1 %) relative to the frequency of occurrence of this homozygous genotype in the comparison group (23.5 %) (OR 0.17; 95% CI: 0.03- 0.87).

For polymorphic variants of *TPH1* and *TPH2* genes no statistically significant associations were detected.

As a result of the study, a regression model was designed to predict the risk of developing HPRL in schizophrenia inpatients, taking into account age, gender, treatment duration, and dosage of drugs in chlorpromazine equivalent as independent covariates and polymorphic variants of genes as factors. The discriminant model using the studied set of SNP and non-genetic characters gives a classification error of about 39% and an AUC value of 0.665.

The best set of predictors was established based on the results of reclassification of patients. For the final model, indicators of sensitivity (0.616 [0.538 – 0.690]), specificity (0.603 [0.526 – 0.676]), AUC (0.665 [0.608 – 0.723]), and positive and negative predictive values were calculated.

Depending on the estimated frequency of cases of HPRL in patients 40-60% (50% in the study sample), the indicators of positive and negative predictions varied between 0.508–0.699 and 0.511–0.701, respectively.

Our study showed that not only genetic but also some demographic and clinical parameters contribute significantly to the pathogenesis of antipsychotic-induced HPRL in schizophrenia (Figure 1).

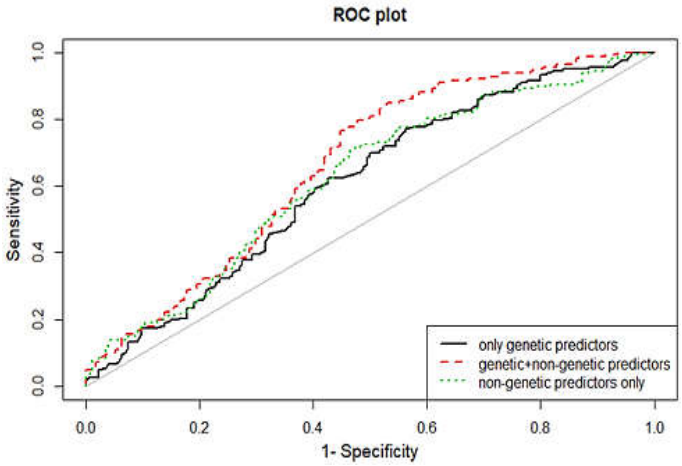

Figure 1 – ROC-curves illustrating models, including both genetic and non-genetic characters in different combinations

B. Discussion

Hyperprolactinaemia is a frequent adverse drug reaction to antipsychotic drugs. The short- and long-term outcomes of HPRL can dramatically impair the life quality: sexual dysfunction, galactorrhea, menstrual disorders, infertility, gynecomastia, and possibly decreased bone mineral density [12]. Suffering from these consequences, particularly loss of libido and disturbances of lubrication or erection, can easily lead the patient to discontinue a necessary drug treatment. Therefore, it may be very important to identify persons with

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schizophrenia who are particularly vulnerable to develop HPRL.

Prolactin is a polypeptide hormone known as lactotrophin, consisting of 199-amino acids. It is synthesized in the adenohypophysis lobe of the pituitary gland by mammatrophic cells. Such cells constitute approximately 20-50% of the total number of cells in the gland. The production and secretion of PRL into the bloodstream occurs in a pulsating form with normal frequency for adult at young age of approximately ten cycles per twenty four hours [14].

PRL secretion into the bloodstream can be stimulated by several bioactive compounds, such as vasoactive intestinal polypeptide (VIP), thyrotropin-releasing hormone (TRH), and 5-hydroxytryptamine (5-HT). Furthermore, some of the neurotransmitters (like 5HT) influence not only the adenohypophysis, but also hypothalamus. Serotonergic terminals from the upper raphe nuclei release 5-HT which activates the paraventricular nucleus of the hypothalamus to liberate oxytocin or VIP. In addition, 5-HT activates 5-HT type 2 receptors (HTR2) on GABAergic fast spiking interneurons (FSI) which inhibit the release of dopamine from the tuberoinfundibular dopaminergic (so-called TIDA) system. Dopamine is the most critical modulator supressing PRL secretion. This tonic inhibition occurs through two major channels: either through tuberohypophysial tract or through the TIDA system. Whether 5-HT also affects PRL release by directly binding to 5-HT receptors of mammatrophic cells is uncertain. For rats, generally, HTR2 can be found in each lobe (anterior, intermediate or posterior) of the pituitary gland. At the same time, the HTR2 expression in the latter two lobes is significantly higher than that in the anterior lobe. Therefore, the common opinion states that 5-HT mainly affects hypothalamus, affecting the production of PRL only indirectly [14, 15]. Atypical antipsychotic drugs may affect the modulating influence of 5-H on PRL production by suppressing HTR2 [16]. In the previous article we studied variants of the genes encoding for *HTR1A, HTR1B, HTR2A, HTR2C, HTR3A, HTR3B,* and *HTR6* and found clear correlation between rs569959 and rs17326429 polymorphic variants of the X-bound *HTR2C* and HPRL [14]. It should be realized that HTR2C have constitutive activity which means that when the concentration of ligands is depleted, such receptors can produce a spontaneous signal to activate the cellular effector mechanisms [16]. Gene variants can also affect this constitutive activity and consequently the HPRL decreased by certain inverse agonists.

It is tryptophan hydroxylase (TPH) that usually limits the speed of the synthesis of 5-HT according to the sequence: L-Tryptophan → 5-Hydroxytryptophan →5-HT [17]. In turn 5-HT is metabolized by monoamine oxidase, particularly the A-form (MAO-A). Two isoforms of TPH exist which are determined by TPH1 and TPH2 genes. TPH1 is expressed by enterochromaffin cells and TPH1 is relatively scarce within the adult brain. It may, however, play an important role within the fetal developing brain [18]. TPH2 is the dominant isoform within the adult brain and has been associated with several psychiatric disorders [19]. We previously found no association between the X-bound MAO-A polymorphisms [12], and the current study also did not show any variants to be associated with the studied variants of the TPH1 and TPH2 genes. We can conclude that we found only limited confirmation that the serotonergic system might have a modulatory role in antipsychotic drug-induced HPRL. It should be mentioned that the effects of selective HTR2C (inverse) agonists and antagonists on prolactin secretion could probably show the relevance of this receptor subtype.

TIDA system can release dopamine, which inhibits PRL secretion. The mechanism for such inhibition in lactotroph cells is through dopamine binding to dopamine D2 receptors (DRD2s) located on the membrane. Other effects of dopamine binding to DRD2s include reduction in the production and release of PRL, as well as reduction in lactotroph proliferation [6]. In humans, the TIDA system (which is situated in the arcuate nucleus of hypothalamus and is comprised of a population of dopaminergic neurons) is the upmost efficient way of regulation of secretion of PRL. Dopamine can be efficiently secreted by such neurons into the perivascular spaces of the medial eminence. It is then carried to the anterior lobe of the pituitary gland through long portal vessels. Antipsychotics disinhibit PRL release by binding to type 2 dopamine receptors (DRD2, DRD3, DRD4). Anyway, studying variants of the genes encoding for these three dopamine receptor subtypes did not reveal any association with HPRL [12].

However, we found *ANKK1* rs2734849 (Ankyrin Repeat and Kinase Domain containing 1) to be associated with the frequency of HPRL [20]. This gene is strongly related to DRD2 gene functioning. Some atypical antipsychotics (i.e., risperidone, paliperidone, amisulpride) cause more often HPRL because of their high affinity to P-glycoprotein (P-gp) transporter which prevent them from readily passing the blood-brain barrier (BBB). Therefore, higher dosages are necessary to sufficient reach intracerebral DRD2, DRD3 and DRD4 receptors and structures not protected by the BBB are exposed to relatively high concentrations. We observed a negative association between hyperprolactinaemia and the single nucleotide polymorphism rs2032582 (G2677T) of the P-glycoprotein (*MDR1/ABCB1*) gene in the subgroup of patients treated with risperidone or paliperidone [13]. Dopamine is synthesized rate-limiting from L-Tyrosin according to the sequence: L-Phenylalanine → L-Tyrosine → L-DOPA → dopamine [17]. Dopamine is catabolized to homovanillic acid (HVA) by catechol-O-methyl transferase (COMT) and MAO. Moreover, dopamine is removed from the synaptic cleft by dopamine transporter (DAT). We have previously found a strong association between *MAO-B* rs1799836 and HPRL in male schizophrenia patients. In addition, the rs40184 and rs3863145 variants in dopamine transporter (*SLC6A3*) gene appeared to be associated with HPRL, but only in the subgroup of patients using the risperidone/paliperidone [12]. In the present study we observed an association between polymorphic variant rs165774 of the *COMT* gene and HPRL both in the total group

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and in the subgroup of patients taking risperidone or paliperidone.

IV. Conclusion

In our paper we demonstrated a clear correlation between *COMT* variants and production of prolactin. We shown that the HPRL occurrence can be predicted by the molecular-genetic panel including rsl65774 in combination with previously identified biomarkers [12-14, 20, 21]. This is especially important, as such prediction can be made prior the beginning of treatment of schizophrenia patients. It can be used to personalise medical interventions for this category of patients.

We believe that our research demonstrated a large potential of the use of genetic markers for the prediction of antipsychotic-related HPRL. Moreover, even more such markers can be discovered in the future using our methodology.

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