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PHARMACOGENETICS AND ANTIPSYCHOTIC TREATMENT RESPONSE

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Abstract

Antipsychotic drugs are widely used in the treatment of schizophrenia and psychotic disorder. The lack of antipsychotic response and treatment-induced side-effects, such as neuroleptic syndrome, polydipsia, metabolic syndrome, weight gain, extrapyramidal symptoms, tardive dyskinesia or prolactin increase, are the two main reasons for non-compliance and increased morbidity in schizophrenic patients. During the past decades intensive research has been done in order to determine the influence of genetic variations on antipsychotics dosage, treatment efficacy and safety. The present work reviews the molecular basis of treatment response of schizophrenia. It highlights the most important findings about the impact of functional polymorphisms in genes coding the CYP450 metabolizing enzymes, ABCB1 transporter gene, dopaminergic and serotonergic drug targets (DRD2, DRD3, DRD4, 5-HT1, 5HT-2A, 5HT-2C, 5HT6) as well as genes responsible for metabolism of neurotransmitters and G signalling pathways (5-HTTLPR, BDNF, COMT, RGS4) and points their role as potential biomarkers in everyday clinical practice. Pharmacogenetic testing has predictive power in the selection of antipsychotic drugs and doses tailored according to the patient's genetic profile. In this perception pharmacogenetics could help in the improvement of treatment response by using different medicinal approaches that would avoid potential adverse effects, reduce stabilization time and will advance the prognosis of schizophrenic patients.

Key words: Pharmacogenetics, antipsychotics, schizophrenia, biomarkers, CYP450, P-glycoprotein, serotonergic receptors, dopaminergic receptors, COMT, BDNF.

Background

Schizophrenia is a serious mental disorder with an annual incidence of 0.23 per 1000 persons and a prevalence rate over life of 1% [1]. According to the World Health Organization and the World Bank, schizophrenia is the 9th most important cause of disability in persons aged 15 to 44 worldwide, and 4th in developed countries [2]. The treatment of schizophrenia is still far from satisfactory with up to 30–50% of patients not responding to pharmacological treatment. The field of schizophrenia is redefining optimal outcome, moving beyond clinical remission to a more comprehensive model including functional recovery and improved subjective well-being. A current therapeutic controversy in the treatment of schizophrenia is the relative merit of using different antipsychotic medications [3]. Antipsychotic drug use is usually accompanied by a number

of severe and long-lasting side effects. Typically, first generation antipsychotics (FGA) have a strong affinity for dopaminergic receptors and they block the D2 receptors in the mesolimbic pathway. As a result of blockade of other dopamine pathways and a decrease of dopamine in these zones, they cause many consequent side effects. Extrapyramidal symptoms (i.e. Parkinsonism, dystonia, akathisias and dyskinesias) appear as a result of increase of acetylcholine in the basal ganglia, caused by blockade of D2 receptors in the nigrostitial pathway which may remain after treatment withdrawal. EPS are mostly correlated with the dosage. Amenorrhea and other disorders due to an increase of prolactin caused by blockade of the tuberoinfundibular pathway and the deficit syndrome (negative and cognitive symptoms) due to the blockade in the mesocortical pathway are also common side effects in antipsychotic treatment [1]. Second generation or atypical antipsychotics (SGA) have a different mechanism of action. Besides being dopamine antagonists they are also antagonists of serotonergic receptors, and even of the cholinergic, histaminergic and adrenergic receptors. SGA have a lower incidence of EPS, but cause other severe side effects such as metabolic syndrome (weight gain, diabetes, hypertension, obesity and dyslipidaemia), sexual dysfunction and, in the case of clozapine, late onset of agranulocytosis. According to the World Association of Psychiatry, the atypical antipsychotics are as effective as the typical ones in the treatment of positive symptoms [4], but superior in the treatment of negative, cognitive and depressive symptoms, with a lower risk of EPS. That is the reason why the atypical antipsychotics are considered as the first line treatment for schizophrenia in all the relevant clinical guidelines. Treatment failure and side effects are caused by a combination of clinical, environmental and genetic factors. Early treatment response and significant weight gain are signs of a good prognosis. On the other hand, early age onset of disease and the presence of EPS are linked with a poor pharmacological treatment response [5]. A high percentage of patients with schizophrenia respond poorly to antipsychotic treatment, or present refractory schizophrenia.

Recently reported are the results of all the randomized phases of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia, a NIMH-funded project that cost over 40 million dollars. The CATIE trial found that antipsychotic drug treatments are generally effective overall but have various limitations as reflected by high rates of discontinuation due to both efficacy and tolerability problems [6]. In addition, the trial found that conventional agents with intermediate potency were comparably effective with atypical agents. Moreover, although numerous studies have evaluated subjective outcomes within the domain of subjective quality of life in patients with schizophrenia, less is known about global evaluations of subjective well-being. Recent studies suggests that, despite antipsychotic medications being effective for symptom-based psychopathology, such clinical effectiveness does not necessarily translate to improved general satisfaction with life. Clinicians should be aware that these two domains are not inextricably linked [7]. Pharmacogenetic studies are focused on determination of inter-individual variations in DNA sequence related to drug response. In recent years, high expectations are given to the capabilities of pharmacogenetics in tailoring personalized psychotropic treatment for each patient according to their genetic profile. The polygenetic and multifactorial etiology of schizophrenia, as well as the polygenetic profile of antipsychotic treatment response which integrate both the genes involved in the pharmacokinetics (basically CYPs) and in the pharmacodynamics (receptors), have to be taken into account when tailoring the antipsychotic treatment. The following review will summarize the most significant pharmacogenetic findings and will give an overview of their potential clinical application.

Pharmacogenetics of drug metabolism and transport

Cytochrome P450 genes

Functional polymorphisms in genes coding the phase I metabolic enzymes had a breakthrough in the 1950s, when it was determined that CYP2D6 polymorphism effects the debrisoquine metabolism. The enzymes of the CYP superfamily catalyse some oxidation reactions of different substrates to increase their hydro-solubility and to enable their biotransformation and excretion. Approximately 18% of neuroleptics are major substrates of CYP1A2

enzymes, 40% of CYP2D6 and 23% of CYP3A4/5 enzymes [8]. Most CYP enzymes exhibit ontogenic, age, sex, circadian and ethnic differences [9] and these variants result in different metabolism of the drugs according to the genetic profile/expression which enables some extent of prediction of treatment response. A dedicated web page for the compilation and description of variants detected in CYP enzymes has been created (http: //www.cypallels.ki.se/).

Cytochrome CYP1A2

The CYP1A2 gene is located in the long arm of chromosome 15, in region 15q24, and has 7 exons, the first of which is non-coding. CYP1A2 accounts for approximately 15% of the CYP enzymes. This enzyme is involved in metabolic transformation of the following antipsychotics: haloperidol, pherphenazine, thioridazine, olanzapine, clozapine and chlorpromazine (Table 1). The CYP1A2 gene, located on chromosome 15, is highly polymorphic. A few common CYP1A2 polymorphisms have been studied intensively. However, the impact of these polymorphisms on enzyme activity is still not totally clear. Caffeine consumption inhibits its activity, whereas smoking induces CYP1A2 activity, especially of the variants containing the -3860G/A (CYP1A2*1C) and -3860G/A (CYP1A2*1C) alleles. The influence of -2467delT (CYP1A2*1D) polymorphism on the enzyme activity is still not clearly exposed. On the other hand, CYP1A2*1K (-163A, -739G, -729T) haplotype is related to reduced CYP1A2 activity compared to CYP1A2*1A (wild type) and CYP1A2*1F (-163A) or CYP1A2*1J (-163A, -739G) haplotypes in nonsmoker volunteers [10–14]. The influence of external factors on the activity of CYP1A2 is important, since the co-administration of antipsychotics competing for the same enzyme leads to its inhibition, reduced treatment efficacy and increased side effects. The CYP1A2 enzyme accounts for up to 70% of clozapine metabolism, so that its variation has been related to drug clearance [15]. Olanzapine uses approximately 60% of the CYP1A2 pathway for formation of its principle metabolites. Considering these facts, pharmacogenetic testing of CYP1A2 is more than justified in patients treated with clozapine and olanzapine. Individuals with CYP1A2 ultrarapid phenotypes are known to experience delay or lack of response to these two antipsychotics [16].

Cytochrome CYP2D6

Cytochrome CYP2D6 is the first metabolizing enzyme documented as polymorphic [17, 18]. CYP2D6 is a gene with nine exons located in the long arm of chromosome 22 in region 22q13 and is highly polymorphic. Currently, about 90 mutations have been described and some of them have up to 13 subtypes [19]. CYP2D6 plays a significant role in metabolic transformation of aripiprazole, chlorpromazine, haloperidol, perphenazine, quetiapine, risperidone and olanzapine (Table 1). Unlike CYP1A2, CYP2D6 activity is not inducible. A number of functional genetic variants that determine the metabolic activity of enzymes as extensive (EM), intermediate (IM), poor (PM) and ultra-rapid (UM) phenotype metabolizers are identified. They are characterized by normal, intermediate, decreased and multiplied ability to metabolise the enzyme's substrates respectively. CYP2D6*3, CYP2D6*4, CYP2D6*5 and CYP2D6*6 variants are associated with complete lack of enzyme activity, leading to PM phenotype, whereas CYP2D6*1XN, *2XN and *35XN, the duplication or multiplication of a functional CYP2D6 gene causes extremely high CYP2D6 activity and leads to UM phenotype. Poor metabolizers (PMs) are characterized by 10–200 slower metabolism of CYP2D6 substrates in comparison to EMs. Among healthy individuals, extensive metabolizers (EMs) account for 55.71% of the population, intermediate metabolizers (IMs) for 34.7%, poor metabolizers (PMs) for 2.28%, and ultra-rapid metabolizers (UMs) 7.31%. It has been reported that the frequencies of UMs may be 1% in Sweden and 7% to 10% in Southern Europe [20]. This percentage refers to subjects with CYP2D6 duplications, but some of the duplicated alleles of CYP2D6 may be without activity or have decreased activity [21, 22]. When the UMs are defined strictly as subjects with at least three active alleles the frequency is lowered and is approximately 1.5%. Remarkable interethnic differences exist in the frequency of PM and UM phenotypes and may explain the differences in treatment response observed between po-

pulations. On average 6.28% of the world population are poor metabolizers [1]. Frequencies are the subject of geographic variations, with 7–10% PMs in the Caucasian population and 1–2% in Asians. Different phenotypes are directly related to drug clearance, with PM variants associated with higher plasma levels and the UM forms with rapid clearance and lower plasma concentration of drugs and their metabolites [8]. Poor metabolizers treated with antipsychotics with narrow dose ranges are more likely to develop adverse reactions to the treatment, whereas ultra-rapid metabolizers will fail to respond to standard doses of antipsychotics. Several studies have investigated the role of genetic polymorphism of the CYP2D6 gene in the occurrence of adverse effects, especially EPS, during antipsychotic treatment [23–25]. Bork *et a*l. [26] showed that PM patients treated with risperodine have a three times greater risk of developing adverse reactions in comparison with EM or IM patients. It was also shown that PMs have a six times greater risk of treatment failure than EMs [27]. As well as in the liver, CYP2D6 is expressed in the brain where it probably plays a significant role in the metabolism of endogenous substances and neurotransmitters such as dopamine. Neuroleptic malignant syndrome (NMS) has been investigated in the Japanese population in association with CYP2D6, and it was confirmed that carriers of CYP2D6*5 have a higher risk of developing NMS [28]. In addition to the genetic variability, external factors can influence the metabolic activity of CYP2D6, such as the concomitant use of common drugs with inhibitory activity to the gene, such fluoxetine and paroxetine.

Table 1

Summary of most commonly used antipsychotics and their main metabolic pathways

Antipsychotic	Type	Main metabolic pathway
Aripiprazole	SGA[2]	CYP2D6, CYP3A
Chlorpromazine	FGA[1]	CYP2D6, CYP1A2
Clozapine	SGA[2]	CYP1A2
Haloperidol	FGA[1]	CYP2D6, CYP3A, CYP1A2
Olanzepine	SGA[2]	CYP2D6, CYP1A2
Perphenazine	FGA[1]	CYP2D6, CYP1A2, CYP3A4
Quetiapine	SGA[2]	CYP3A, CYP2D6
Risperidone	SGA[2]	CYP2D6, CYP3A
Thioridazine	FGA[1]	CYP2D6, CYP1A2

[1] FGA First Generation Antipsychotics; [2] SGA Second Generation Antipsychotics

Cytochrome CYP3A

The CYP3A family is involved in the metabolism of 45–60% of all known drugs. Among the antipsychotic drugs, it is important for metabolic transformation of aripirprazole, haloperidol, perphenazine and risperidone (Table 1). The interindividual differences in CYP3A enzyme expression influence the oral bioavailability and systemic clearance of its substrates. The CYP3A gene family consists of four genes (CYP3A4, CYP3A5, CYP3A7 and CYP3A43). They are located in the long arm of chromosome 7 in the region q21-q22.1 in the tandem structure of 220kb. The most relevant isoforms in adults are CYP3A4 and CYP3A5. CYP3A7 is the major cytochrome P450 isoform in embryonic, foetal and newborn infants [29, 30] and it is slightly expressed in the adult liver and intestine [31]. CYP3A4 is the predominant hepatic form, but CYP3A5 contributes significantly to the total liver CYP3A activity. CYP3A4 is the most abundant CYP isoform in the human liver with large interidividual variability in its expression. About 347 SNPs have been identified in the CYP3A4 (CYP3A4*1A: wild type) and 25 of them are of clinical relevance. Only CYP3A4*17 and *18A display functional variability with decreased or increased activity, respectively [32]. No significant response association of these polymorphisms with antipsychotics response has been published. Most of the studies performed on Cauca-

sian individuals consider the CYP3A4 isoenzyme as the principle one in the human liver because the CYP3A5 expression is low in the population (it is present in 33% of North American Caucasians and in 60% of Afro-Americans) [33]. Only subjects carrying at least one functional CYP3A5*1 allele express the CYP3A5 protein. But it has been presented that in individuals in whom CYP3A5 is expressed it has approximately equal metabolic activity as CYP3A4. CYP3A4*1B, located in the promoter region of the gene, influences the transcription efficiency and thus the overall enzymatic activity of CYP3A4 [34]. CYP3A4*3 variant leads to alternative substrate specificity as a result of Met445Thr substitution near the active site of the enzyme [35] and CYP3A4*4 variant is characterized by an Ile118Val substitution decreased enzyme activity [36].

So far, a series of allele variations are defined in regard to a wild type allele (CYP3A5*1). In wild type allele carriers CYP3A5 represent almost 50% of the total CYP3A protein. CYP3A5*3C mutant allele is the major defective allele and is responsible for alternative splicing and protein truncation which results in decreased enzyme activity and absence of CYP3A5 expression in more than 70% of Caucasians [33]. CYP3A5*2 and CYP3A5*6 code for an enzyme without activity [37]. In the Caucasian population, 87.75% are EMs (CYP3A5*3/*3), 15.88% are IMs (CYP3A5*1/*3) and 1.37% are UMs (CYP3A5*1/*1) [1].

ABCB1

P-glycoprotein (P-gp) is a member of the adenosine triphosphate-binding cassette (ABC) superfamily of transporters and is widely expressed in normal tissue such as intestine, liver, kidney and brain. Its physiological role is to act as an efflux pump and to serve as a barrier to the entry of xenobiotics and cellular metabolites [38], but it also influences intestinal drug absorption and elimination and influences drug bioavailability [39]. Polymorphic variations on ABCB1 (MDR1) gene influence its expression [40, 41], their association with pharmacokinetics and bioavailability of drugs [42, 43] and their association with clinical effects [44, 45]. Several second generation antipsychotics, amisulpride, aripiprazole, olanzapine, perospirone, risperidone and paliperidone are substrates for P-gp in therapeutic concentrations. Clozapine and quetiapine are not likely to be substrates of P-gp, but most antipsychotics act as inhibitors of P-gp, and can therefore influence plasma and brain concentrations of other substrates. With this fact in consideration this transporter plays a significant role in their pharmacokinetics [46, 47]. It has been confirmed that the C3435T SNP in exon 26 and G2677T>A SNP of the ABCB1 gene affect the level of duodenal ABCB1 expression possibly as a result of the decrease in mRNA stability [48] and alter the absorption and distribution of many drugs that are their substrates [40, 49–51]. These two variations and the C1236T silent polymorphism in the exon 12 are supposed to be in close linkage disequilibrium [52, 53]. The frequency of 2677A variant is 2% among whites, but the other variants 1236T, 2677T and 3435T, are very common (41–56%) [54]. Kimchi-Sarfaty *et al*. have confirmed similar mRNA and protein concentration in wild-type and variant protein but, on the other hand, they confirm altered conformation of the variant protein, thereby affecting the structure of substrate and inhibitor interaction sites.

The relevance of polymorphic variations on ABCB1 in antipsychotic treatment response has been widely studied, but further investigation is needed for confirmation of their biological importance. It has been suggested that ABCB1 2677T/T and 3435T/T genotypes in drug naïve first episode schizophrenic patients have a higher active moiety (risperidone + 9-OH risperiodne) in comparison with non-carriers of this genotype [56]. Recent studies have shown 3435T allele and 2677T/3435-T haplotype carriers have a better response to risperidone with lower frequency of extrapyramidal side effects [57]. It is suggested that this pharmacogenetic profile presents protective activity against the development of EPS side effects in risperidone treatment. ABCB1 C3435T polymorphism has also been related to greater risk of polydipsia-hypernatremia [58]. It has been addressed that 1236TT genotype is associated with better improvement of BARS score in the Chinese population [59]. On the other hand Suzuzki Y *et al*. [60] have recently shown that risperidone,

9-OH-RIS and total active moiety levels were significantly correlated with ABCB1 3435C>T genotypes, whereas the ABCB1 2677G>T/A genotypes did not affect plasma RIS, 9-OH-RIS, or total active moiety levels. Carriers of ABCB1 1236T/2677T/3435T haplotype had higher serum and cerebrospinal fluid olanzapine concentrations than patients without this haplotype [61]. It has been suggested that the P-gp C3435T genotype may also help to determine positive symptom reduction from olanzapine clinically, but these findings should be replicated on a larger sample of subjects [62]. The T allele of 2677G/T/A polymorphism is related to better response to olanzapine treatment in women [63]. Kuzman *et al*. [64] additionally suggested that ABCB1 G2677T and C3435T MDR1 genetic polymorphisms influence the development of metabolic abnormalities among female patients treated with olanzapine and risperidone.

Pharmacogenetics of treatment response

Many pharmacogenetic studies have confirmed the clinical validity and importance of some brain neurotransmitter systems in mediating treatment efficacy and onset of side effects. The genetic variability of dopamine and serotonin receptors play a significant role in antipsychotic drug efficacy.

Dopaminergic system

Dopamine D2 receptors are mainly expressed in the striatum, cortex and limbic system and belong to the G-protein coupled receptor superfamily. An average occupancy of 65% of brain dopamine receptors is necessary for therapeutic efficacy, but over 72% occupation induces prolactin elevation and 77% or higher occupation induces EPS [65]. First generation antipsychotics have strong dopamine affinity, whereas second generation antipsychotics display moderate to high affinity for D2, D3 and D4 receptors [8]. Neuroleptics influence the positive symptoms of schizophrenia dominantly through blockade of D2 receptors. This antagonistic action mechanism is responsible for the onset of Parkinsonian-like side effects. The dopamine D2 receptor gene, DRD2, is located on chromosome 11 and contains a number of SNPs. The most significant polymorphism associated with poorer antipsychotic treatment response on the DRD2 promoter gene is-141Cdel variant, located in 11q23 region, which is responsible for lower expression of the protein [66]. Significant weight gain is confirmed after 6 weeks of risperidone or olanzapine treatment in the patient population with -141Cdel allele [67]. On the other hand, Japanese schizophrenia patients with -141Cins allele treated with risperidone have improved positive symptoms [68]. Patients with -141-C del have a higher incidence of neuroleptic malignant syndrome (NMS) characterized by severe hypofunction of the dopaminergic system [69]. -141C del allele is associated with lower expression of D2 receptor protein *in vitro* [70]. Another frequently examined polymorphism on the dopamine D2 receptor shown to be predictive of drug response is Ser311Cys. It is postulated that this polymorphic variant modulates receptor G protein interaction and alters receptor function. Patients with Ser311 allele are related with a better outcome for positive, negative and cognitive symptoms, as well as a more robust response to antipsychotics [71]. A D2 restriction polymorphism known as TaqIA has been associated with risk of tardive dyskinesia and increased risk of EPS during treatment with antipsychotics and selective serotonin reuptake inhibitors [72, 73]. Patients with A1 allele had a better response to dopamine antagonists [74]. This variant is also associated with lower density of receptor and decreased function [66]. It has been reported that Taq1A1 led to reduced striatal D2 receptor binding [75, 76].

Another polymorphism, A241G, was correlated to risperidone and olanzapine treatment response by Xing *et al*. [77]. Patients with A allele havea better response to risperidone treatment and have shown greater improvement, whereas G carriers have a lower response time [78].

The D3 receptor is mainly localized in the mesolimbic area in the brain and it is associated with cognitive, emotional and motor functions [79]. Pharmacogenetic testing on the D3 receptor is justified because of the high affinity of different antipsychotics for this receptor. Among the SNPs of DRD3 gene, the most interesting variant which is extensively studied is Gly9Ser. The 9Gly variant confers higher binding affinity and better antipsycho-

tics response regarding the positive symptoms, but it also increases the risk of tardive dyskinesia [5, 80, 81].

Variable numbers of tandem repeat (VNTR) polymorphisms in exon 3 of dopamine D4 receptor (DRD4) gene are associated with multiple psychiatric illnesses. The allele size of 7R is less frequent in the Asian population (Japanese 0.5%) than in Caucasians (20%). The ancestral haplotype and the most common is 4R variant. Although direct association of VNTR and TD are not confirmed, some four taq polymorphism haplotype analysis suggest that DRD4 may be involved in TD in Caucasians [82].

Serotonergic system

Second-generation antipsychotics display a high affinity for serotonin (5- Hydroxytriptamine, 5-HT) receptors. The influence of 5-HT2A and 5-HTC polymorphic variations in the etiology of schizophrenia and antipsychotic treatment response is justified in many studies.

5-HT1A

5-HT1A receptor is another potential target for prediction of treatment response with atypical antipsychotic drugs. -1019C/G SNP, located in the upstream regulatory region, is the most widely studied polymorphism and it influences the gene transcription. G allele carriers are characterized by elevated levels of 5HTR1A. As 5HTR1A is involved in the modulation of dopaminergic activity, -1019C/G variant may affect cortical dopamine release. While an increased dopamine level in the cortical region is crucial for improvement of negative symptoms of schizophrenia, this polymorphism may potentially be important for antipsychotic drug treatment response prediction. It was confirmed in two recent studies conducted on Chinese and Caucasian schizophrenia patients treated with risperidone. In both studies CC genotype carriers showed an improvement of negative symptoms [83, 84].

5-HT2A receptor

The 5-HT2A receptors are widely expressed in cortical brain areas, additional to the hypothalamus, limbic system and striatum [85]. It is a postsynaptic G-protein receptor with a high affinity for clozapine, risperidone and olanzapine [86]. The 5-HT2A receptor coding gene, HTR2A, is located on the chromosome region 13q14-21. The most relevant polymorphisms are 1438A/G promoter polymorphism associated with decreased promoter activity and a lower expression of the receptor protein [87], 102T/C a silent polymorphism within the coding region, in complete linkage disequilibrium with the previous one [88] and His452Tyr (1354C/T) polymorphism responsible for an amino acid substitution within the cytoplasmic C-terminal tail of the receptor. This change does not affect the expression and does not prevent the substrate binding to the receptor, but it makes it ineffective. The 452Tyr allele is more frequently found in a group schizophrenic patients non-responding to clozapine treatment. This variant reduces the serotonin induced calcium mobilization in platelets [89]. The 102C allele is correlated to lower protein expression, increased risk of schizophrenia and EPS, and poorer response to treatment in Caucasians [90, 91]. This allele is significantly overexpressed among the clozapine non-responders and in schizophrenic patients with developed TD [92, 93]. As this is silent polymorphism, it is hypothesized that an epigenetic mechanism such as methylation is responsible for 102C>T SNP functionality [94].

5-HT2C receptor

The 5-HT2C receptors are coupled to stimulatory G-protein and involved in the regulation of feeding behaviour, anxiety and motor functions. These receptors are expressed in the choroid plexus, prefrontal cortex, basal ganglia and limbic regions in the brain [95, 96]. The 5-HT2C receptor coding gene, HTR2C, is located on the Xq24 chromosome and is an excellent candidate for pharmacogenetic testing and conformation of its association with disease and treatment response. The 997G/A polymorphism in the promoter region is in complete linkage disequilibrium with -759C/T polymorphism [97]. C to T substitution in the promoter region of the gene leads to decreased promoter activity [98]. The 759T allele presents a protective role against antipsychotic-induced weight gain in patients treated with clozapine, olanzapine, risperidone and chlorpromazine [99–102]. The protective role of -759C/T polymorphism exerts mostly on weight gain in short-term treatment of drug naïve patients and this association is constantly confirmed mostly in the European

population, but also in the less studied Asian population [103]. 697G/C is another promoter polymorphism where C allele is associated with decreased promoter activity and the onset of persistent tardive dyskinesia [98, 104, 105]. The study in the European population confirmed the protective role of C allele in a 10% increase of BMI and weigh gain, and the other found no correlation. Due to an initial positive result -697C/T remains a promising candidate for future studies. Cys23Ser (68G/C) polymorphism leads to a higher constitutive activity of the 23Ser compared to the 23Cys variant *in vitro* [106]. This finding could not be reproduced in mammalian cells expressing the mRNA edited 5-HT2C isoforms [107]. It has been reported that HTR2C 23Ser allele is responsible for a better response to clozapine treatment [108] and increased risk of tardive dyskinesia [109]. The functional haplotype studies hypothesized that an increased HTR2C transcription, leading to a more active 5-HT2C system, might be protective against antipsychotic induced weight gain, since subjects may be less sensitive to the metabolic changes caused by medication [110].

5-HT6 receptor

Genetic variations in serotonin 6 (5-HT6) receptors might be associated with the pathophysiology of schizophrenia. 267C/T polymorphism of 5HTR6 is related to antipsychotics treatment response. The 267T/T genotype has a confirmed superior response to risperidone [111], particularly for positive symptoms and general symptoms (e.g. anxiety, depression and cognitive symptoms), but not for negative symptoms in schizophrenic patients [112].

5-HTTLPR

Serotonin recovery on the presynaptic level depends on the 5-HTT transporter (5-hydroxytryptamine transporter). It is a high affinity transporter and has a predominant role in termination of the extracellular effects of serotonin through re-uptake. The gene encoding this transporter is located in the 17q11.1-q12 region, and two principle polymorphisms are confirmed. They did not influence the protein structure, rather they modify the gene transcriptional activity. The repeat polymorphism called 5-HTTLPR (5-HTT gene linked polymorphic region) has 44 base pair deletion/insertion in the promoter region giving rise to two alleles, L (long) and S (short). This polymorphism influences transporter expression and in patients with schizophrenia it probably modulates severity, acting as a disease modifying gene. L-allele carriers are better antipsychotic responders using any of the diverse clinical scales [114–116]. Another study confirmed that S allele is associated with lower improvement of BPRS scores in risperidone and haloperidol treated patients [117]. According to recent studies, the 5-HTTLPR L/S genotype could be generating a modification in the serotonergic system in the brain that leads to an enhancement of antipsychotic activity and efficacy in negative symptoms treatment [118]. All these findings are in agreement with the fact that antipsychotics with a more serotonergic profile could give much better results in negative symptom treatment [119]. The other is tandem repeat polymorphism, called 5HTTVNTR. The most frequent alleles correspond to 9, 10 and 12 repeats in the second intron. One recent haplotype study on both polymorphisms confirmed that the presence of L/12 was associated with good treatment response [120].

COMT

The catechol-O-methyltransferase (COMT) gene is located in the 22q11.21-23 chromosome region. It has been considered as candidate gene for schizophrenia and an important biomarker due to its role in degradation of chateholamines, among which dopamine is included. The human COMT gene has three common variations (A22S, A52T and V108M). A22S and V108M change the protein prone to temperature and oxidation, whereas A52T mutation did not affect the protein structure. The V108M polymorphism rearranges the active site residues and A22S mutation reorients the critical residues away from the substrate-binding pocket [1]. The decreased activity ofA22S and V108M are important for increased risk of schizophrenia. The 108M variant is correlated with a better response to antipsychotic drugs and fewer side effects [121, 122]. These are confusing results, as the Met variant is associated with decreased enzyme activity and dopamine accumulation. Contradictive results are also presented by two different groups of rese-

archers. A study of Japanese patients declines the correlation between risperiodne and COMT [123], but the recent study of Chinese Han patients confirms the association of risperidone treatment with V108M COMT variant [124]. Met allele is also associated with better cognitive improvement in patients treated with clozapine, as well as with the overall schizophrenia symptoms improvement in olanzapine treated patients [16]. Moreover, recent meta-analysis results confirmed the protective role of Mat on the appearance and severity of tardive dyskinesia, as a common side effect in treatment with neuroleptics [125].

BDNF

The brain-derived neurotropic factor (BDNF) has an important role in the long-term potentiation-a cellular mechanism of learning and memory. Several genetic studies have shown a significant association between certain polymorphic variations within BDNF and psychiatric disorders. BDNF interacts with other neurotransmitter systems implicated in schizophrenia, such as dopamine, glutamate, serotonin and GABA [126]. The most extensively studied polymorphic variants are dinucleotide repeat polymorphism (GT) in the promoter region [127], Val166Met (196G/A) polymorphism [128], the -270C/T substitution and the -256G/A polymorphism [129]. The first two polymorphisms are associated with BDNF expression level, whereas Val66Met polymorphism affects the intracellular activity and activity-dependent secretion of BDNF. A growing body of evidence suggests that BDNF plays a significant role in antipsychotic treatment response and the pathogenesis of TD, but the data are inconsistent. Patients with schizoaffective disorder are significantly more likely to be carriers of the most common haplotype (containing the valline allele of the Val66Met SNP) in comparison with healthy volunteers [130]. One recent study showed that the Val/Val genotype was observed more frequently in treatment responders to olanzapine, and this genotype was associated with an improvement in clinical symptoms [131]. In another recent study it was confirmed that the responders to risperidone treatment have a higher frequency of the 230-bp allele of the (GT)n dinucleotide repeat polymorphism than non-responders [132]. One other haplotype study confirmed that patients with 230-bp allele (GT)n dinucleotide repeat polymorphism and 230bp/C270/rs6265G haplotype have a better riperidone response than patients with a 234-bp allele and 234-bp/C270/rs6265A haplotype [133].

RGS4

Regulator proteins of G signalling pathways, RGS4 was recently linked with antipsychotic response variability and adverse drug reactions [134–137]. Lane HY *et al*. confirmed in their study that RGS4 variances influence clinical manifestations of schizophrenia, as well as the treatment response to risperidone, suggesting that RGS4 plays a role in the fundamental process of disease pathophysiology. A/A genotype at SNP1 was associated with greater improvement only in social function, whereas A/A genotype at SNP18, beside the greater improvement in social function, has a positive effect at PANSS total score.

Future perspectives

Personalized medicine is becoming a promising tool for the prediction of disease predisposition and development, as well as a treatment response using genetic and clinical variables. This approach allows individualization of the treatment, tailored to achieve maximized response and avoidd side effects. The lack of antipsychotic response and treatment-induced side effects are two main reasons for non-compliance and increased morbidity in schizophrenic patients. Algorithms where multiple genetic, epigenetic and clinical variables are combined could obtain the predictive powerful selection of the high-risk group of patients. In this perception pharmacogenetic tastings could help to increase treatment response by using different medicinal approaches that would avoid potential side effects, reduce stabilization time and improve the prognosis of schizophrenic patients.

Determination of CYP, transporter and receptor genetic profiles of the patient before starting the treatment is very useful and provides beneficial information. Dose adjustments according to the patient's genetic profile may results in around 15% efficacy improvement, more than 20% reduction in adverse effects. Unfortunately theses tastings are still not wi-

dely used in clinical practice. The final purpose of pharmacogenetics is to provide therapeutic action guidelines based on the analysis of genetic variations. These guidelines will show the directions in treatment modifications, such as decreasing or increasing the dose regarding the usual dose or switching the drugs. Nowadays, in spite of the supporting evidence, pharmacogenetic testing is not widely used in psychiatric clinical practice. The conduct of prospective studies where the clinical and economic benefits will be evaluated could convince psychiatrists of the value of pharmacogenetic information for the improvement of drug efficacy and safety.

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Р е з и м е

ФАРМАКОГЕНЕТСКИ ТЕСТИРАЊА И ОДГОВОР КОН ТРЕТМАН СО АНТИПСИХОТОЦИ

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Антипсихотиците се лекови што се употребуваат во третман на шизофренија и психотични нарушувања. Отсуство на одговор при третманот со антипсихотици и несаканите ефекти што се јавуваат, како што се невролептичен синдром, полидипсија, метаболни нарушувања, зголемување на телесната тежина, екстрапирамидалните симптоми, тардивна дискинезија или зголемено ниво на пролактин, се двете круцијални причини за непридржување на пациентите кон пропишаната терапија и зголемен морбидитет кај пациентите со шизофренија. Во текот на изминатите неколку децении се спроведени бројни истражувања со цел да се одреди влијанието на генетските варијации врз дозниот режим, ефикасноста и безбедноста при третманот со антипсихотици. Овој труд дава преглед на современите сознанија за молекуларната основа на третманот на шизофренијата. Во него се истакнати најзначајните откритија за влијанието на функционалните полиморфизми на гените што ги кодираат CYP450 метаболните ензими, ABCB1 генот што го кодира транспортниот П-гликопротеин, допаминските и серотонинските рецептори (DRD2, DRD3, DRD4, 5-HT1, 5HT-2A, 5HT-2C, 5HT6) и гените одговорни за метаболизмот на невротрансмитерите, како и Г сигналните патишта (5-HTTLPR, BDNF, COMT, RGS4) и ја истакнува нивната улога како потенцијални биомаркери во секојдневната клиничка практика. Фармакогенетските тестирања имаат предиктивна моќ во селекцијата на вистинскиот антипсихотик и неговото дозирање е во согласност со генетскиот профил на пациентот. Во таа насока фармакогенетиката може да даде значен придонес во подобрување на терапевтскиот одговор кон антипсихотиците со што ќе се избегнат потенцијални несакани реакции, ќе се скрати периодот на стабилизација и ќе се подобри прогнозата кај пациентите со шизофренија.

Клучни зборови: фармакогенетика, шизофренија, биомаркери, CYP450, П-гликопротеин, серотонински рецептори, допаминski рецептори, COMT, BDNF.