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Original Article

Exploring Pharmacogenetic Variation in a Bulgarian Psychiatric Cohort

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Abstract

Introduction: Pharmacogenetics in psychiatry is currently gaining momentum. The efficiency of antipsychotic therapy is often limited by the lack of response and the presence of side effects. Pharmacogenetic variation is probably one of the causative factors for the observed interindividual differences in the response to and the side effects of antipsychotics, which could be addressed and whose negative effects could be avoided or mitigated.

Aim: The present study aimed to conduct a comprehensive analysis of the frequency of DRD2 rs1799732, COMT rs4680, MC4R rs489693, and HTR2C rs3813929 in Bulgarian psychiatric patients.

Materials and methods: The frequency of genotypes and the alleles of variants DRD2 rs1799732, COMT rs4680, MC4R rs489693, and HTR2C rs3813929 were studied in a cohort of 515 Bulgarian psychiatric patients using the polymerase chain reaction (PCR) method.

Results: We found no significant difference between our cohort and the dataset of the 1000 Genomes Project. Moreover, we found that 433 out of 515 patients carried at least one, and 191 out of 515 carried at least two variants which, based on multiple scientific sources with consistent findings, could potentially alter the expected response rate, time to respond and/or risk of side effects to antipsychotic medications.

Conclusions: Considering the consistent data about the frequency of these pharmacogenetic variants, testing these genetic variants may prove useful in clinical practice. Further studies regarding the clinical interpretation and frequency distribution in larger cohorts and different populations are warranted.

Keywords

antipsychotics, COMT, DRD2, HTR2C, MC4R, pharmacogenetics

INTRODUCTION

Pharmacogenetics studies the influence of genetic variants on clinical response. Antipsychotics are the first-line therapy for schizophrenia. They are frequently used as monotherapy or in a combination with mood stabilizers or antidepressants for bipolar disorder and major depression, respectively.[1] Despite their efficacy, frequent side effects include weight gain and metabolic syndrome, which increase the morbidity and mortality rates in psychiatric patients.[2]

The efficiency and side effects of the therapy are related to the presence of pharmacogenetic variants of specific genes.[3]

AIM

The present study aimed to conduct a comprehensive analysis of the frequency of variants of the genes DRD2 rs1799732, COMT rs4680, MC4R rs489693, and HTR2C rs3813929 in a cohort of 515 psychiatric patients with various psychiatric conditions.

MATERIALS AND METHODS

Study population

The present retrospective, cross-sectional, observational study included 515 Bulgarian patients with psychiatric disorders (major depressive disorder, anxiety disorder, bipolar disorder, schizophrenia, schizoaffective disorder, and obsessive compulsive disorder), tested with pharmacogenetics panel between October 2017 and December 2019. The mean age of patients was 37.4 years (age range, 8 to 88 years). The distribution by gender was as follows: 250 of the patients were male and 265 female. The place of residence was mainly Sofia and Plovdiv, but also included other cities in Bulgaria such as Varna, Ruse, Stara Zagora, Lovech, and others.

Genotyping

Samples were collected using self-sampling buccal-swab kits. DNA was isolated using MagMax 96 DNA Multi Sample magnetic bead technology with the KingFisher Flex Purification System (ThermoFisher Scientific, Carlsbad, CA). The genotyping was performed by Genomind Ltd. using standard and custom TaqMan reagents (qPCR) for all variants. CYP2D6 Copy Number Variation was tested by PCR. The only difference was that the CNV assay did not use a probe, just primers. In total, variants in 18 genes were tested.

Statistical analysis

Chi-square test of homogeneity was performed for the four variants of main interest in order to test for identical distribution using the study sample (515 individuals) and the 1000 Genomes sample (503 individuals). The calculations were performed on R (https://www.r-project.org/), version 3.9.0 using the base function "chisq.test". The tests were applied both for the distribution of the genotypes and the alleles with one exception. We did not perform a test for the alleles of variant rs3813929 since we did not have the exact count of the hemizygous genotype for our sample as it was merged with the count of the homozygous genotype. When we performed the chi-square test for the genotype distribution of the same variant, we added the number of the hemizygous genotype to the number of the respective homozygous genotype in the sample 1000 Genomes.

RESULTS

We did not find any statistically significant differences for any of the tests (**Table 1**). The smallest p-value was 0.078 for the test of the alleles for variant rs1799732.

The test for the genotypes of variant rs1799732 may not be reliable since we had too small number of people with DEL/DEL genotype for both samples (2 for each sample), which makes the conclusions from the test questionable. Still, the p-value of this test was 0.15 which is way above the threshold of the statistical significance.

The frequency of the COMT rs4680 G allele (**Table 1**) is statistically similar to the one reported for the 1000 Genomes cohort (50% compared to 50% for 1000 Genomes European cohort, $\chi^2=0$, $p=1$). The test for the genotypes of variant rs4680 did not show a statistically significant difference compared to the 1000 Genomes dataset ($\chi^2=2.09$, $p=0.35$). This variant frequency was studied in other publications.[4-6] Huang et al.[4] reported a frequency of 52% for a European cohort. The frequency reported by Sobolev et al.[5] is 51.1% in patients with psoriasis and 48.2% in controls, and frequency of 47.95% in a European cohort was reported by Ghisari et al.[6]

In our cohort, the frequency of the DRD2 rs1799732 DEL allele was statistically similar to the one reported for the 1000 Genomes European cohort (6% vs. 8%, $\chi^2=3.1$, $p=0.078$). The test for the genotypes of variant rs1799732 was statistically similar to the genotype distribution for the 1000 Genomes dataset ($\chi^2=3.85$, $p=0.15$). Other authors also report the frequency for the allele of this variant.[7] Frequencies of 10% and 12% are reported by Ghosh et al.[7] for patients with attention deficit hyperactivity disorder (ADHD) and controls, respectively.

No statistical test was performed for the alleles for variant HTR2C rs3813929 as we did not have the exact count of the hemizygous genotype for our sample. The test for the genotypes variant rs3813929 yielded statistical similarity with the 1000 Genomes dataset ($\chi^2=2.44$, $p=0.3$).

The frequency of the MC4R rs489693 A allele was statistically similar to the one reported for the 1000 Genomes European cohort (31% vs. 32%, $\chi^2=0.305$, $p=0.58$). The distribution of the genotypes for variant rs489693 was statistically similar to the one for the 1000 Genomes dataset ($\chi^2=0.39$, $p=0.82$). Another publication reports frequency for the allele.[8] The frequency reported by Zhang et al.[8] for an American cohort is 33%.

DISCUSSION

The present study is, to our knowledge, the first one conducted in a cohort of Bulgarian patients with different

Table 1. Frequencies of genotypes and alleles of the investigated polymorphisms in our sample and in the 1000 Genomes dataset and values from the χ^2 test for homogeneity

SNP	n	Genotype			χ^2	p	Allele		χ^2	*p*
COMT rs4680		**AA (%)**	**GA (%)**	**GG (%)**			**A (%)**	**G (%)**		
Our sample	515	125 (24.3)	266 (51.7)	124 (24.1)	2.09	0.35	516 (50)	514 (50)	0	1
1000 Genomes	503	133 (26.4)	237 (47.1)	133 (26.4)			503 (50)	503 (50)		
DRD2 rs1799732		**CC (%)**	**CDEL (%)**	**DELDEL (%)**			**C (%)**	**DEL (%)**		
Our sample	515	452 (87.8)	61 (11.8)	2 (0.388)	3.85	0.15	965 (94)	65 (6)	3.1	0.078
1000 Genomes	503	420 (83.5)	81 (16.1)	2 (0.398)			921 (92)	85 (8)		
HTR2C rs3813929		**CC (%)**	**CT (%)**	**TT (%)**						
Our sample	515	396 (76.9)	82 (15.9)	37 (7.18)	2.44	0.3				
1000 Genomes	503	388 (77.1)	68 (13.5)	47 (9.34)						
MC4R rs489693		**CC (%)**	**CA (%)**	**AA (%)**			**C (%)**	**A (%)**		
Our sample	515	245 (47.6)	221 (42.9)	49 (9.51)	0.39	0.82	711 (69)	319 (31)	0.305	0.58
1000 Genomes	503	232 (46.1)	218 (43.3)	53 (10.5)			682 (68)	324 (32)		

p-values of the χ^2 test for homogeneity for genotypes and alleles

psychiatric conditions that reveals the frequencies of genotypes and alleles of certain polymorphisms (DRD2 rs1799732, COMT rs4680, MC4R rs489693, and HTR2C rs3813929) with pharmacogenetic implementation, whose testing might be useful in clinical practice. In the Bulgarian population, several association studies including both patient and healthy control groups have been previously conducted to find a relationship between specific gene polymorphisms or gene variants and the development of separate psychiatric disorders, the bipolar affective disorder[9,10] and schizophrenia[11]. Along with exploring the genetic background of etiology and pathogenesis of psychiatric disorders, research in the field of pharmacogenomics is also needed and could add clinical value refining the therapeutic approach to these diseases.

Without the knowledge of pharmacogenetic variants, clinicians often rely on trial-and-error procedures in order to select the optimal medication for each patient. Pharmacogenetics informs clinicians about the selection of the most suitable antipsychotic, for optimal response and fewer side effects.[12] Apart from being used to treat schizophrenia, antipsychotics are prescribed for the management of major depressive disorders, bipolar disorders, and anxiety. The number of depressed inpatients treated with antipsychotics increased significantly from 37.9% in 2000 to 45.8% in 2007.[13] In bipolar disorder patients, the use of second-generation antipsychotics increased from 34.1% (2000-2005) to 44.8% (2006-2011).[14] Among non-psychotic/non-bipolar patients with anxiety disorder, 53.6% of inpatients and 16.6% of outpatients received antipsychotic medication.[15]

Since all antipsychotics target the dopamine system to a various degree by binding to dopamine D2 receptors, pharmacogenetic studies have largely focused on dopamine system-related genes, including those encoding the dopamine D2 receptor (DRD2) and catechol-O-methyltransferase (COMT).

The DRD2 gene encodes the D2 subtype of the dopamine receptor. Most antipsychotics antagonize DRD2 as part of their pharmacological action. Chlorpromazine and haloperidol are typical antipsychotic drugs, their antipsychotic actions are ascribed to their high affinity DRD2 antagonism.[16] Olanzapine, quetiapine, and ziprasidone are atypical antipsychotics that still antagonize DRD2, but they have a more pronounced serotonin antagonism than dopamine antagonism.[16] Aripiprazole[17] and bifeprunox[18] are novel atypical antipsychotic drugs that act as partial DRD2 agonists, unlike the other antipsychotics.

The DRD2 rs1799732 SNP comprises a C deletion in the 5′ untranslated region of DRD2 which is a functional polymorphism associated with decreased basal levels of receptor expression.[19] The -141C Ins/Del (rs1799732) polymorphism of DRD2 has been demonstrated to affect the outcome of antipsychotic treatment.[20]

A number of studies have shown that the Del allele polymorphism of DRD2 is associated with increased response time upon treatment with antipsychotic drugs.[20-23] Lencz et al.[21] found an association of allele Del with increased response time upon treatment with olanzapine and risperidone in people with schizophrenia, as compared to genotype GG (Ins/Ins)[21], reported as CC in our cohort due to analysis performed on the complementary DNA strand. Wu et al.[22] found that patients with schizophrenia with Ins/Ins genotype have increased response to chlorpromazine when compared to patients with genotypes DEL/DEL or Ins/Del.[22] An association of GG (Ins/Ins) allele and increased improvement in anxiety-depression symptoms upon treatment with bromperidol and nemonapride in patients with schizophrenia, as compared to genotypes DELDEL and GDEL (Ins/Del) was found by Suzuki et al.[23] A couple of studies[24,25] exploring association between rs1799732 SNP and the response to treatment with aripiprazole and clozapine in patients with schizophrenia did not find a difference

between Ins/Ins and Ins/Del, Del/Del genotypes. We could speculate that no association was found because these two drugs have different pharmacological profiles compared to the other antipsychotic drugs. Clozapine is a serotonin antagonist with a strong binding to 5-HT 2A/2C receptor subtype. It also displays a strong affinity to several dopaminergic receptors, but shows only weak antagonism to the dopamine D2 receptor.[26] Aripiprazole acts as partial DRD2 agonist.[17]

Lastly, a recent meta-analysis examined the relationship of DRD2 genetic variation and clinical response to antipsychotic treatment.[20] The authors found that the group of Del allele carrier was significantly associated with a poorer antipsychotic drug response relative to the Ins/Ins genotype.

Based on literature review, we may conclude that the rs1799732 genetic variation in DRD2 might be significantly associated with antipsychotic drug response and may be particularly important in predicting clinical response to antipsychotic drug treatment.

The COMT enzyme degrades cortical dopamine.[27] The Val158Met variant rs4680 is located within exon 4 of the COMT gene and represents a G-to-A nucleotide substitution, leading to a valine (Val) to methionine (Met) substitution at the position of codon 158. The Met form of the enzyme is less thermostable and confers reduced enzyme activity, leading to increased cortical dopamine levels. A number of studies investigate the cognitive response of carriers of the two alleles to antipsychotics. Bertolino et al.[28] demonstrated that Met alleles are associated with greater improvement in negative symptoms, in working memory performance, and in prefrontal cortical physiology. Moreover, patients homozygous for the COMT Met allele demonstrated significant improvement on the working memory task after treatment, as compared to patients homozygous for the Val allele.[29] Furthermore, pairwise comparisons showed that individuals with the Val/Val genotype experienced significantly greater cognitive deterioration than individuals with the Met/Met genotype.[30] The results of Rebollo-Mesa et al.[31] demonstrate that the verbal abilities of Val homozygotes of the COMT gene are impaired by higher doses of antipsychotic medication, an association that is reversed in Met carriers. Finally, Met/Met individuals were significantly more likely to respond to treatment with antipsychotics than Val-carriers and Met/Met patients experienced significantly greater improvement in positive symptoms relative to Val carriers.[4]

The HTR2C gene, which is located on chromosome Xq21, encodes the 2C subtype of serotonin receptor (5-HT2C). Experimental studies demonstrated the relevance of 5-HT2C receptors in regulating appetite and food consumption, and 5-HT2C agonists such as dexfenfluramine and lorcaserin can decrease food consumption, leading to significant loss of weight.[32] In contrast, 5-HTR2C antagonists, including many antipsychotics, may increase food consumption, causing weight gain in animal models.[33] The most studied SNP in HTR2C, rs3813929, is in the promoter region of the gene and may play a role in the regulation of gene expression. The rs3813929 C allele was associated with significantly more weight gain than the T allele.[8] Several studies found that the T allele is associated with increased transcriptional activity of the gene, compared to the C allele, leading to protection against antipsychotic-related weight gain by partially counteracting the antagonistic antipsychotic effect. Moreover, the T allele has a protective function in preventing significant weight gain from clozapine.[34]

Another gene that has moderate evidence for its association with antipsychotic-related weight gain is MC4R, located in chromosome 18q21. The MC4R gene encodes the protein which is a membrane-bound receptor and is a member of the melanocortin receptor family. MC4R mutations were demonstrated to confer inherited human obesity.[35] MC4R mutations have been associated with extreme early-onset obesity, and mice knockout for the MC4R gene develop obesity (Huszar et al., 1997). MC4R neurons in the hypothalamus paraventricular nucleus, stimulated by α-melanocyte stimulating hormone (α-MSH) generated by the neurons expressing pro-opiomelanocortin (POMC), can induce decreased consumption of food and increased expenditure of energy.[36] Variant rs489693 was significantly associated with weight gain, as AA homozygotes of this SNP gained more weight than the C allele carriers.[8] Among 341 Caucasian inpatients receiving at least one SGA drug (olanzapine, clozapine, risperidone, paliperidone, quetiapine or amisulpride), carriers of the rs489693 AA-genotype demonstrated weight increase, compared to carriers of the CC-genotype.[37] A genome-wide association study found that MC4R rs489693 showed consistent effects on weight gain and on the levels of triglycerides, leptin and insulin, the homeostasis model assessment insulin resistance index (HOMA-IR index), and total fat mass.[38] These data implicate the MC4R locus in extreme SGA-induced weight gain and related metabolic disturbances.[38]

According to our findings, 433 out of 515 patients ($\hat{p}$=85%, 95% CI: 81%–87%) carry at least one variant, 191 out of 515 patients ($\hat{p}$=37%, 95% CI: 33%–41%) carry at least two variants, 58 out of 515 patients ($\hat{p}$=11%, 95% CI: 8.7%–14.4%) – at least three variants, and 7 out of 515 patients ($\hat{p}$=1.4%, 95% CI: 0.6%–2.9%) carry all four interpretable/functional variants, which alter the expected response rate and/or side effects risk. Considering the literature accumulated in recent years, showing gene-drug interactions between antipsychotic drugs and the described variants and the consistent data about their overall significant frequent distribution including our current study of patient specific population, testing of these and similar genetic variants, may prove especially useful in routine practice. Taking into consideration the high cumulative incidence of PGx variants and the aforementioned, we would suggest that panel testing could be implemented into the clinical practice with subsequent consultation intended for the treating physician and conducted by trained pharmacogeneticists/geneticists. Further studies regarding the actionable interpretation and frequency of distribution in larger cohorts and different populations are warranted.

CONCLUSION

Considering the literature accumulated in recent years, showing gene-drug interactions between antipsychotic drugs and the described variants and the consistent data about their overall significant frequent distribution including our current study of patient specific population, testing of these and similar genetic variants, may prove especially useful in routine practice. Taking into consideration the high cumulative incidence of PGx variants and the aforementioned, we would suggest that panel testing could be implemented into the clinical practice with subsequent consultation intended for the treating physician and conducted by trained pharmacogeneticists/geneticists. Further studies regarding the actionable interpretation and frequency of distribution in larger cohorts and different populations are warranted.

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Изучение фармакогенетических вариаций в когорте пациентов с психическими заболеваниями из Болгарии

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Резюме

Введение: Фармакогенетика в психиатрии в настоящее время набирает популярность. Эффективность нейролептической терапии часто ограничивается отсутствием ответа и наличием побочных эффектов. Фармакогенетические вариации, вероятно, являются одним из факторов, вызывающих наблюдаемые межиндивидуальные различия в ответах и побочных эффектах нейролептиков, которые можно рассматривать и чьи неблагоприятные эффекты можно избежать или смягчить.

Цель: Настоящее исследование направлено на проведение углублённого анализа заболеваемости DRD2 rs1799732, COMT rs4680, MC4R rs489693 и HTR2C rs3813929 среди болгарских пациентов с психическими заболеваниями.

Материалы и методы: Методом полимеразной цепной реакции (ПЦР) изучали частоту генотипов и аллелей вариантов DRD2 rs1799732, COMT rs4680, MC4R rs489693 и HTR2C rs3813929 в когорте из 515 пациентов с психическими заболеваниями из Болгарии.

Результаты: Мы не обнаружили существенной разницы между нашей когортой и набором данных проекта «1000 геномов». Кроме того, мы обнаружили, что 433 из 515 пациентов были носителями как минимум одного, а 191 из 515 пациентов имели как минимум два варианта, которые, основываясь на нескольких научных источниках с аналогичными результатами, потенциально могли изменить ожидаемую частоту ответа, время ответа и / или риск побочных эффектов к нейролептикам.

Заключение: Учитывая аналогичные данные о частоте этих фармакогенетических вариантов, изучение этих генетических вариантов может быть полезным в клинической практике. Это даёт основание для дальнейших исследований, связанных с клинической интерпретацией и распространённостью в более крупных когортах и различных популяциях.

Ключевые слова

нейролептики, COMT, DRD2, HTR2C, MC4R, фармакогенетика