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THE COMBINED EFFECT OF CYP2D6 AND DRD2 Taq1A POLYMORPHISMS ON THE ANTIPSYCHOTICS DAILY DOSES AND HOSPITAL STAY DURATION IN SCHIZOPHRENIA INPATIENTS (OBSERVATIONAL NATURALISTIC STUDY)

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SUMMARY

Background: *To assess the correlation between the antipsychotics (AP) mean daily doses, hospital stay duration and CYP2D6, DRD2 polymorphisms in naturalistic study.*

Subjects and methods: *CYP2D6 polymorphisms *3, *4, *5, *6, *1XN and DRD2/ANKK1 Taq1A polymorphisms were genotyped in a cohort of 226 Caucasian schizophrenic inpatients. AP daily doses, hospital stay duration and AP treatment duration were taken from medical records. To compare mean daily doses of AP among CYP2D6 PMs, EMs, UMs and DRD2/ANKK1 Taq1A carriers the actual AP doses were converted to chlorpromazine (CPZ) equivalents and DDD (defined daily dose).*

Results: *Significant correlation (p=0.004) between CYP2D6 metabolic activity and AP mean daily doses was observed only among DRD2/ANKK1 Taq1A polymorphic allele carriers: 250.53 (95%CI: 154.90-346.17), 473.82 (95%CI: 426.99-520.64) 602.77 (95%CI: 469.65-735.88) CPZ equivalents in PMs, EMs and UMs, consequently. PMs with DRD2/ANKK1 Taq1A CT genotype received significantly lower doses of AP comparing to CC genotype (p=0.02). Mean hospital stay duration of PMs+UMs was significantly higher comparing to EMs (66.4 days (95% CI: 56.9-75.8) vs 50.2 days (95%CI: 45.5-54.7); p=0.047).*

Conclusions: *In a cohort of schizophrenia inpatients CYP2D6 metabolic activity affects mean AP daily dose only in the presence of DRD2 Taq1A polymorphic allele. CYP2D6 metabolic activity correlates independently from DRD2 Taq1A polymorphism with hospital stay duration. Subpopulation of schizophrenia inpatients with altered CYP2D6 activity (PMs and UMs) carriers of Taq1A polymorphisms needs special attention of clinicians in aligning of AP treatment.*

Key words: *CYP2D6 - DRD2 – schizophrenia – antipsychotics – pharmacogenetics - polymorphism*

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INTRODUCTION

The prevalence of schizophrenia is about 0.7% (McGrath et al. 2008), it is one of the top 25 disability reasons which has serious medical, social and economic consequences (Owen et al. 2016). From 20 to 50% of schizophrenic patients do not achieve stable remission and less than 26% of outpatients meet the complete remission criteria (Mosolov et al. 2012a, 2014). Due to lost of productivity, frequent hospitalizations, disability in young age and social burden schizophrenia is estimated as the seventh most costly illness (Awad & Voruganti 2008).

Antipsychotics (AP) are the first choice treatment for schizophrenia but their effectiveness and safety are characterized by a broad interindividual variability (Brandl et al. 2014, Leucht et al. 2011, Juckel et al. 2014, Hasan et al. 2013, 2015, 2012). This variability is partially explained by a genetic heterogeneity of schizophrenia (Chen et al. 2015) and metabolism of antipsychotics (Moore et al. 2014). The standard prescribed antipsychotic daily dose is not always optimal in clinical practice. Genetic variability of biotransformation and bioavailability of AP may significantly influence on therapeutic effect and tolerability (Brandl et al. 2014).

Antipsychotics are metabolized in liver mainly by cytochrome P450 isoenzymes family: CYP2D6, CYP1A2, CYP3A4 and CYP2C19 (Ravyn et al. 2013) which are highly polymorphic. Genetic polymorphisms of CYPs lead to significant interindividual differences in enzyme metabolic activity affecting the drug pharmacokinetics, efficacy and safety (Nebert 1997). CYP2D6 is involved in the metabolic pathway of more than 80% of currently used AP.

Among Caucasians the incidence of poor (PM) and ultra-rapid (UM) CYP2D6 metabolizers is about 2-5%

and 5-10%, respectively (Bradford 2002). Despite more than 100 polymorphisms described in CYP2D6 gene the determination of CYP2D6 *3, *4, *5, and *6 alleles (Gaikovitch et al. 2003), predicts from 93.0% to 97.5% of all PMs in Caucasian population (Hersberger et al. 2000).

Dopaminergic system plays an important role in the pathogenesis of schizophrenia, and the most antipsychotics realize their effects via dopamine receptors of various subtypes, particularly through type 2 receptors (DRD2). Several polymorphisms have been described in DRD2 gene, among which the most studied is DRD2/ANKK1 Taq1A, (rs1800497). The frequency of polymorphic A1 (T) allele in Caucasian population is 22% (Mi et al. 2011). This polymorphism causing the replacement of amino acid (Glu713Lys) is believed to be functional and to alter the dopamine neurotransmission. A1 (T) allele carriers have reduced level of DRD2 receptor affinity in the striatum (Savitz et al. 2013), A1 (T) allele heterozygotes (CT genotype) have a significantly increased activity of DOPA-decarboxylase. Taq1A is also able to modulate the expression of the DRD2 gene (Doehring et al. 2009).

Objective: to evaluate the effect of CYP2D6 and DRD2/ANKK1 Taq1A polymorphisms on mean daily dose of antipsychotics and hospital stay duration in schizophrenia inpatient population.

SUBJECTS AND METHODS

The study involved 331 Caucasian schizophrenia (F20.0) inpatients. Inclusion criteria in the study were: age 18-45 years; current AP treatment (monotherapy or combination). All patients were interviewed by investigators and the diagnosis was verified according to M.I.N.I criteria (Sheehan et al. 1998). The reason for inclusion of young participants was the difference in dopaminergic system activity, i.e. D2/3 receptor occupancy in young and older patients clearly shown in PET studies (Uchida et al. 2012, Iwata et al. 2016) which can influence the results. Concomitant use of anticholinergic drugs as EPS correctors was permitted. Exclusion criteria were: history of acute (ALT and AST > 40 U/l) or chronic liver disease; hospital stay due to social reasons, concomitant use of CYP inducers (phenobarbital, carbamazepine etc.) and benzodiazepines. Patients flow diagram is presented in Figure 1.

In the final sample of 226 patients genotyped for CYP2D6 and DRD2 polymorphisms the average age was 39 years (95% CI 37-41), the proportion of women - 46.5%. Patient clinical data were obtained from medical records. For each patient the following parameters were determined and entered into the database: prescribed drugs during the hospitalization (AP, concomitant drugs), doses, route of administration, duration of the therapy, duration of the hospitalization.

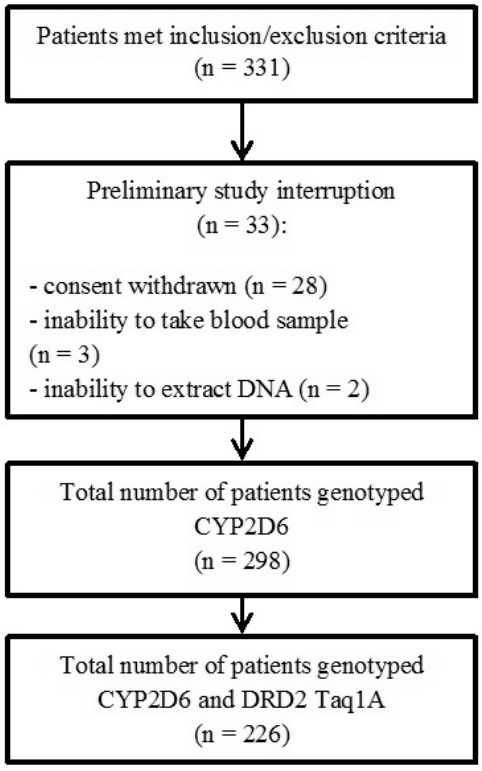


Figure 1. Patient flow diagram

Genotyping

The blood samples (5 ml) for genotyping were collected in plastic tubes containing EDTA (Vacuette ® #456034, Greiner Bio-One, Austria) and were kept at -70°C until analysis. DNA was extracted from whole blood with the use of the DNA-sorb-B kit (InterLabService Ltd., Russia). Taq1 DRD2 (ANKK1) polymorphism (rs1800497) was genotyped by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism as described by Grandy et al. (Grandy et al. 1993). Allele specific PCR as previously described by Chou WH et al. (Chou et al. 2003) was used to determine CYP2D6 *3 (rs35742686), *4 (rs3892097), *6 (rs5030655) polymorphisms. Long range PCR described earlier by Sheng H. et al. (Sheng et al. 2007) was used to determine CYP2D6* 5 and duplication (1xN) For all PCRs "Tercyc" multi-block amplifier (Company DNA-Technology LLC, Russia) was used. PCR products were detected by electrophoresis in agarose (0.8-2.0%) gel.

The study design and data analysis

The study design was observational retrospective and naturalistic. The metabolic status was assessed by the number of functional CYP2D6 alleles as described previously (Gaedigk et al. 2017, Zanger et al. 2004). PM group included patients with no functional alleles, extensive metabolizers (EM) group - patients with 1 or 2 functional alleles, UM group - patients with 3 or more

copies of functional alleles. Patients were divided into 3 group by the presence of Taq1A polymorphism: CC genotype – no polymorphic allele, CT genotype and TT genotype – heterozygous and homozygous by Taq1A polymorphic alleles, consequently. The data from each patient was collected retrospectively from the patients medical records and then groups by CYP2D6 metabolic status and Taq1a polymorphism were compared. Each patient groups by CYP2D6 metabolic status and Taq1A we dived into two subgroups in which first or second generation AP were used. The CYP2D6 and DRD2 Taq1A genotyping results did not influence the AP therapy prescribed.

Daily dose of each AP prescribed during the hospitalization were recalculated in chlorpromazine (CPZ) equivalents (Andreasen et al. 2010, Mosolov et al. 2012b) and DDD (defined daily dose) according to the WHO methodology (World Health Organisation). In case of monotherapy number of daily CPZ equivalents or DDDs were summarized, given the total number of CPZ equivalents or DDDs received by patient during hospitalization. In case of combination therapy daily dose of each antipsychotic prescribed was recalculated in CPZ equivalents or DDDs. The prescribed daily CPZ equivalents or DDDs of two or more AP prescribed in one day were summarized given the number of CPZ equivalents or DDDs prescribed per day as described previously by Nose et al. (Nosè et al. 2008). Then we summarized the number of CPZ equivalents or DDDs prescribed per day given the total number of CPZ equivalents or DDDs received by patient during hospitalization.

The period of treatment duration was calculated by subtracting the date of first day of prescription (first day of first AP prescribed in combination) from date of the last day of prescription (last day of last AP prescribed in combination).

Mean daily CPZ equivalents or DDD was calculated as total number of CPZ equivalents or DDDs received by patient during hospitalization dived to the period (days) of treatment duration.

Statistical analysis

Patients were grouped by CYP2D6 metabolic activity and DRD2 polymorphisms. Analyses were performed using the Statistica 6.0 package (StatSoft. Inc.). Parametric (ANOVA: Gamma distribution with Log link function; covariates: age, length of hospital stay) and nonparametric (ANOVA Kruskal-Wallis and Mann-Whitney U-test) statistical methods were used to compare the number of CPZ equivalents and DDD used among different patients groups. Duration of illness was used as covariate.

Ethical considerations

The local ethics committee of the SPb GBUZ "P.P. Kaschenko 1st City Mental Hospital" approved the study design, methods, blood sample interventions, and the text of the patient information list in compliance with the Declaration of Helsinki. All included patients provided separate informed consent for participation in the study.

RESULTS

Patients distribution according to the number of CYP2D6 and Taq1A polymorphic alleles is listed in Table 1.

Patients groups did not differ in gender and in average age ($p>0.05$) (Table 2). The PMs frequency was 3.9%, EMs - 92.4%, UMs - 3.5%. The frequency of Taq1A polymorphisms are: CC - 63.3%, CT - 28.3%, TT - 8.4%. Taq1A polymorphic T allele frequency was 22.5%. There were no patients in the group of PM who had the TT Taq1A genotype.

The most frequently used APs were haloperidol (47.2% of patients), risperidone (7.9%), trifluoperazine (7.9%), olanzapine (7.4%) and quetiapine (6.6%). Other AP were prescribed in less than 5% of patients.

Mean daily dose in CPZ equivalents in study groups by CYP2D6 metabolic status and Taq1A polymorphism are presented in Figure 1.

Mean daily dose in CPZ equivalents did not differ between the groups (Factorial ANOVA Wald test, $p=0.77$) (Figure 2). Mean daily dose was lower in the subgroup of Taq1A polymorphic allele carriers in all the CYP2D6 groups by metabolic activity. At the same time, there is a tendency that UMs carriers of CT and TT Taq1A allele had maximum mean daily dose in CPZ equivalents.

Table 1. Patients distribution according to the number of CYP2D6 and Taq1A polymorphic alleles

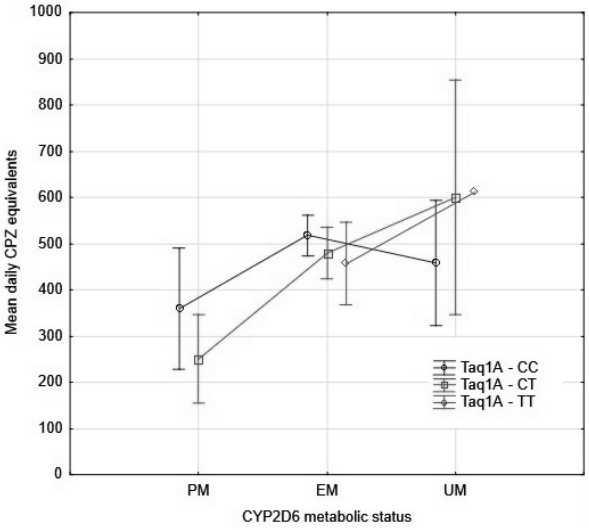
Taq1A	Number of functional CYP2D6 alleles, metabolic status				Total
	0	1	2	> 2	
	PM	EM		UM	
CC	4	52	81	4	143
CT	5	23	32	3	64
TT	0	9	9	1	19
Total	9	85	124	8	226

CC – non-polymorphic Taq1A allele homozygotes; CT – Taq1A polymorphic allele heterozygotes; TT - Taq1A polymorphic allele homozygotes; PM – CYP2D6 poor metabolizers; EM – CYP2D6 extensive metabolizers; UM – CYP2D6 ultra-rapid metabolizers

Table 2. Patients characteristics according to the number of CYP2D6 and Taq1A polymorphic alleles

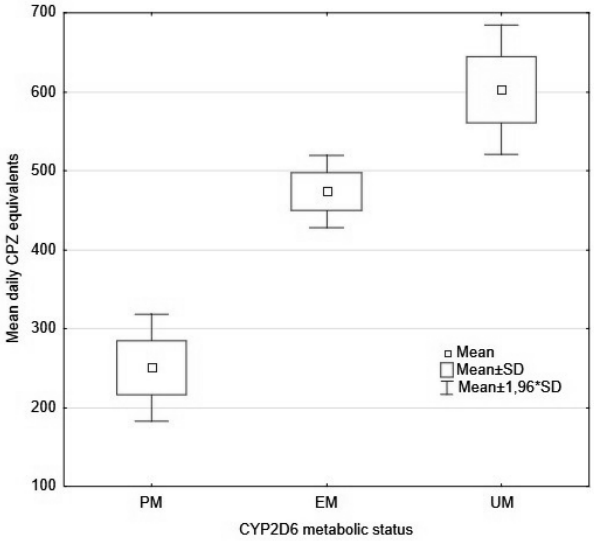
Demographic characteristics	Taq1A	Number of functional CYP2D6 alleles, metabolic status			
		0	1	2	> 2
		PM	EM		UM
Median age (min-max)	CC	44 (20-67)	39 (36-43)	39 (36-42)	30 (25-64)
% of females		75%	44%	49%	0%
Median age (min-max)	CT	38 (28-49)	41 (35-47)	37 (32-41)	26 (18-40)
% of females		40%	60%	39%	33%
Median age (min-max)	TT	-	38 (29-47)	34 (30-39)	31
% of females			33%	50%	100%

CC – non-polymorphic Taq1A allele homozygotes; CT – Taq1A polymorphic allele heterozygotes; TT - Taq1A polymorphic allele homozygotes; PM – CYP2D6 poor metabolizers; EM – CYP2D6 extensive metabolizers; UM – CYP2D6 ultra-rapid metabolizers



PM – poor metabolizers; EM – extensive metabolizers; UM – ultra-rapid metabolizers

Figure 2. Mean daily dose of AP in CPZ equivalents



SD – standard deviation; PM – poor metabolizers; EM – extensive metabolizers; UM – ultra-rapid metabolizers

Figure 3. Mean daily dose of AP (CPZ equivalents) in the subgroup of patients carriers of CT and TT Taq1A polymorphisms

To clarify these differences we performed a subgroup analysis: 1) CT and TT Taq1A carriers (Figure 2); 2) CC Taq1A carriers.

We found significant differences between PMs, EMs and UMs in the group of patients with CT and TT Taq1A genotypes and positive correlation between the number of functional CYP2D6 alleles and mean daily dose in CPZ equivalents (K-W test, p=0.004) (Figure 3). There is a tendency (K-W test, p=0.06) in the differences between PMs, EMs and UMs in the group of patients with CT and TT Taq1A genotypes and positive correlation between the number of functional CYP2D6 alleles and mean DDD. However, we did not observe significant differences between PMs, EMs and UMs in carriers of the CC Taq1A genotype neither by mean daily dose in CPZ equivalents (K-W test, p=0.32) nor by mean DDD (K-W test, p=0.41).

The difference in mean daily dose in CPZ equivalents in PM group between carriers of CT and CC Taq1A polymorphic alleles was significant: patients with CT genotype received lower AP doses comparing to CC carriers (250.5 (95% CI: 154.9-346.1) vs 359,5 (95% CI: 227.9-491.0); ANOVA Wald test, p=0.02).

The difference in mean daily dose in CPZ equivalents and DDDs in patients groups by CYP2D6 metabolic status, Taq1A and first/second generation AP used did not reach significance because of low number of patients among PMs and UMs.

We also analyzed hospital stay duration among the patients with different CYP2D6 metabolic status and Taq1A polymorphism carriers. In patients sample with available CYP2D6 genotype data (n=298) the mean hospital stay duration in PMs, EMs and UMs didn't differ significantly (Wald test, p=0.29) and consequently was 66.1 days (95% CI:53.7-78.4), 50.2 days (95% CI:45.5-54.7) and 66.7 days (95% CI: 49.7-83.7). Hospital stay duration in PM and UM group was higher comparing to EMs and for further analysis we combined PMs and UMs in the subgroup of patients with altered CYP2D6 activity. The mean hospitalization time in unified group of patients with altered CYP2D6 activity (PM+UM) was higher (66.4 days (95% CI:56.9-75.8)) comparing to EM group (50.2 days (95% CI:45.5-54.7)) (K-W test: p=0.047). We did not find correlation between Taq1A polymorphism and hospital stay duration.

DISCUSSION

In this study we compared AP mean daily doses in schizophrenia patients differing by CYP2D6 metabolic activity and Taq1A polymorphisms in real world clinical practice. Frequency of PM in Russian population of schizophrenia inpatients is 3.9% which is close to the world numbers in Caucasians.

Among the AP used, quetiapine (6.6%), sulpiride (1.7%) and amisulpiride (3.5%) are metabolized predominantly by CYP3A4 and are not CYP2D6 substrates (Spina & de Leon 2015, Stingl & Viviani 2015). Among PMs and UMs were no patients received quetiapine, sulpiride or amisulpiride, thus we believe that this issue caused by the naturalistic study design have no effect on the results.

We were unable to find in the literature the data on combined influence of CYP2D6 and DRD2 Taq1A polymorphisms on the efficacy or safety of AP. Jürgens et al. (2012) showed that daily dose of AP, expressed in chlorpromazine equivalents, significantly differs in groups of poor and rapid metabolizers by CYP2D6, but they did not estimate the effect of polymorphisms of DRD2.

There are conflicting data on the relationship of Taq1A polymorphisms and AP effectiveness in schizophrenia. Meta-analysis by Zang et al. concluded that there is no correlation between AP effect and polymorphisms of Taq1A allele (Zhang et al. 2010). Ikeda et al. found that a response to risperidone is lower in group of Taq1A TT genotype carriers (Ikeda et al. 2008). In our study, we found no direct link between mean daily doses of AP and CYP2D6 metabolic activity or different alleles of DRD2 Taq1A carriers. However, when assessing the combined effect of CYP2D6 and DRD2 Taq1A polymorphisms we found that a higher mean daily dose is routinely prescribed in UMs carriers of DRD2 Taq1A polymorphic allele. It could be explained not only by lower plasma concentrations of AP in such patients but also at least partly by decreased expression of D2 receptors in brain or their altered sensitivity. As a consequence a lack of therapeutic efficacy requires from a clinician an increasing of AP daily dose to the range maximum.

A similar design study was conducted by Alenius M. et al. in which authors noted a significantly lower average AP doses in the CYP2D6 PMs comparing to EMs and UMs (Alenius et al. 2008). The authors also found no association between AP response and DRD2 Taq1A polymorphisms. In contrast to our study the authors did not report the results of the combined effect of CYP2D6 and DRD2 polymorphisms.

Higher daily dose observed in the PM patients with heterozygous for the DRD2 Taq1A allele may be explained by an additive effect of decreased AP metabolism and low affinity for D2 receptors. To our knowledge the reasons for such difference is still unclear and could be due to the influence of other factors which were not accounted in our study.

When accounting for first/second generation AP used in the groups by CYP2D6 metabolic activity and DRD2 Taq1A polymorphisms the low total number of observations in each subgroup limits the analysis given statistical insignificancy.

Longer hospital stay in the subgroup of patients with altered CYP2D6 activity (PM+UM) has been demonstrated. The similar results were shown by Kropp et al.: mean hospital stay duration 57.5 and 40.0 days in PM and EM patients groups consequently (Kropp et al. 2006). Ruaño G et al. also showed that PMs are characterized by 36% longer hospital stay duration (Ruaño et al. 2013). Chou at al. demonstrated that mean duration of hospitalization in PMs received CYP2D6 substrates was 24 days/year, while in EMs – 17 days/year (no significant differences). Laika et al. (Laika et al. 2009) reported the hospital stay duration of 52 days in PMs, 64 days in intermediate metabolizers (IMs) and 63 days in both EMs and UMs, with some trend to lower duration in PMs which is contrary to our results. It seems that patients with altered CYP2D6 activity (PMs and UMs) having DRD2 Taq1A polymorphisms need some more time for clinician to align the antipsychotic therapy. The determination of the CYP2D6 and DRD2 polymorphisms before starting the AP could be helpful for the clinician for treatment personalization.

To better evaluate the role of CYP2D and DRD2 polymorphisms in the psychiatric clinical practice large scale naturalistic studies and prospective clinical trials with more than 1000 patients are needed.

Study limitations

The limitations of our study are: retrospective design leading to the non-balanced comparison groups by the number of patients; absence of PMs with TT Taq1A polymorphisms. We did not perform therapeutic drug monitoring, treating the existing evidence of correlation between CYP2D6 polymorphisms and metabolic status enough to detect PM and UM. We also did not assess the patient remission by psychiatric rating scales as they are not widely used in routine clinical practice in Russia. When calculating the AP mean daily dose we used mean daily dose approach and CPZ equivalents, described first by Davis J.M. et al. (Davis 1974), this approach then was extended by Leucht S. et al. to second generation AP (Leucht et al. 2015). Recently, Patel et al. reviewed all existing methods of dose equivalence and stated that all methods have weaknesses and that a gold standard method does not exist (Patel et al. 2013). The limitations of the method we used is the summarization of CPZ equivalents in combination therapy of AP with different pharmacodynamic properties, but we believe it has limited effect on study results as 70% of patients in the final cohort received monotherapy and 47.2% received haloperidol.

CONCLUSIONS

Our study showed the significant positive correlation of prescribed AP daily dose between CYP2D6 PMs, EMs and UMs carriers of DRD2 Taq1A polymorphic allele with the highest dose in UM group and the lowest one in PM group. Only in CYP2D6 PM group the mean AP daily dose was lower in DRDD2 Taq1A CT genotype carriers comparing to CC genotype carriers.

We showed longer hospital stay duration in PMs and UMs groups comparing to EMs (66.4 vs 50.2 days, consequently).

Subpopulation of schizophrenia inpatients with altered CYP2D6 activity (PMs and UMs) carriers of Taq1A polymorphisms needs special attention of clinicians in aligning of AP treatment.

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Contribution of individual authors:

Alexey A. Kurylev: patients enrollment, data collection, statistical analysis, manuscript preparation;

Vadim M. Brodyansky: data collection, genotyping, manuscript preparation;

Boris V. Andreev: study design, statistical analysis, manuscript preparation;

Alexander O. Kibitov: study design, genotyping, manuscript preparation;

Oleg V. Limankin & Sergey N. Mosolov: study design, manuscript preparation.

References

1. *Alenius M, Wadelius M, Dahl M-L, Hartvig P, Lindström L, Hammarlund-Udenaes M: Gene polymorphism influencing treatment response in psychotic patients in a naturalistic setting. Journal of Psychiatric Research 2008; 42:884–893*
2. *Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho B-C: Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biological Psychiatry 2010; 67:255–262*
3. *Awad AG, Voruganti LNP: The burden of schizophrenia on caregivers: a review. PharmacoEconomics 2008; 26:149-162*
4. *Bradford LD: CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics 2002; 3:229–243*
5. *Brandl EJ, Kennedy JL, Müller DJ: Pharmacogenetics of antipsychotics. Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie 2014; 59:76–88*
6. *Chen J, Cao F, Liu L, Wang L, Chen X: Genetic studies of schizophrenia: an update. Neuroscience Bulletin 2015; 31:87–98*
7. *Chou W-H, Yan F-X, Robbins-Weilert DK, Ryder TB, Liu WW, Perbost C et al.: Comparison of two CYP2D6 genotyping methods and assessment of genotype-phenotype relationships. Clinical Chemistry 2003; 49:542–551*
8. *Davis JM: Dose equivalence of the antipsychotic drugs. Journal of Psychiatric Research 1974; 11:65–69*
9. *Doehring A, Hentig N von, Graff J, Salamat S, Schmidt M, Geisslinger G et al.: Genetic variants altering dopamine D2 receptor expression or function modulate the risk of opiate addiction and the dosage requirements of methadone substitution. Pharmacogenetics and Genomics 2009; 19:407–414*
10. *Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS: Prediction of CYP2D6 phenotype from genotype across world populations. Genetics in Medicine: Official Journal of the American College of Medical Genetics 2017; 19:69–76*
11. *Gaikovitch EA, Cascorbi I, Mrozikiewicz PM, Brockmöller J, Frötschl R, Köpke K: Polymorphisms of drug-metabolizing enzymes CYP2C9, CYP2C19, CYP2D6, CYP1A1, NAT2 and of P-glycoprotein in a Russian population. European Journal of Clinical Pharmacology 2003; 59:303–312*
12. *Grandy DK, Zhang Y, Civelli O: PCR detection of the TaqA RFLP at the DRD2 locus. Human Molecular Genetics 1993; 2:2197*
13. *Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF et al.: World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry 2012; 13:318–378*
14. *Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF et al., WFSBP Task force on Treatment Guidelines for Schizophrenia: World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry 2013; 14:2–44*
15. *Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF et al., WFSBP Task Force on Treatment Guidelines for Schizophrenia: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia. Part 3: Update 2015 Management of special circumstances: Depression, Suicidality, substance use disorders and pregnancy and lactation. The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry 2015; 16:142–170*
16. *Hersberger M, Marti-Jaun J, Rentsch K, Hänseler E: Rapid detection of the CYP2D6*3, CYP2D6*4, and CYP2D6*6 alleles by tetra-primer PCR and of the CYP2D6*5 allele by multiplex long PCR. Clinical Chemistry 2000; 46:1072–1077*
17. *Ikeda M, Yamanouchi Y, Kinoshita Y, Kitajima T, Yoshimura R, Hashimoto S et al.: Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia. Pharmacogenomics 2008; 9:1437–1443*
18. *Iwata Y, Nakajima S, Caravaggio F, Suzuki T, Uchida H, Plitman E et al.: Threshold of Dopamine D2/3 Receptor Occupancy for Hyperprolactinemia in Older Patients With Schizophrenia. The Journal of Clinical Psychiatry 2016; 77:e1557–e1563*

19. Juckel G, de Bartolomeis A, Gorwood P, Mosolov S, Pani L, Rossi A: Towards a framework for treatment effectiveness in schizophrenia. Neuropsychiatric Disease and Treatment 2014; 10:1867–1878
20. Jürgens G, Jacobsen CB, Rasmussen HB, Werge T, Nordentoft M, Andersen SE: Utility and adoption of CYP2D6 and CYP2C19 genotyping and its translation into psychiatric clinical practice. Acta Psychiatrica Scandinavica 2012; 125:228–237
21. Kropp S, Lichtinghagen R, Winterstein K, Schlimme J, Schneider U: Cytochrome P-450 2D6 and 2C19 polymorphisms and length of hospitalization in psychiatry. Clinical Laboratory 2006; 52:237–240
22. Laika B, Leucht S, Heres S, Steimer W: Intermediate metabolizer: increased side effects in psychoactive drug therapy. The key to cost-effectiveness of pretreatment CYP2D6 screening? The Pharmacogenomics Journal 2009; 9:395–403
23. Leucht S, Heres S, Kissling W, Davis JM: Evidence-based pharmacotherapy of schizophrenia. The International Journal of Neuropsychopharmacology 2011; 14:269–284
24. Leucht S, Samara M, Heres S, Patel MX, Furukawa T, Cipriani A: Dose Equivalents for Second-Generation Antipsychotic Drugs: The Classical Mean Dose Method. Schizophrenia Bulletin 2015; 41:1397–1402
25. McGrath J, Saha S, Chant D, Welham J: Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiologic Reviews 2008; 30:67–76
26. Mi H, Thomas PD, Ring HZ, Jiang R, Sangkuhl K, Klein TE: PharmGKB summary: dopamine receptor D2. Pharmacogenetics and Genomics 2011; 21:350–356
27. Moore TR, Hill AM, Panguluri SK: Pharmacogenomics in psychiatry: implications for practice. Recent Patents on Biotechnology2014; 8:152–159
28. Mosolov SN, Potapov AV, Ushakov UV: () Remission in schizophrenia: results of cross-sectional with 6-month follow-up period and 1-year observational therapeutic studies in an outpatient population. Annals of General Psychiatry 2012a; 11:1
29. Mosolov SN, Tsukarzi EE, Kapiletti SG. Антипсихотическая фармакотерапия шизофрении: от научных данных к клиническим рекомендациям. [Antipsychotic pharmacotherapy of schizophrenia: from scientific data to clinical recommendations]. Москва: Социально-политическая мысль; 2012b. M: p. 1080. Russian
30. Mosolov SN, Potapov AV, Ushakov UV, Shafarenko AA, Kostyukova AB: Design and validation of standardized clinical and functional remission criteria in schizophrenia. Neuropsychiatric Disease and Treatment 2014; 10:167–181
31. Nebert DW: Polymorphisms in drug-metabolizing enzymes: what is their clinical relevance and why do they exist? American Journal of Human Genetics 1997; 60:265–271
32. Nosè M, Tansella M, Thornicroft G, Schene A, Becker T, Veronese A, Leese M, Koeter M, Angermeyer M, Barbui C: Is the Defined Daily Dose system a reliable tool for standardizing antipsychotic dosages? International Clinical Psychopharmacology 2008; 23:287–290
33. Owen MJ, Sawa A, Mortensen PB: Schizophrenia. The Lancet 2016; 388:86–97
34. Patel MX, Arista IA, Taylor M, Barnes TRE: How to compare doses of different antipsychotics: a systematic review of methods. Schizophrenia Research 2013; 149:141–148
35. Ravyn D, Ravyn V, Lowney R, Nasrallah HA: CYP450 Pharmacogenetic treatment strategies for antipsychotics: A review of the evidence. Schizophrenia Research 2013; 149:1–14
36. Ruaño G, Szarek BL, Villagra D, Gorowski K, Kocherla M, Seip RL et al.: Length of psychiatric hospitalization is correlated with CYP2D6 functional status in inpatients with major depressive disorder. Biomarkers in Medicine 2013; 7:429–439
37. Savitz J, Hodgkinson CA, Martin-Soelch C, Shen P-H, Szczepanik J, Nugent AC, Herscovitch P et al.: DRD2/ANKK1 Taq1A polymorphism (rs1800497) has opposing effects on D2/3 receptor binding in healthy controls and patients with major depressive disorder. The International Journal of Neuropsychopharmacology 2013; 16:2095–2101
38. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E et al.: The Mini-International Neuro Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of Clinical Psychiatry 1998; 59(Suppl 20):22-33;quiz 34-57
39. Sheng H, Zeng A, Zhu W, Zhu R, Li H, Zhu Z et al.: Allelic distributions of CYP2D6 gene copy number variation in the Eastern Han Chinese population. Acta Pharmacologica Sinica 2007; 28:279–286
40. Spina E, de Leon J: Clinical applications of CYP genotyping in psychiatry. Journal of Neural Transmission 2015; 122:5–28
41. Stingl J, Viviani R: Polymorphism in CYP2D6 and CYP2C19, members of the cytochrome P450 mixed-function oxidase system, in the metabolism of psychotropic drugs. Journal of Internal Medicine 2015; 277:167–177
42. Uchida H, Suzuki T, Graff-Guerrero A, Mulsant BH, Pollock BG, Arenovich T et al.: Therapeutic Window for Striatal Dopamine D2/3 Receptor Occupancy in Older Patients With Schizophrenia: A Pilot PET Study 2012; Oct 31
43. Zanger UM, Raimundo S, Eichelbaum M: Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn-Schmiedeberg's Archives of Pharmacology 2004; 369:23–37
44. Zhang J-P, Lencz T, Malhotra AK: D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. The American Journal of Psychiatry 2010; 167:763–772
45. Sartorius N, Fleischhacker W, Gjerris A, Kern U, Knapp M, Leonhard Be, Lieberman A, Lopes-Ibor Jj, van Raay B, Tornquist E, Twomey E, et al.: The usefulness and use of second-generation antipsychotic medications – an update. Current Opinion in Psychiatry 2002; 15:S1-S2
46. World Health Organization: World Health Collaboration Center for Drug Statistics Methodology ATC/DDD Index 2017. URL: https://www.whocc.no/atc_ddd_index/

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