



Pharmacogenetics of Antidepressant Drugs: An Update

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SUMMARY

Pharmacological treatment of depressive disorders is characterized by poor predictability of individual response. In recent years, the increasing evidence has demonstrated that genetic factors play a critical role in determining the differences in treatment outcome to antidepressant drugs. A number of pharmacogenetic studies on antidepressant drugs has been conducted, and genetic variations at level of drug metabolizing enzymes, drug transporters and drug targets, possibly influencing the clinical response, have been identified. Pharmacogenetics may hopefully provide the basis for individualized pharmacotherapy of depressive disorders in order to maximize the probability of a favorable response and minimize the risk of adverse drug reactions. In this article, the major findings related to the pharmacogenetics of genes involved in the pharmacokinetics and pharmacodynamics of antidepressant drugs are critically reviewed.

Keywords: pharmacogenetics; antidepressants; gene; depression

INTRODUCTION

Major Depressive Disorder (MDD) is a complex and highly prevalent psychiatric disorder that is usually manifested with the episodes of low mood generally accompanied by low self-esteem and generalized loss of interest for any activity. This debilitating condition has a severe impact on quality of life-social relationship and psychological state that has been shown to be at least equal if not greater than other major chronic medical conditions (arthritis, diabe-

tes, heart disease) [1, 2, 3]. According to World Health Organization (WHO), MDD will be the second leading cause of death and disability worldwide by 2020 among people between 15-44 years [4, 5].

Unfortunately, depressed patients are not totally satisfied with the current effectiveness and tolerance of the available antidepressant drugs (ADs). Many clinical studies have shown that about 30%-40% of the MDD individuals fail to respond to the first treatment [6], and even after several trials around 30% of patients

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do not fully recover from depressive disorder [7]. Treatment resistant depression (TRD) is an extremely common problem, affecting a large proportion of all patients suffering from MDD [8, 9]. Moreover, adverse drug reactions (ADR) also have to be considered when selecting antidepressant treatment. In fact, ADRs are major causes of non-adherence and non-compliance to treatment. Given the high frequency of ADRs, the American College of Physicians recommends that the selection of an antidepressant should be based on ADR profiles, cost and patient preferences [10]. The main reason for this is still incomplete knowledge of the pathophysiologic basis of depression and the mechanism of action of ADs.

The increasing evidence has demonstrated that genetic factors play a critical role in the variation of treatment response [5, 11, 12]. For this reason, one of the most important and promising aspect of medicine is the personalization of therapy. It may be achieved by adapting the therapy to individual patient by means of genetic and other molecular tools. Pharmacogenetic studies suggest that single nucleotide polymorphisms (SNPs) can be used in clinical association studies to determine the contribution of genetic variance in drug response. Moreover, associating novel candidate genes with antidepressant response may lead to the development of a new class of medications [13, 14, 15]. In recent years, the development of pharmacogenetics has provided more opportunities for individualized pharmacotherapy of depressive disorders [15]. So far, most pharmacogenetics studies have investigated genes involved in the pharmacokinetics and pharmacodynamics of ADs [15]. Several genetic variations at level of drug metabolizing enzymes, drug transporters, drug targets and other biomarker genes, possibly influencing clinical response, have been identified [15]. Present article will update the major findings related to the pharmacogenetics of genes affecting the response to ADs.

ANTIDEPRESSANT DRUGS (ADs)

All commercially available ADs target the monoaminergic system by either selectively or non-selectively blocking one of the three monoamine transporters (serotonin, noradrenaline and/or dopamine), by interfering with monoamine metabolism or by altering

the pre- or postsynaptic transmission of the main receptors in these systems [16]. They can be divided into first- and second generation drugs. First-generation antidepressants (FGAs) include monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA), which became available for therapy in the 1960s. MAOI increase monoamine levels by preventing their breakdown through blockage of the MAO. TCA mainly target both serotonergic and noradrenergic systems, by blocking the serotonin and noradrenaline transporters, therefore, interfering with pre- and post-synaptic monoamine transmission [17, 18]. Second-generation antidepressants (SGAs) include several different classes of drugs with more selective profile and fewer side effects brought on the market in the early 1980s. These include the selective serotonin reuptake inhibitors (SSRI), serotonin–noradrenaline re-uptake inhibitors (SNRI), noradrenaline–dopamine reuptake inhibitors (NDRI) and noradrenaline reuptake inhibitors (NRI) which block more or less specifically the respective re-uptake transporter molecules. Noradrenergic and specific serotonergic antidepressants (NASSA), with mirtazapine as the only representative, block the presynaptic alpha 2 noradrenergic receptors as well as several serotonergic receptors. Moreover, there is a class of third-generation drugs (TGAs), characterized by compounds with non-monoaminergic mechanisms. Most of these compounds are based on peptidergic, glutamatergic or circadian rhythm related mechanisms, but a few still relate to a monoaminergic mechanism [19].

PHARMACOKINETICS

Cytochrome P450

The cytochrome P450 (CYP) system is a group of isoenzymes located primarily in the endoplasmic reticulum of hepatic cells. They catalyze oxidative or reductive reactions of endogenous lipophilic (steroids, bile acids, fatty acids, prostaglandins) and exogenous compounds (drugs) into more polar (hydrophilic) products, allowing their elimination in the urine. The human genome comprises 57 CYP genes which are classified according to sequence homology into 18 families and 44 subfamilies. The CYP 1 to 3 families are involved in phase I drug metabolism, whereas CYP 4 to 51 are associated with

endobiotic metabolism [20]. The metabolic activity of CYPs is genetically determined and mutations or polymorphisms in genes coding for CYP isoforms can result in enzyme variants with higher, lower or no activity. As shown in Table 1, the isoenzymes CYP1A2, CYP2C9/19, CYP2D6, and CYP3A4 are the major enzymes that catalyze antidepressant metabolic reactions [21]. In particular, most ADs are metabolized by polymorphic CYP2D6 and CYP2C19, and the differences in pharmacokinetic parameters like clearance or half-lives between the specific genotypes are extensively large [22, 23].

The *CYP2D6* gene is highly polymorphic. More than 100 known allelic variants and subvariants have been identified, and there are substantial ethnic differences in the observed allele frequencies (Cytochrome P450 Nomenclature Committee at <http://www.cypalleles.ki.se>) [24]; however, many alleles are not typically tested for it in the clinical trials. The most commonly reported alleles are categorized into functional groups as follows: functional (e.g., *CYP2D6**1 and *2), reduced function (e.g., *CYP2D6**9, *10, and *41), and nonfunctional (e.g., *CYP2D6**3–*6) [24, 25]. As *CYP2D6* is subject to deletions or duplications, most clinical laboratories also report copy number. Deletions are indicated by the *CYP2D6**5 allele, and gene duplications are denoted by an “xN” following the allele (e.g., *CYP2D6**1xN, where xN represents the number of *CYPD6* gene copies) [10, 24]. According to

the number of gene copies or alleles inherited, individuals are classified as poor (PM), intermediate (IM), extensive (EM), or ultrarapid metabolizers (UM). Several studies have investigated the influence of CYP2D6 variants on clinical outcomes in patients treated with ADs [15]. Indeed, while some investigations reported positive association with therapeutic effects or side effects [26], other found lack of association [27]. Interestingly, the Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association established dose recommendations for several TCA, SSRI and SNRI on the basis of CYP2D6 genotype [28]. Unfortunately, the heterogeneity of studied populations caused controversy about the association between CYP2D6 genotype and therapeutic effects or side effects [15].

Similar to *CYP2D6*, the *CYP2C19* gene is highly polymorphic; at least 35 allelic variants and subvariants (*1B to *28) have been identified [29]. Although there are ethnic differences in allele frequencies, the majority of patients carry a *CYP2C19**1, *2, or *17 allele [29]. *CYP2C19**1 is the wild-type allele encoding a fully functional enzyme, and *CYP2C19**2 is the most common loss-of-function allele. The *CYP2C19**17 allele results in the enhanced gene transcription probably with an increase of its metabolic activity. Pharmacogenetic studies investigating the influence of CYP2C19 variants on antidepressant outcome actually did

Table 1. CYP isoforms responsible for the biotransformation of antidepressants. Based on Spina et al., 2008 [21]

Antidepressant	Enzymes responsible for biotransformation
Tricyclic antidepressants (demethylation)	CYP2C19, CYP1A2, CYP3A4
Tricyclic antidepressants (hydroxylation)	CYP2D6
Fluoxetine	CYP2D6, CYP2C9, CYP2C19, CYP3A4
Paroxetine	CYP2D6, CYP3A4
Fluvoxamine	CYP1A2, CYP2D6
Sertraline	CYP2C9, CYP2C19, CYP2D6, CYP3A4
Citalopram	CYP2C19, CYP2D6, CYP3A4
Escitalopram	CYP2C19, CYP2D6, CYP3A4
Venlafaxine	CYP2D6, CYP3A4
Duloxetine	CYP2D6, CYP1A2
Milnacipran	CYP3A4
Mirtazapine	CYP2D6, CYP1A2, CYP3A4
Reboxetine	CYP3A4
Trazodone	CYP3A4
Nefazodone	CYP3A4
Bupropion	CYP2B6
Agomelatine	CYP1A2
Vilazodone	CYP3A4, CYP2C19, CYP2D6

not reach univocal results. While some studies indicated that *CYP2C19*17* increased the probability of therapeutic failure for antidepressants due to altered drug plasma concentrations, other did not confirm this finding [30-35]. Interestingly, de Vos et al. [31] investigated the relationship between *CYP2C19* genotypes and metabolic parameters, including serum levels corrected for dose and metabolic ratio (MR), and found a significant association between *CYP2C19*17* allele and decreased MR for citalopram and amitriptyline. Moreover, homozygous *CYP2C19*17* genotype was associated with lower serum concentration of escitalopram, which might imply increased risk of therapeutic failure [32].

P-glycoprotein

Polymorphisms in the drug transporter gene *ABCB1*, coding for P-glycoprotein (P-gp), a member of the ATP-binding cassette superfamily of membrane transport, account for differences in the clinical efficacy of many ADs, most likely by influencing their access to the brain [36]. The polymorphisms within *ABCB1* could influence intracerebral drug concentrations and, thereby, clinical response of patients treated with ADs which are substrates of P-gp like paroxetine, venlafaxine, fluoxetine and citalopram [36]. Several studies have investigated the possible association between *ABCB1* variants, including the three most important SNPs rs1045642, rs2032582, and rs2032583, and antidepressant response and/or frequency of ADR [37-42]. However, the results of these investigations are somewhat controversial. Roberts et al. [37] showed no association between clinical response to nortriptyline (or fluoxetine) and rs1045642. A significant positive association was reported between the rs2032582 and response to paroxetine treatment [39]. Furthermore, *ABCB1* gene polymorphisms were associated with the clinical response to paroxetine in patients with MDD [39]. On the other hand, a subsequent study failed to replicate these findings [43]. Furthermore, the associations observed between *ABCB1* SNPs and paroxetine treatment response were not noted with other antidepressants [40]. Uhr et al. [44] used a tagging approach to investigate the influence of *ABCB1* SNPs in patients treated with various ADs (venlafaxine, citalopram, paroxetine, amitriptyline

and mirtazapine). They evaluated the possibility of a link between remission rates in antidepressant-treated patients and all the *ABCB1* gene variants identified. No association was found between treatment response and the rs1045642 or rs2032582 polymorphisms [44]. This finding in relation to the rs1045642 or rs2032582 was subsequently replicated for citalopram, following the analysis of data from the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) sample of depressed patients [37]. Furthermore, negative findings were also reported for rs10280101, rs7787082, rs2032583, rs2235040 in patients treated with duloxetine [45] and for rs2032582 in patients receiving amitriptyline [46].

PHARMACODYNAMICS

Monoamine metabolic enzymes

Tryptophan hydroxylase (TPH)

Tryptophan hydroxylase (TPH) catalyzes the first, rate-limiting step in serotonin (5-HT) synthesis, the hydroxylation of the essential amino-acid tryptophan to 5-hydroxytryptophan, which is further decarboxylated to 5-HT by the aromatic L-amino-acid decarboxylase. There are two different *TPH* genes that encode two different homologous enzymes TPH1 and TPH2. TPH1 is mostly expressed in the skin, gut and pineal gland but it is also expressed in the central nervous system, while TPH2 is exclusively expressed in neuronal cell types and is the predominant isoform in the central nervous system [47, 48]. Several studies suggested a role of TPH1 and TPH2 polymorphisms and response to ADs. In particular, rs1800532 polymorphism within TPH1 showed an association with both antidepressant clinical response and side effect profile [49, 50, 51]. Other polymorphisms such as rs1843809, rs1386494, rs1487276, rs10897346, rs1487278 and rs2171363 within TPH2 showed an association with antidepressant response [52, 53, 54]. These data suggest a role of these genes in the clinical outcome to antidepressant treatment.

Catechol-O-methyl transferase (COMT)

Catechol-O-methyltransferase (COMT) is one of several enzymes involved in the metabolism of catecholamines (dopamine, adrenaline and noradrenaline) [55]. Among several polymorphisms, the *COMT* functional polymorphism

val(158)met (rs4680) is one of most intensively studied variants in psychiatric genetics. This polymorphism is associated with three-to-four-fold variation in COMT enzyme activity and it is also associated with an individual variation in COMT thermal instability [56]. Several studies investigated and showed an association between rs4680 and response to treatment with paroxetine, fluoxetine or mirtazapine [57-61]. However, other studies failed to replicate such an association [62, 63]. Other COMT SNPs were studied for association with antidepressant treatment. In a clinical trial in patients with MDD, Perlis et al. [64] found an association between rs165599GG, rs174696CC and rs165774GG genotypes and response to duloxetine treatment. Furthermore, Kocabas et al. [65] carried out a study to define the functional impact of COMT genotypes/haplotypes on susceptibility and treatment response phenotypes of MDD. None of the seven SNPs under investigation (rs2075507, rs737865, rs6269, rs4633, rs4818, rs4680, and rs165599) was significantly associated with MDD after permutation correction in single SNP analyses [65]. However, the combinations of G-T-G-G haplotype for rs6269, rs4633, rs4818 and rs4680 were only present in the MDD group and some haplotypes predicted response to treatment as well [65]. Although no replication studies have been performed so far, this result supports the role of COMT gene variants in the antidepressant response.

Monoamine Oxidase A (MAO-A)

There are two types of monoamine oxidases (MAO) in humans: MAO-A and MAO-B, and both are found in the central nervous system, in particular in neurons and astroglia. MAO-A is a major degrading enzyme in the metabolic pathways of monoamine neurotransmitters (dopamine, noradrenaline and serotonin). For this reason, polymorphisms within the MAO-A gene may influence treatment outcomes in patients with MDD. In particular, polymorphism in the promoter region of the MAOA gene, consisting of the repetitive sequence (VNTR), has been linked to variations in biological activity and, consequentially, in serotonin concentrations [66]. However, the results of studies examining the influence of this polymorphism on antidepressant response are inconsistent [67-71]. Others polymorphisms within this gene were more marginally studied, with some positive, but not replicated results. In particular, Peters et al. [52] found an association

between rs1465108 and rs6323 and fluoxetine response, while Tadic et al. [67] reported an association between rs1799835 and mirtazapine response, but only in female patients. Finally, the MAOA gene may be involved in placebo response [72].

Serotonergic system

Serotonin transporter (SLC6A4)

The serotonin transporter (SERT) gene, *SLC6A4*, encodes the protein responsible for the reuptake of serotonin from the synapse after its release from the serotonergic neurons. It is a target of primary interest in the pharmacogenetics of antidepressants because it is the principal site of action of many ADs (mainly SSRI, SNRI, TCA). The *SLC6A4* gene is located on chromosome 17 (17q11.1-q12) and has two well-studied polymorphisms [73]. The most investigated variant of this gene is located in the promoter region (5-HTTLPR) and it is able to impact the expression of SERT. It is a 44 bp insertion/deletion involving two units in a sequence of sixteen repeated elements: the long (l) allele has twice the expression in the basal state than the short (s) form. This polymorphism has been associated with several psychiatric disorders (i.e. bipolar disorder, anxiety disorders, eating disorders, substance abuse) and to pathological behaviors and personality traits related to anxiety, impulsivity and stress [73]. Concerning the antidepressant pharmacogenetics, the increasing evidence suggest that in Caucasian l allele is generally associated with better response to ADs, although negative findings were reported as well [73]. A recent meta-analysis showed that in Caucasians 5-HTTLPR may be a predictor of antidepressant response and remission, while in Asians it does not appear to play a major role [74]. Moreover, Murphy et al. [75] showed an interaction between the HTTLPR genotype and the antidepressant used in the side effect profile suggesting that the effect of this polymorphism on outcome may depend on the mechanism of antidepressant action. Finally, other investigations suggested possible interactions between 5-HTTLPR genotype and drug plasma concentration, augmentation strategies, life events and gender [76-79]. Another polymorphism influencing SERT expression, described as 17bp VNTR polymorphism, was identified within intron 2 (STin2) [80]. Several studies reported an influence of STin2 on response to ADs, but

other investigations were not able to repeat these findings [81-85]. Moreover, it was proposed that STin2 10/12 genotype may be associated with poorer antidepressant effect, especially in Asian populations [86]. While a pilot study suggested that Stin2 10/12 allele was associated with the occurrence of ADRs during the treatment with SSRI [87], a subsequent investigation did not confirm this finding [88]. More recently, rs25531, a single nucleotide polymorphism located just upstream of the 5HTTLPR, has been found to impact the response to ADs and shown to modulate the effect of the other 5HTTLPR alleles [89, 90]. Nevertheless, the results are still controversial with both negative [91, 92, 93], and positive findings [94].

Serotonin receptors

Activation of one or more serotonin receptors may play a role in mediating the antidepressant effects [95].

The 5-HT_{1A} receptors are present pre- and postsynaptically in different brain regions that receive serotonergic input from the raphe nuclei: the frontal cortex, septum, amygdala, hippocampus and hypothalamus [96]. Converging lines of evidence from the animal studies suggest that agonists of 5-HT_{1A} receptors produce antidepressant-like effects [96]. Moreover, its desensitization is thought to be one possible antidepressant mechanism [97]. The 5-HT_{1A} receptor is coded by the *HTR1A* gene that contains about 50 known SNPs. The most investigated *HTR1A* polymorphisms are: rs6295, rs1800042, rs1799921, rs1800044 and rs1799920. The majority of results suggests an effect of the rs6295, functional variant in the promoter region, on treatment outcome with several classes of ADs, but negative results were also reported [97, 98, 99].

The 5HT_{2A} receptor is a post-synaptic G-protein coupled receptor coded by the *HTR2A* gene. The 5HT_{2A} receptors have been reported to mediate some of antidepressant effects seen in the experimental animal models of depression. Three important common variants of the 5HT_{2A} gene, rs6311, rs6313 and rs6314, have been investigated as functional candidates in several psychiatric disorders [15, 100]. These SNPs which are within the coding region of the gene have also been implicated in antidepressant response, although with contradictory results [15, 100].

The 5HT₃ receptors are expressed throughout the central and peripheral nervous system

and mediate a variety of physiological functions. Five different subunits, A-E, of 5-HT₃ genes have been identified. Association studies have been carried out to establish the causal relationships between genetic variants within genes encoding 5HT_{3A} and 5HT_{3B} and side effects profile rather than clinical response [15]. These investigations focused only on SSRI and were performed on Japanese patients exclusively [15].

The 5HT₆ receptor is a G protein-coupled receptor which is expressed almost exclusively in the brain. These receptors have been suggested to play a role in cognitive processes and in mood control, as well as in depression and anxiety [101]. Recently, the C267T variant (rs1805054), in the first exon of the gene, has been investigated for association with response to ADs in several studies. Despite preliminary negative results [102], a subsequent study reported that C/T carriers showed better AD response [103]. Nevertheless, this finding was not replicated by further studies [82, 104].

Noradrenergic system

Noradrenaline transporter (SLC6A2)

Noradrenaline transporter (NET), encoded by *SLC6A2*, mediates reuptake of the released noradrenaline, thus playing a role in the limitation of signaling strength in the central and peripheral nervous systems. NET is also a target for TCA, NET-selective reuptake inhibitors and psychostimulants, including cocaine, methylphenidate and amphetamine [105, 106]. Moreover, NET mutations have been implicated in depression or in some other psychiatric disorders [107, 108]. Several polymorphisms have been identified in the human NET gene such as rs5566, rs5563, rs5558, rs5569, rs36024 and rs2242446 variants which were proved to be functional and impact the effect of ADs [109, 110]. In particular, rs2242466 and rs5569 have been associated with antidepressant response to milnacipran [109] or nortriptyline [110]. Rrs36024, an intronic SNP in the *SLC6A2* was associated with response to treatment with olanzapine-fluoxetine combination in patients with TRD [111]. Interestingly, stressors in early life may interact with polymorphisms in *SLC6A2* to influence the response to antidepressant treatment [112]. In particular, the interaction between exposure to childhood trauma and the AA genotype of rs5569 in *SLC6A2* was found

to be associated with reduced response to ADs. This finding suggested that early life stress, like childhood maltreatment, could interact with genetic variants resulting in significantly poorer antidepressant response [112, 113, 114]. However, results are not unequivocal, and replication studies are warranted.

Adrenoreceptors

Among different adrenergic receptor subtypes, β_1 and α_2A receptors (ADRB1 and ADRA2A) seem to play a role in response to antidepressant treatment. The β_1 -adrenergic receptor is the most abundant subtype in the mammalian brain and known to regulate potently the synaptic plasticity activating the cAMP signaling cascade, as well as non-cAMP pathways such as ion channels. A functional polymorphism in this gene (Gly389Arg) was found to be implicated in the therapeutic response in patients with MDD, causing better and even faster response to treatment with TCA and SNRI [115]. However, another study failed to confirm the relevance of this gene in modulating the response to citalopram treatment [116]. With regard to ADRA2A gene, Perroud et al. [117] showed an association between rs11195419 polymorphism and nor-triptyline treatment-associated suicidal ideation in the GENDEP study.

Dopaminergic system

Dopamine transporter (SLC6A3)

The dopamine transporter (DAT) acts to terminate dopaminergic neurotransmission through reuptake of dopamine from the synaptic cleft into presynaptic neurons. DAT is thought to be implicated in several dopamine-related disorders and, being the target for therapeutic and illicit psycho-stimulant drugs like antidepressants and cocaine, it has been studied intensively [118, 119, 120]. There are at least 502 known variants of this gene. A VNTR polymorphism in the 3'UTR of gene *SLC6A3* encoding the high-affinity dopamine transporter DAT1 was shown to be associated with various psychiatric phenotypes [121], including bipolar affective disorders [122, 123]. Levels of *SLC6A3* expression were higher in carriers of the 10-repeat allele than in carriers of the 9-repeat allele [124]. Kirchheiner et al. [125] showed an association between the 9/10 and 9/9 genotypes and higher risk of poorer and slower response to various ADs than the 10/10

genotype. Moreover, the 10/10 genotype was found to respond preferentially to methylphenidate added to SSRI [126].

Dopamine receptors

Dopaminergic receptors are divided into D1-like family (D1 and D5) and D2-like family (D2, D3, D4) based on their localization in dopaminergic synapses (presynaptic and pre/postsynaptic, respectively) and on their link to different G proteins (Gs and Gi, respectively) [127]. D2-like family was associated with depressive disorder and some evidence suggested an implication of D2 receptors in treatment response [128]. Perlis et al. [129] showed an association between the genetic variants rs167770, rs6280 and rs2134655 within D3 and the olanzapine/fluoxetine combination in patients with bipolar depression. Serretti et al. [130] investigated VNTR polymorphism in exon 3 of D4 receptor gene, in relationship with antidepressant response, unfortunately with negative results.

Glutamatergic system

According to monoaminergic theory, depression is caused by underactivity of brain monoamines (serotonin, dopamine and noradrenaline) and can be improved by medications which correct such imbalance. In recent years, the glutamatergic theory of depression has gained growing interest, as many studies have documented the important role played by the glutamatergic system in the pathophysiology of depression and mechanism of action of ADs [131, 132]. A number of pharmacogenetic studies have evaluated the effect of different glutamatergic polymorphisms on treatment outcome in MDD. In particular, GRIK4 (glutamate receptor, ionotropic, kainate 4) has been repeatedly investigated with controversial results [133, 134, 135]. Recently, Fabbri et al. [136] have investigated 44 glutamatergic genes in 1541 patients with MDD from the STAR*D genome wide dataset. The rs1083801 within the GRM7 (glutamate receptor, metabotropic 7) gene was identified as putative predictor of an early antidepressant response (2nd week) compared to later (from the week 4 to 14), or non-response.

Signal Transduction and Transcription Factors

Guanine nucleotide binding protein (G protein), beta polypeptide 3 (coded by the GNB3 gene)

is present in all cells of the body and it has a key role in the downstream signalling cascade following the monoamine receptor activation [137]. The C825T (rs5443) polymorphism in the *GNB3* gene has been associated with antidepressant treatment response [138]. Keers et al. [139] reported the analysis of data from GENDEP in which the TT genotype of rs5443 was significantly associated with a superior response to nortriptyline. In addition, the same genotype predicted fewer incidents of treatment-emergent insomnia and greater weight gain in the same drug. While one study found that the T allele predicted better antidepressant response [140], another investigation reported an opposite association [141]. On the other hand, Kang et al. [142] found no evidence that this polymorphism was related to therapeutic response in Korean MDD patients treated with mirtazapine.

Glycogen synthase kinase 3 alpha (GSK3-A) is involved in the control of gene expression, cell behavior, cell adhesion and cell polarity, and plays a major role in neurodevelopment, regulation of neuroplasticity and cell survival [143]. Glycogen synthase kinase beta (GSK3-b) is implicated in signaling cascades in response to serotonin, 5HT1 receptor agonists, lithium and antidepressants [144]. Particularly, GSK3A may be an important mediator of serotonin action in the brain and, consequently, of depressive-like behaviors [145]. A promoter single nucleotide polymorphism (rs334558) within GSK3A is associated with transcriptional strength and the T allele has greater activity [146]. This polymorphism is likely to be associated with antidepressant response, as suggested by a study in bipolar depressed patients treated with total sleep deprivation where the TT homozygote showed better response [147]. In contrast to these results, other investigations reported that the C allele resulted in favorable variant [148, 149].

cAMP responsive element binding protein 1 (CREB1) is a member of the leucine zipper family of DNA binding proteins and is under the inhibitory control of several kinases including GSK3A [143]. An increasing number of studies has been recently focused on the role of CREB1 in antidepressant response mechanism. A preliminary investigation suggested that some alleles or haplotypes of CREB1 gene could be related to TRD, but not to response to antidepressant treatment [150]. A recent case-control study of 14 genetic variants within the CREB,

CREB binding protein (CREBBP) and cAMP response element-modulator (CREM) found no association between these genes and diagnosis and treatment response in patients with MDD and bipolar disorder [151]. In conclusion, referring to signal transduction and transcription factors, the above genes have been only marginally investigated and a number of promising genes for their biological function have been proposed (e.g., CAMK2 subtypes, MAPK3 and 1, PRKAR subtypes), but not yet investigated [132].

Hypothalamic-pituitary-adrenal (HPA) axis and stress hormone system

CRH receptors (CRHR1 and CRHR2)

Corticotropin releasing hormone (CRH) receptors 1 and 2 (CRHR1 and CRHR2) are mediators of the effect of glucocorticoids in the central nervous system and, interestingly, CRHR1 antagonists have demonstrated antidepressant effect both in animals and humans [152-155]. The CRHR1 rs242941 G/G genotype and one haplotype block including two other SNPs, rs1876828 and rs242939, were associated with response to fluoxetine [156, 157]. These results were not confirmed by the following studies [158, 159]. On the other hand, rs4792888 showed marginal evidence of association with desipramine response [160]. Other investigations showed a possible involvement of rs2270007 [158] and rs2267716-rs255105 [159] within CRHR2 in citalopram response, and of rs917195 in desipramine efficacy [161].

Glucocorticoid receptor (GR)

The glucocorticoid receptor (GR, coded by the *NR3C1* gene) has been investigated in pharmacogenetic studies. Several polymorphisms within this gene have been described and associated with MDD and antidepressant treatment. In particular, the BclI and ER22/23EK (rs6189 and rs6190) polymorphisms were associated with susceptibility to develop MDD [162, 163]. In addition, both polymorphisms may affect clinical response to antidepressant treatment [163]. Moreover, the rs852977, rs10482633, rs10052957 polymorphisms were associated with the nortriptyline and escitalopram response in the GENDEP study [164]. Notwithstanding, the GENDEP study has not corroborated the role of rs6190 in response to antidepressant treatment [164].

Brain-Derived Neurotrophic Factor (BDNF)

There are several lines of evidence suggesting that Brain-Derived Neurotrophic Factor (BDNF) is involved in both pathogenesis and treatment of depression. An increase in BDNF expression has been recently confirmed in the peripheral cells of depressed patients during the treatment with escitalopram or nortriptyline [165]. Indeed, several treatment modalities (e.g. antidepressant therapy, electroconvulsive therapy, transcranial magnetic stimulation) of depression upregulate the expression of cerebral BDNF [166-169]. Quite a few evidence support an influence of BDNF polymorphisms in antidepressant response. In this respect, the most investigated variant within the BDNF gene is rs6265 (196G/A or Val66Met) [170]. Pharmacogenetic studies mainly suggested a positive molecular heterosis effect [171, 172, 173], together with a more favorable outcome in Met allele carriers [174-177]. On the other hand, Chi et al. [178] and Domschke et al. [179] showed better response in the rs6265 Val/Val genotype. Moreover, several negative findings were also found [180, 181] in the large GENDEP sample [164]. A similar heterosis effect was also reported for another SNP within BDNF (rs90887) [182]. Preliminary findings were provided for other BDNF SNPs (rs90887, rs61888800, rs7124442 and rs11030104) [179, 182, 183]. A strong association was established between rs962369 and an increase in suicidal ideation during antidepressant treatment [117]. Interestingly, some SNPs of the BDNF receptor gene NTRK2 were also associated with AD response [184]. In addition, some variants within NTRK2 and also interactions between variants of BDNF and NTRK2 genes might have effect on antidepressant treatment-associated suicidality [117, 185, 186].

Other gene variants

Besides those described, there are many genes that may influence both the onset and evolution of MDD and the effects of antidepressant treatment. The vascular endothelial growth factor (VEGF) has been implicated in neuroprotection and neurogenesis [187]. Dysbindin gene (dystrobrevin-binding-protein 1, DTNBP1) variants have been associated with several psychiatric conditions including mood disorders and antidepressant efficacy. Pharmacogenetic

studies reported both negative and positive findings concerning the possible association between variants of DTNBP1 gene (rs3213207, rs2005976, rs760761 and rs2619522) and clinical response to SSRI [188-191]. The angiotensin converting enzyme (ACE) acts in the central nervous system to degrade several neuropeptides including substance P. Substance P receptor (NK1) antagonists have been suggested to have possible antidepressant effects. The presence of a deletion variant (D/) in the ACE gene was found to be associated with higher ACE plasma levels, higher substance P levels and faster response to antidepressant treatment [192, 193]. Concerning the Circadian Locomotor Output Cycles Kaput (CLOCK) gene, one study demonstrated significant association between rs3736544 and response/remission to fluvoxamine treatment in a Japanese population [194, 195].

Genome Wide Association Studies (GWAS)

Very recent data have shown that genome-wide association studies (GWAS) and, in particular, copy number variations (CNVs) have created a revolution in our knowledge about many disorders and response to treatment. GWAS is an approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with particular disease. Recently, GWAS have been proposed as most promising technique to overcome the major limitations of candidate gene studies. One of the limits of this methodology is the risk of false positive results [196]. The number of GWAS performed on pharmacogenetics of ADs is limited and the results need replication. Recently, GWAS have been performed within the GENDEP project and the STAR*D [7, 186, 197-200]. One of the major limits of GWAS is their incapacity to detect rare genetic variants (<1% of the population). Indeed, current GWAS technologies are able to detect only association of genetic variants present in 5% or more of the population [197]. So far, the results obtained by GWAS have been disappointing, and, therefore, large meta-analysis to achieve genome-wide significance are needed [201]. Recently, pathway analysis has been proposed in order to balance the limitations of GWAS hypothesis free approach. The basic principle of the method is

Table 2. Summary of the pharmacogenetic association studies focused on antidepressant pharmacological treatment

Genes	Polymorphisms	Drug	Reference		
ABCB1	Rs2032582	Paroxetine	[39; 37-42]		
	Rs2032583		[37-42]		
	Rs1045642				
TPH1	Rs1800532	ADs	[49-51]		
TPH2	Rs1843809	ADs	[52-54]		
	Rs1386494				
	Rs1487276				
	Rs10897346				
	Rs1487278				
COMT	Rs2171363	ADs (in particular Paroxetine; Fluoxetine; Mirtazapine)	[57-63; 65]		
	Rs4680				
	Rs165599			ADs (in particular Duloxetine)	[64; 65]
	Rs174696			Duloxetine	[64]
	Rs165774				
	Rs2075507			ADs	[65]
	Rs737865				
	Rs6269				
MAO-A	Rs4633	ADs	[67-71]		
	Rs4818				
	promoter VNTR				
	Rs1465108			Fluoxetine	
SLC6A4	Rs6323	Fluoxetine	[52; 67]		
	Rs1799835	Mirtazapine			
	5-HTTLPR ins	ADs	[73]		
SLC6A4	STin2	ADs; SSRI	[81-88]		
	Rs25531	ADs	[89-94]		
	Rs6295	ADs	[97-99]		
Rs1800042					
Rs1799921					
Rs1800044					
HTR1A	Rs1799920	ADs	[97-99]		
	Rs6311				
	Rs6313				
HTR2A	Rs6314	ADs	[15; 100]		
	Rs6314	ADs	[82; 103; 104]		
HTR6	Rs1805054				
SLC6A2	Rs5566			ADs	[109; 110]
	Rs5563				
	Rs5558				
	Rs36024				
	Rs5569	ADs (in particular milnacipran, nortriptyline)	[109; 110; 112-114]		
SLC6A2	Rs2242446	Olanzapine-Fluoxetine(combination)	[111]		
	Rs36024				
ADRB1	Gly389Arg	Citalopram; TCA, SNRI	[115; 116]		
ADRA2A	Rs11195419	Nortriptyline	[117]		
SLC6A3	9/10 and 9/9 VNTR	ADs	[125]		
	10/10 VNTR	Methylphenidate plus SSRI	[126]		
D3	Rs167770	Olanzapine-Fluoxetine(combination)	[129]		
	Rs6280				
	Rs2134655				

Genes	Polymorphisms	Drug	Reference
D4	VNTR in exon3	ADs	[130]
GRM7	Rs1083801	ADs	[136]
GNB3	Rs5443	ADs (in particular Nortriptyline, Mirtazapine)	[139-142]
GSK3A	Rs334558	ADs	[146-147]
CRHR1	Rs242941	Fluoxetine	[156-159]
	Rs1876828-Rs242939		
	Rs4792888	Desipramine	[160]
CRHR2	Rs2270007	Citalopram	[158]
	Rs2267716-Rs255105		[159]
	Rs917195	Desipramine	[161]
NR3C1	Rs6189	ADs	[163]
	Rs6190		[163; 164]
	Rs852977	Nortriptyline; Escitalopram	[164]
	Rs10482633		
	Rs10052957		
BDNF	Rs6265	ADs	[164; 170; 174-181]
	Rs90887		
	Rs61888800		
	Rs7124442		
	Rs11030104		
DTNBP1	Rs962369	SSRI	[117]
	Rs3213207		
	Rs2005976		
	Rs760761		
	Rs2619522		
CLOCK	Rs3736544	Fluvoxamine	[194; 195]

the analysis of variants within genes involved in the same biological pathway [202, 203]. Other than pathway analysis, gene - gene interactions can be investigated through the study of epistatic effects, that is, the statistical finding of an interaction between polymorphisms in different genes [204, 205].

CONCLUSIONS

There is great hope that the field of pharmacogenomics will offer personalized medicine treatments based on genetic profiles. Pharmacogenetic studies of antidepressant response have suggested several strong candidate genes involved in the pharmacokinetics and pharmacodynamics of these agents (Table 2). However, comparisons across studies are complicated by a variety of critical methodological aspects such as differences in inclusion criteria, type of medication, outcome measure,

evaluation of adverse effects, genetic coverage and ethnicity. Even when certain polymorphisms appear to show replicable association with the antidepressant treatment response, effect sizes across studies can be very different and it is difficult to discriminate whether the observed differences are chance findings or in fact related to clinical differences in the sample. Some genes also appear to interfere specifically with the response to selected treatments, while others modulate response to various antidepressant treatments, including non-pharmacological interventions. In summary, with more GWAS still outstanding, no clinically tested predictive markers have been yet established and larger, more refined studies on phenotypic and genetic level are needed.

Conflict of Interest Statement

The authors certify that there are no potential conflicts of interest.

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Farmakogenetika lekova protiv depresije: najnovija saznanja

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Farmakološko lečenje depresivnih oboljenja odlikuje se time što postoji loša predvidljivost individualnog odgovora. Poslednjih godina sve veći broj dokaza je pokazao da genetski faktori igraju ključnu ulogu u utvrđivanju razlika u ishodu lečenja antidepresivnim lekovima. Vrš se brojne farmakogenetičke studije o ovim lekovima i otkrivene su genske varijacije na nivou enzima koji metabolišu lekove, transportera leka i ciljnih mesta za dejstvo leka, koji najverovatnije utiču na klinički odgovor. Nadamo se da farmakogenetika može da stvori osnovu za individualizovanu farmakoterapiju depresivnih oboljenja, kako bi se maksimalno povećala mogućnost za dobijanje povoljnog odgovora i smanjio rizik od nastanka neželjenih reakcija na lek. U ovom članku dat je kritički pregled glavnih nalaza u vezi s farmakogenetikom gena uključenih u farmakokinetiku i farmakodinamiku antidepresivnih lekova.

Ključne reči: farmakogenetika; antidepresivi; gen; depresija

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