Pharmacogenetics of antidepressive drugs: a way towards personalized treatment of major depressive disorder

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Major depressive disorder is one of the most prevalent psychiatric disorders, and in spite of extensive ongoing research, we neither fully understand its etiopathological background, nor do we possess sufficient pharmacotherapeutic tools to provide remission for all patients. Depression is a heterogenous phenomenon both in its manifestation and its biochemical and genetic background with multiple systems involved. Similarly, the employed pharmaceutical agents in the treatment of depression also effect multiple neurotransmitter systems in the brain. However, we do not yet possess sufficient tools to be able to choose the medication that treats the symptoms most effectively while contributing to minimal side effects in parallel and thus provide personalized pharmacotherapy for depression. In the present paper we review genetic polymorphisms that may be involved in the therapeutic effects and side effects of antidepressive medications and which, in the future, may guide customized selection of the pharmacotherapeutic regimen in case of each patient.

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Major depressive disorder (MDD) is one of the most prevalent psychiatric diseases with a 5-17% life-time prevalence (Rihmer and Angst, 2005), associated with devastating consequences such as suicide and substantial negative impact on social functioning, including unemployment, academic malachievements, poor interpersonal relationships and substance abuse (Fergusson and Woodward, 2002). In spite of the increasing awareness to the disorder and the persistent efforts concerning early diagnosis and efficient treatment, several phenomena, including "kindling" affecting progression and severity of the disorder, the fact that the number of past depressive episodes increases the likelihood of recurrence, and that rates of recovery diminish with each recurrence, contribute to high treatment failure rates (Frank et al., 1990) making depressive disorders among the leading cause of disability and mortality worldwide. According to a recent survey, it has been estimated that unipolar depression ranks third in terms of disability-adjusted life years (DALYs) and is estimated to become first by the year 2030 (Moller et al., 2012).

Despite the enormous progress made in the understanding of the neurobiology of MDD, treatment outcomes have improved only slightly in the past few decades in spite of the broadening of the target spectrum of antidepressants (ADs). The recent Sequence Treatment Alternatives to Relieve Depression (STAR*D) study indicate that even with systematic measurement-based treatment, only approximately 50% of patients show response to treatment after one treatment trial, and only 30% of patients reach full remission. There is a significant decrease in remission rate after two failed trials, with only 60% reaching full remission after four treatment trials (Rush et al., 2006). The long duration required to conclude treatment success or failure (eight to twelve weeks) can prove to be a difficult and frustrating experience for the patient and the family and may even increase the risk of suicide, and the extended period of time elapsing between partial response and full remission, provides the patients enough power to act out on their suicidal ideations (Sadock et al., 2007). Besides failure to reach remission, relapse rate is also over 40%, especially in patients who did not achieve full remission (Zisook et al., 2008; Sinyor et al., 2010). Treatment resistant depression (TRD) is an extremely common problem, affecting a large proportion of all patients suffering from major depressive episodes (Rush et al., 2006; Trivedi et al., 2006).

Besides efforts to optimize treatment efficacy, adverse drug reactions (ADR) also have to be considered when selecting antidepressive treatment. ADRs are major causes of non-compliance and non-adherence to treatment. Given the frequency of ADRs estimated about 40-90%, the American College of Physicians recommends that when clinicians choose a pharmacologic therapy to treat patients with an acute episode of major depression, they select one of the twelve second-generation ADs available on the market on the basis of ADR profiles, cost and patient preferences (Gartlehner et al., 2008).

Since genetic factors contribute for about 50% of the AD response (Porcelli et al., 2012; Crisafulli et al., 2011), pharmacogenetic researchers have assumed that in order to minimize disorder duration and reduce the occurrence of ADRs it would be useful to be able to predict the pharmacological intervention likely to be effective and tolerable for each patient according to the patient's specific genetic makeup. Evidence from pharmacogenetic research suggests 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 AD response might lead to the development of a new class of medications. With this as a goal, personalized medicine refers to the application of patient-specific profiles incorporating genetic and genomic data as well as clinical and environmental factors, with the perspective of providing more effective treatment individually tailored to a given patient or small patient sub-populations sharing important genotypical and phenotypical features on the level of pharmacokinetic and pharmacodynamics processes (Porcelli et al., 2012; Crisafulli et al., 2011).

PHARMACOKINETICS

Cytochrome P450 enzyme system

The cytochrome P450s (CYPs) are members of a superfamily of oxidative enzymes, and act as the major system for phase I oxidative metabolism of approximately 80% of the commonly used therapeutic substances (Lee and Kim, 2011). This important endogenous system has received the most attention by pharmacogenetic researchers, leading to the discovery of 58 different human CYP genes (Nelson, 2009) with various polymorphisms that affect drug metabolism (Dorne et al., 2005). The variations of DNA within the coding genes may contribute to excessive metabolism as well as diminished or absent metabolism of a drug, leading to the prolonged presence of a toxic dose or failure to reach therapeutic dose of the given medication (Johansson and Ingelman-Sundberg, 2011).

The clinically most important isoenzymes of hepatic CYPs, regarding AD metabolism, are CYP1A2, CYPC9/19, CYP2D6, CYP3A4 and CYP2B6 (Ingelman-Sundberg et al., 2007; Porcelli et al., 2011a). The majority of ADs (fluoxetine; fluvoxamine; paroxetine; venlafaxine; mirtazapine; amitriptyline; imipramine; trimipramine; desipramine; nortriptyline) are metabolized primarily by CYP2D6 (Porcelli et al., 2011b; Porcelli et al., 2011a). CYP2C19 is responsible for the metabolism of moclobemide, sertraline, citalopram, escitalopram, amitriptyline and imipramine, while CYP1A2 plays a major role in the metabolism of fluvoxamine, duloxetin, agomelatine and mianserin. CYP3A4 metabolizes citalopram, escitalopram, mirtazapine, trazodone, nefazodone, reboxetine and mianserine. The metabolism of bupropion is solely related to the CYP2B6 izoenzyme (Porcelli et al., 2011b; Lee and Kim, 2011).

It is mentionable that ADs may interact with other CYP izoenzymes than those which are primarily responsible for their metabolism. For example bupropion is a moderate CYP2D6 inhibitor (but it is metabolized by CYP2B6) and duloxetine is also a moderate CYP2D6 inhibitor (but CYP2D6 takes only a minor part in the metabolism of duloxetine) (Spina et al., 2012).

CYP2D6

CYP2D6 is the most researched gene in the field of pharmacogenetics, and more than 100 different alleles were identified which determine the level of activity of the enzyme — and consequently the effects of drugs metabolized by the 2D6 pathway, including the majority of ADs (Porcelli et al., 2011b). According to the number of gene copies inherited, individuals are classified as poor (PM), intermediate (IM), extensive (EM), or ultrarapid metabolizers (UM). The "wild" genotype of EM individuals carrying two active alleles serves as the reference genotype for other studies. PM patients carrying two partially or totally defective alleles, due to the markedly reduced AD metabolism and the consequential high levels of the drug in the blood frequently complain of ADRs at lower dosages and are occasionally determined as non-compliants (D'Empaire et al., 2011). UM individuals usually have multiple copies of the allele contributing to significantly increased enzymatic activity, causing a need

of higher dosages to reach therapeutic plasma level (Gaikovitch et al., 2003).

Comparing side effects of amitriptyline in subjects with different CYP2C19 and CYP2D6 genotypes, Steimer et al. (2005) showed that the lowest risk of ADRs and drug toxicity was in individuals carrying two functional CYP2D6 alleles and only one functional CYP2C19 allele. This may be used to reduce treatment cost, since amitriptyline, despite its high efficacy, has been replaced in various countries by more expensive drugs due to its low tolerability and high toxicity in some patients (Steimer et al., 2005). Lobello et al. (2010) reanalyzed data from four previous studies on MDD patients and concluded that venlafaxine treatment was associated with greater efficacy in EMs compared to PMs, without important tolerability differences (Lobello et al., 2010). Results from the STAR*D study suggest that response or tolerance to citalopram therapy does not depend on CYP2D6 and CYP2C19 genotype (Peters et al., 2008; Narasimhan and Lohoff, 2012). At the same time, IM status regarding CYP2D6 metabolic activity was demonstrated to be associated with better treatment response to escitalopram in a Chinese population (Tsai et al., 2010; Porcelli et al., 2011a).

CYP1A2

A gene x environment effect has been shown concerning the CYP1A2 izoenzyme, in which the presence of an exogenous inducer, tobacco smoke affects transcription and translation and may contribute to an UM phenotype, resulting in an up to 50% reduction in plasma concentration of ADs (e.g. fluvoxamine and duloxetine) metabolised primarily by this CYP isoenzyme (Sachse et al., 1999; Sepulveda, 2012; Knadler et al., 2011). Some CYP1A2 polymorphisms (rs4646425; rs2472304; rs2470890) may also influence treatment response to paroxetine according a report by Lin et al. (Lin et al., 2010).

CYP2C19

Several allelic variants were discovered in the past decades for CYP2C19 (Lee and Kim, 2011). The proportion of PMs is approximately 3-5% among Caucasian and 20% among Asian individuals (Lee and Kim, 2011). In contrast to the above discussed results of Peters et al. (Peters et al., 2008), Mrazek et al. (Mrazek et al., 2011) reported that genetic variations of CYP2C19 are associated with citalopram response and tolerance. Another study in a Chinese population found an association between some CYP2C19 variants and adverse effects of citalopram (Yin et al., 2006; Sepulveda, 2012).

P-Glycoprotein

P-glycoprotein (P-gp) is a member of the ATP-binding cassette superfamily of membrane transport proteins encoded by the ABCB1 gene also known as the multidrug resistance protein 1 (MDR1) gene. P-glycoprotein 1 is found in various human tissues, including the endothelial cells of the blood-brain barrier (BBB) and is responsible for the efflux of many exogenous and endogenous substances against a concentration gradient influencing antidepressant concentrations in the brain as well. In various animal studies, most ADs have been shown to be substrates of P-gp (e.g., amitriptyline, nortriptyline, citalopram, venlafaxine, sertraline and trimipramine) (Uhr et al., 2008). Although several investigations were conducted about the effects of genetic variations in ABCB1 gene and treatment response to /side effects profile of different ADs, results of these studies are contradictory (Narasimhan and Lohoff, 2012; Horstmann and Binder, 2009).

PHARMACODYNAMICS

Monoamine transporters

Serotonin Transporter (SLC6A4)

The human serotonin transporter (5-HTT) gene is potentially involved in mood regulation and the great majority of currently used ADs influences the activity of 5-HTT, making it an ideal candidate for pharmacogenetic studies. A 44-bp insertion/deletion polymorphism with 2 allelic forms within the serotonin transporter gene promoter region (5-HTTLPR) that could affect SLC6A4 expression (Heils et al., 1996) was shown to have functional significance with the long allele (l) associated with two times higher 5-HTT expression in the basal state compared to the s allele according to in vitro studies (Homberg and Lesch, 2011). Although some results are contradictory and some metaanalyses (Taylor et al., 2010) did not find an association between 5-HTTLPR and treatment response, more recent and exhaustive metaanalytic studies in Caucasian subjects report that presence of the s allele is associated with lower response and remission (Porcelli et al., 2012). An SNP of the SLC6A4 gene promoter (rs25531) may also influence treatment response (Narasimhan and Lohoff, 2012). Results on association between another VNTR varia-

tion of the SLC6A4 gene (STin2) and treatment point to a role of this polymorphism in AD response as well (Narasimhan and Lohoff, 2012).

Noradrenalin Transporter (SLC6A2)
According to the results of a recent GWAS study certain genetic variations of the noradrenalin transporter may be associated with the risk of MDD (Bosker et al., 2011; Sepulveda, 2012). In addition, the noradrenalin transporter is the principal site of action of some ADs (e.g. NARIs, SNRIs). Yoshida et al. (Yoshida et al., 2004) reported that the A/A genotype of the noradrenalin transporter G1287A polymorphism (rs5569) is associated exclusively with a slower onset of response to milnacipran but with no effect on the final clinical improvement (they also reported that carrying the T-allele of the -182C/T (rs 2242446) polymorphism is associated with greater response to milnacipran). Moreover, Kim et al. (Kim et al., 2006) showed a positive association between rs5569 G/G genotype and better response to nortriptyline, although no effect on SSRI response has been detected. At the same time, findings from the GENDEP study did not confirm the role of rs5569 in the treatment response to nortryptiline, but suggest that other variants of the noradrenalin transporter gene (rs36029 and rs1532701) may predict AD response (Uher et al., 2009). Baffa et al. (Baffa et al., 2010) have found that an insertion/deletion polymorphism (rs58532686) in the enhancer region of the noradrenalin transporter gene was significantly associated with treatment response (Baffa et al., 2010; Narasimhan and Lohoff, 2012).

Dopamine Transporter (SLC6A3)
It is assumed that dopaminergic mechanisms play an important role in AD drug action, since AD drugs, in particular dopamine/norepinephrine reuptake inhibitor bupropion and specific members of SSRIs (mainly sertraline) modulate activity of the dopamine transporter.

A 40-base pair VNTR polymorphism in the SLC6A3 gene, encoding for the dopamine transporter (DAT) has been associated with expression levels of the transporter. Kirchheiner et al. (2006) showed an association between the number of repeats and the response to AD drugs concluding that the 9/10 and 9/9 genotypes have a higher risk of poorer and slower response to various AD drugs compared to the 10/10 genotype. Moreover, the 10/10 genotype seems to be associated with late-life depression that responds preferentially to methylphenidate added to SSRI treatment (Porcelli et al., 2011a; Lavretsky et al., 2008).

Monoamine Metabolic Enzymes

Tryptophan hydroxylase
The tryptophan hydroxylase (TPH) gene encoding the rate-limiting enzyme in serotonin synthesis has been studied intensively in psychiatric disorders, yielding mixed results. Among the two distinct TPH genes, which encode two different homologous enzymes, the TPH2 form is expressed solely in neuronal cell types and is the predominant isoform in the CNS. Thus, the TPH2 gene is a credible candidate for an association with MDD. Several studies have found that different genetic variations of TPH2 gene (e.g. the functional SNP Arg441His; rs1843809; rs10897346; rs1386494) are associated with response to treatment with ADs or ECT (Narasimhan and Lohoff, 2012; Anttila et al., 2009). However, there are also many negative results concerning SNPs of TPH2 gene (Narasimhan and Lohoff, 2012).

Although the expression of TPH1 is limited in the CNS (it is mainly expressed in the pineal gland) several pharmacogenetic investigations targeted the possible involvement of TPH1 SNPs in treatment response to ADs, however, with inconsistent results (Narasimhan and Lohoff, 2012; Horstmann and Binder, 2009).

Catechol-O-Methyltransferase (COMT)
The COMT enzyme is responsible for the inactivation of various catecholamines including dopamine, adrenalin and noradrenalin It has been hypothesized that there is an interaction between the dopaminergic and serotonergic systems in the development of depression and the response to AD treatment (Arias et al., 2006). The COMT gene has several allelic variants, including the most extensively studied rs4680 variant. A functional G to A SNP at codon 158 leading to a Val to Met substitution was identified contributing to a high activity Val/Val, intermediate activity Val/Met, low activity in Met/Met genotype (Lachman et al., 1996). It has been shown that the Met allele results in a 3- to 4-fold lower enzymatic activity than the Val allele (Lachman et al., 1996). A pharmacogenetic study indicated that the Val variant was associated with better response to mirtazapine (but not paroxetine) (Szegedi et al., 2005). In other studies this variant was not associated with treatment response to duloxetine, and the Met allele was associated with better treatment response to paroxetine, fluoxetine and fluvoxamine and faster (but not greater) response to milnacipran (Perlis et al., 2009; Narasimhan and Lohoff, 2012; Benedetti et al., 2010). Effects of other SNPs in the

COMT gene were also investigated on AD response with inconclusive results (Houston et al., 2011).

Monoamine Oxidase A (MAO-A)

MAO-A is one of the enzymes responsible for the degradation of monoamine neurotransmitters. One polymorphism in the promoter region of the MAO-A gene consisting of a repetitive sequence (VNTR) has been linked to variations in the biological activity and consequentially serotonin concentrations (Sabol et al., 1998). Variants with 3.5 or 4 copies of the repeat sequence ("MAO-A High") are expressed 2-10 times more efficiently than those with 2, 3 or 5 copies of the repeat ("MAO-A Low") (Sabol et al., 1998; Porcelli et al., 2011a). Because the activity of MAO-A influences neurotransmitter concentrations, the above discussed VNTR may affect AD response, results of studies are, however, inconsistent (Narasimhan and Lohoff, 2012; Porcelli et al., 2011a) Tadic et al., 2007; Tzeng et al., 2009). Similarly, the effect of this polymorphism on AD treatment-associated side effects is also contradictory (Porcelli et al., 2011a). Another polymorphic site of the MAO-A gene, rs6323 (an SNP associated with diminished MAO-A activity) also has been associated with AD-treatment outcome is (Narasimhan and Lohoff, 2012).

Monoamine Receptors

Monoamine receptors are among the most plausible candidates for modulation of AD response, since most ADs act to increase monoamine concentration in the synaptic cleft.

5-HT$_{1A}$ Receptor

The 5-HT$_{1A}$ receptor is located both pre- and post-synaptically and widely distributed in regions that receive serotonergic input from the raphe nuclei: the frontal cortex, septum, amygdala, hippocampus and hypothalamus (Narasimhan and Lohoff, 2012; Sharp et al., 2007). It also serves as the predominant (somatodendritic) autoreceptor of the raphe nuclei, reducing the firing rate of neurons in these, the amount of serotonin released per action potential, and the synthesis of the neurotransmitter; and thus by implication the serotonergic activity of its projection areas (Kreiss and Lucki, 1994). Converging lines of evidence from animal studies suggest that agonists of 5-HT$_{1A}$ receptors produce antidepressant-like effects (Carr and Lucki, 2011). A role for this gene in the AD response has been postulated because several ADs, similar to pindolol and buspirone, desensitize raphe 5-HT$_{1A}$ autoreceptors, leading to an enhancement of the serotonergic neurotransmission that might accelerate the AD action (as desensitization comes true only after ≈2 weeks of continuous AD treatment it lasts 2-3 weeks for ADs to begin to act) (Shrestha et al., 2012).

About 50 known SNPs have been described regarding the 5-HT$_{1A}$ autoreceptor. One of the most intensively investigated functional polymorphism (rs6295; a.k.a. 1019C/G) is in the promoter region of the gene for 5-HT$_{1A}$ receptor (Stahl, 1994). The majority of results suggests an effect of the rs6295 on treatment outcome with several classes of ADs, but negative results were also reported (Narasimhan and Lohoff, 2012; Porcelli et al., 2011a). Noteworthy, some studies suggest that the effect of rs6295 on AD response is confined to some subpopulations of patients (e.g. females or patients with melancholic depression) (Yu et al., 2006; Baune et al., 2008; Porcelli et al., 2011a).

Some other variations of this gene (rs10042486 and rs1364043) were found to be associated with altered AD response while the role of others (Gly272Asp; a.k.a. rs1800042) remained dubious (Porcelli et al., 2011a; Narasimhan and Lohoff, 2012).

5-HT$_{2A}$ Receptor

The 5-HT$_{2A}$ receptor is a post-synaptic G-protein coupled receptor expressed widely throughout the CNS playing a role in mediating anxiety, sleep and sexual function (Landolt and Wehrle, 2009). Interest in this receptor has been stimulated by its possible roles in hallucination and psychosis, concluded from the fact that it has a role in mediating the action of atypical antipsychotics such as clozapine (Meltzer et al., 1989). Furthermore, agonists at the 5-HT$_{2A}$ receptor, including lysergic acid diethylamide (LSD), have hallucinogenic properties that correspond to their affinities for these receptors (Glennon et al., 1984). More importantly, several findings suggest that 5-HT$_{2A}$ is deeply involved in the pathophysiology of depression and its treatment (Meyer et al., 2001; Yamauchi et al., 2006; Bhagwagar et al., 2006). For example, 5-HT$_{2A}$ receptors are downregulated during AD treatment and ECT (Carr and Lucki, 2011; Yatham et al., 2010). In addition, antagonists of 5-HT$_{2A}$ have antidepressant effects in animal models (Carr and Lucki, 2011; Millan, 2006). Furthermore, the administration of 5-HT$_{2A}$ antagonists diminishes stress-induced reduction in BDNF expression (McMahon et al., 2006).

Three important common SNPs of the 5HTR2A gene are 102T/C (rs6313), 1438A/G (rs6311) and

452His/Tyr (rs6314). In postmortem studies the C variant of 102T/C was associated with lower mRNA and lower protein expression compared to the T variant (Polesskaya and Sokolov, 2002) and the A variant of 1438A/G significantly enhanced promoter activity compared to the G variant (Parsons et al., 2004). Overall, several studies have found that rs6313, rs6311 and rs6314 SNPs are associated with response to AD treatment, but negative results also exist (Narasimhan and Lohoff, 2012; Horstmann and Binder, 2009). Another genetic variant of the 5HTR2A gene (rs7997012) is also associated with success of AD treatment (but results are somewhat ambiguous) (Horstmann and Binder, 2009; Horstmann et al., 2010; Porcelli et al., 2011a; Narasimhan and Lohoff, 2012).

Several studies found significant association of 1438G/G or 102C/C with appearance of ADRs (Narasimhan and Lohoff, 2012; Kato et al., 2006; Wilkie et al., 2009). There were inconsistent results between Asian and Caucasian samples, a fact which may lead to the hypothesis that other SNPs or cultural or social differences could also influence ADs response (gene x environment interaction). These results suggest that these SNPs could be useful in predicting intolerance to SSRIs, and have a possibility to be a marker of treatment response to SSRIs in Asian-origin individuals (Kato and Serretti, 2010).

5-$HT_{3A/3B}$ Receptors

These receptors are expressed throughout the CNS and peripheral nervous system and mediate a variety of physiological functions. Up to now, five subtypes of 5-HT_3 genes have been cloned and 5-HT_{3A} and 5-HT_{3B} have been best characterized and identified to have some genetic polymorphisms (Porcelli et al., 2011a). A study in an Asian sample showed an association of 5-HT_{3A} 178 C/T (rs1062613) polymporphism with treatment response to SSRIs (Kato et al., 2006). The same study also reported that an AAG deletion variant in the 5-HT_{3B} also influences treatment response (Kato et al., 2006; Narasimhan and Lohoff, 2012). Furthermore, the AAG deletion variant and another polymorphism (129Tyr/Ser; a.k.a. rs1176744) of 5-HT_{3B} gene and the 178C/T variation of 5-HT_{3A} gene were also associated with SSRI treatment-evoked ADRs in some studies, but not in others (Narasimhan and Lohoff, 2012; Kato et al., 2006; Suzuki et al., 2006; Porcelli et al., 2011a; Sugai et al., 2006; Tanaka et al., 2008). However, all of these studies focused only on SSRIs and were performed on in Japanese samples exclusively. Given the small number of studies performed, and the lack of diversity in the studied group, further studies are needed.

5-HT_6 Receptor

The 5-HT_6 receptor is a Gs coupled receptor expressed almost exclusively in the brain. The 5-HT_6 receptor gene is an interesting candidate gene since the 5-HT_6 receptor influences the release of several neurotransmitters (ACh, NE, GABA and DA); furthermore, some specific ligands of this receptor have antidepressant effects in animal models. In addition, 5-HT_6 agonists – similarly to SSRIs – stimulate BDNF secretion in the hippocampus and the cortex and several psychotropic agents (including antidepressants and antipsychotics) exert antagonistic activity on these receptors (Carr and Lucki, 2011) (Yun and Rhim, 2011). Within the 5-HT_6 receptor gene there is a silent SNP (rs1805054; a.k.a. C267T) associated with treatment response to ADs according to some studies, but not others (Narasimhan and Lohoff, 2012).

Adrenoreceptors

According to our current knowledge, among the different adrenergic receptor subtypes, the β_1 and α_{2a} receptors seem to play a role in response to AD treatment (Porcelli et al., 2011a). The β_1 adrenoreceptor regulates various neural functions (e.g. memory, mood, neuroendocrine regulation) (Porcelli et al., 2011a). Furthermore, several treatment modalities (e.g. pharmacotherapy; electroconvulsive therapy; sleep deprivation; transcranial magnetic stimulation) for depression lead to the down-regulation of β receptors (Fleischmann et al., 1996; Millan, 2006). A recently identified functional polymorphism G(1165)C (a.k.a. rs1801253) in the ADRβ1 gene (encoding adrenergic β_1 receptor), resulting in the amino acid variation Gly389Arg, has been linked to enhanced coupling to the stimulatory Gs protein and increased adenylate cyclase activation. This SNP might be responsible for faster response to AD treatment (Zill et al., 2003). Nevertheless, a study analyzing data from the STAR*D study was unable to confirm the relevance of this gene in modulating the response to citalopram treatment (Porcelli et al., 2011a).

Regarding ADRα2A gene (encoding the α_{2a} adreneregic receptor), recently Perroud et al. (Perroud et al., 2009) showed an association between rs11195419 polymorphism and nortriptyline treatment-associated suicidal ideation in the GENDEP study.

Dopamine Receptors

The dopaminergic system has a pronounced contribu-

tion to the symptomatology of depressive the spectrum. Anhedonia and loss of motivation have recently been linked to catecholaminergic – including dopaminergic – dysfunction (Yadid and Friedman, 2008; Davidson et al., 2010). In addition, the D3 receptor is upregulated in the nucleus accumbens as a consequence of antidepressant pharmacotherapy and ECT treatment, suggesting that a common neurobiological mechanism of different AD treatment modalities lead to enhanced responsiveness of the mesolimbic dopaminergic system (Lammers et al., 2000).

Dopaminergic receptors are divided into D1-like family (D1 and D5) and D2-like family (D2, D3, D4) based on their link to different G proteins (G_s and G_i, respectively) and their localization in dopaminergic synapses (presynaptic and pre/postsynaptic, respectively) (Beaulieu and Gainetdinov, 2011). Members of the D2-like family have a well-established role in the response to antipsychotic treatment, as they are the primary target of antipsychotic medications. Based on recent pharmacogenetic studies, it has been concluded that these receptors are also associated with treatment response in MDD. Perlis et al. (2010) showed an association between D2 rs4245147 SNP and lamotrigine response in bipolar depression. According to some results, the Taq1A allele 1 (rs1800497) in the D2 gene is associated with SSRI-induced extrapyramidal symptoms (Narasimhan and Lohoff, 2012). Negative results about the effect of rs1801028 SNP of the D2 gene on SSRI response were reported by Serretti et al (Serretti et al., 2001). rs1801028 also does not seem to affect efficiency of sleep deprivation in patients with bipolar depression (Benedetti et al., 2003).

Concerning the D3 receptor, Perlis et al. (Perlis et al., 2010) found an association between three SNPs (rs167770; rs6280; rs2134655) and response to olanzapine/fluoxetine combination in patients with bipolar depression.

Another frequently investigated genetic variation is the 48bp exon 3 VNTR polymorphism in the gene encoding the D4 receptor. There is growing evidence that this genetic variation is associated with personality traits (e.g. novelty seeking) and psychiatric disorders (e.g. ADHD and mood disorders) (Simpson et al., 2010). At the same time its effect on AD response is not evident since both positive and negative results were reported (Narasimhan and Lohoff, 2012). Perlis et al. (Perlis et al., 2010) found a marginal association between rs936461 in D4 gene and lamotrigine response in patients with bipolar depression (Perlis et al., 2010; Porcelli et al., 2011a).

Intracellular Signal Transduction Pathways

G Protein β3 subunit

The β3 subunit of the G protein is present in all cells of the body and has a key role in the downstream signaling cascade following monoamine receptor activation (Hamm, 1998). About 80% of hormones, neurotransmitters and neuromodulators elicit cellular responses through G protein coupled to a variety of intracellular effectors. The high degree of complexity generated by the interactions of G protein-coupled receptors may be one mechanism by which neurons acquire the flexibility for generating the wide range of responses observed in the CNS, suggesting a possible involvement in the pharmacogenetics of AD response (Zill et al., 2000; Keers et al., 2011; Narasimhan and Lohoff, 2012).

The C825T (a.k.a. rs5443) functional polymorphism is the most investigated variant within the GNβ3 gene in this field. It was associated with AD treatment response; particularly the T variant seems to predict better AD response. However, both opposite and negative results have been reported, making further research necessary to reach reliable results (Zill et al., 2000; Keers et al., 2011; Narasimhan and Lohoff, 2012).

Hypothalamic-Pituitary-Adrenal Axis and Stress Hormones

Dysregulation or hyperactivity of the HPA axis is one of the most prominent findings in up to 70% of patients with MDD (Porcelli et al., 2011a). It has been reported that alterations of CRH function contribute to the pathogenesis of depression. Studies have found an epigenetic modulation effect in regard to the HPA axis in response to stress, showing that parental stress may influence the HPA reactivity in children for the long term (Entringer et al., 2009). Furthermore, HPA axis dysregulation is responsible not only for the development of depression, but also for the common physical disorders and somatic morbidity associated with depression (Musselman et al., 1998). Administration of most ADs, lithium and valproic acid seems to diminish dysregulation of the HPA axis in depression (Millan, 2006; Porcelli et al., 2011a). In addition, ECT treatment and chronic administration of several antidepressants leads to up-regulation of cerebral mineralocorticoid receptors which result in reinforced inhibitory feedback control of the HPA axis and to a decrease in levels of glucocorticoids available to central glucocorticoid receptors (Millan, 2006).

CRH Receptors (CRHR1 and CRHR2)
Corticotropin releasing hormone (CRH) is a potent mediator of endocrine, autonomic, behavioral, and immune responses to stress. The corticotropin releasing hormone receptor 1 (CRHR1) subtype is considered to play a key role in mediating the CRH-elicited effects in depression and anxiety (Van Pett et al., 2000). Moreover, some studies suggest that CRHR1 antagonists have antidepressive properties (Porcelli et al., 2011a; Seymour et al., 2003).

An association between the rs242941 G/G genotype and homozygous GAG haplotype of the 3 SNPs (rs1876828, rs242939, and rs242941) and therapeutic response to fluoxetine demonstrates relevance of these CRHR1 variants on AD response in Mexican-American population (Licinio et al., 2004). Later this finding was replicated in a Han-Chinese population (Liu et al., 2007). Another study did not find associations between some other variants of CRHR1 gene (rs110402; rs242937) and treatment response to citalopram (Papiol et al., 2008; Horstmann and Binder, 2009). The role of genetic variants of CRHR1 gene in response to citalopram was also raised in the STAR*D study (Horstmann and Binder, 2011). In reference to corticotropin releasing hormone receptor 2 (CRHR2) gene a study has found an association between rs2270007 and citalopram response (Papiol et al., 2008).

Glucocorticoid Receptor (GR)
Hyperactivity of the HPA axis in depression might be caused by impaired glucocorticoid signaling, thus the investigation of effects of genetic variations of GR gene (NR3C1) on AD response is an intensively growing field of pharmacogenetics. It was found that BclI and ER22/23EK (rs6189 and rs6190) polymorphisms were associated with susceptibility to develop MDD (Keers and Uher, 2012; van Rossum et al., 2006). In addition, both polymorphisms may affect clinical response to AD treatment (van Rossum et al., 2006; Narasimhan and Lohoff, 2012). The GENDEP study identified three SNPs (rs852977, rs10482633 and rs10052957) which may predict response to both ADs used in the study (nortriptyline and escitalopram) (Narasimhan and Lohoff, 2012; Uher et al., 2009). Notwithstanding, the GENDEP study has not corroborated the role of rs6190 in response to AD treatment (Uher et al., 2009).

FK506 binding protein 5 (FKBP5)
FKBP5 – a co-chaperone of the hsp-90 – functions as a part of the mature GR heterocomplex, regulating the sensitivity level of this receptor and perhaps modulating treatment response and recurrence of MDD (Binder et al., 2004). This gene is a good candidate on the basis of its relevance to the HPA axis pathways. The possibility that some genetic variants in the FKBP5 gene (rs1360780; rs4713916; rs3800373) may influence AD treatment outcome were suggested by some studies, but results are contradictory. Accordingly, a recent meta-analysis has found that AD treatment outcome is associated with FKBP5 gene rs4713916 polymorphism, but not rs1360780 and rs3800373 (Zou et al., 2010; Narasimhan and Lohoff, 2012). The GENDEP study was also unable to confirm the association between rs1360780 and response to AD treatment (Uher et al., 2009). At the same time, results of "Geneva Outpatient Depression Study" (GODS) and "Treatment of Resistant Depression in Adolescents" (TORDIA) studies suggest that rs1360780 is associated with the risk of AD treatment-associated suicidal behaviour (Perroud et al., 2011; Perroud, 2011).

c-AMP Response-Element Binding protein (CREB)
The c-AMP response-element binding (CREB) protein, a transcription factor, enhances the transcription of genes containing the cAMP response element in their promoter region (Ren et al., 2011; Porcelli et al., 2011a). Products of many of these genes are deeply involved in the pathogenesis of depression (e.g. BDNF; VEGF; CRH) (Porcelli et al., 2011a). Furthermore, several other observations support the involvement of CREB in depression. AD and ECT treatment both up-regulate CREB expression in the brain and accordingly CNS and peripheral (fibroblast; leukocyte; lymphocytes) CREB levels are altered in subjects with depression (Ren et al., 2011; Millan, 2006).

Despite of expectations fuelled by the role of CREB in the pathogenesis of depression, the role of CREB1 variants in AD response was not verified (Dong et al., 2009; Porcelli et al., 2011a; Wilkie et al., 2009). At the same time, a recent preliminary study suggested that some alleles or haplotypes of CREB1 gene could be related to TRD but not to response to AD treatment (Serretti et al., 2011). Furthermore, two SNPs (rs4675690; rs7569963) were found to have a role in treatment-emergent suicidal ideation in patients with MDD during citalopram treatment, but only in males, suggesting a significant gene x sex interaction (Porcelli et al., 2011a; Perlis et al., 2007).

Brain-Derived Neurotrophic Factor (BDNF)

There are several lines of evidence that suggest that BDNF is involved in both pathogenesis and treatment

of depression. Chronic stress leads to decreased levels of BDNF in the brain, and serum/plasma BDNF levels of patients with mood disorders are decreased, while intrahippocampal administration of BDNF has antidepressant actions (in contrast BDNF injection to the ventral tegmental area exerts depression-like state in animals) and several treatment modalities (e.g. AD therapy; ECT; TMS) of depression upregulate the expression of cerebral BDNF (Millan, 2006; Yu and Chen, 2011; Castren and Rantamaki, 2010; Jacobsen and Mork, 2004). The most investigated SNP within this gene is rs6265 which results in valine to methionine (V66M) substitution (Egan et al., 2003). Nonetheless, results on the association between this polymorphism and AD response are still controversial (Narasimhan and Lohoff, 2012; Porcelli et al., 2011a). Results of the GENDEP study have raised the possibility that that there is an association between rs10835210 variation in the BDNF gene and response to escitalopram and a strong association between rs962369 in the BDNF gene and an increase in suicidal ideation during AD treatment (the same study identified some other suicidality related regions in the BDNF gene (a haplotype including rs6265 and the GT(n) repeat) (Uher et al., 2009; Narasimhan and Lohoff, 2012; Perroud et al., 2009; Perroud, 2011). At the same time, a recent investigation in a Korean population has not found an association between rs10835210 and treatment outcome (Pae et al., 2012). The role of other variations of the gene for BDNF (rs61888800, rs7124442 and a haplotype of rs12273363, rs908867 and rs1491850) influencing AD response have also emerged in some studies (Narasimhan and Lohoff, 2012). Interestingly, some SNPs of the BDNF receptor gene NTRK2 are also associated with AD response (Dong et al., 2009; Porcelli et al., 2011a). In addition, some variants of NTRK2 (rs1822420) and also interactions between variants of BDNF and NTRK2 genes may have effects on AD treatment-associated suicidality (Porcelli et al., 2011a; Perroud, 2011; Perroud et al., 2012; Perroud et al., 2009).

Other relevant genes

Angiotensin-Converting Enzyme (ACE)

ACE acts in the CNS to degrade several neuropeptides including substance P. Substance P receptor (NK1) antagonists have been suggested to have possible AD effects, and the level of substance P is decreased after administration of monoamine uptake inhibitors, so the influence of substance P on depressive biological mechanisms and treatment has been hypothesized (Rotzinger et al., 2010; Porcelli et al., 2011b). The presence of an insertion (I/) and deletion (D/) polymorphism in the ACE gene were investigated, reaching a conclusion that the (D/) variant is associated with higher substance P levels and a faster response to AD treatment and total sleep deprivation, particularly among women (Bondy et al., 2005; Narasimhan and Lohoff, 2012; Baghai et al., 2004).

Circadian Locomotor Output Cycles Kaput (CLOCK)

Since depression is often characterized by a disturbance of the circadian rhythms and sleep deprivation and bright light therapy have antidepressant effects, and some polymorphisms in genes of the internal clock system are associated with mood disorders it seems to be obvious to investigate the possible association between genes encoding important actors in the internal circadian timing system and treatment response to AD therapy (Kronfeld-Schor and Einat, 2012; Porcelli et al., 2011a). Although a recent meta-analysis concluded that genetic variations of the CLOCK gene do not keenly influence the risk of mood disorders, one study has demonstrated significant association between rs3736544 and response/remission to fluvoxamine treatment in a Japanese population (Kishi et al., 2011; Kishi et al., 2009).

Glutamatergic system

Glutamate is the primary excitatory neurotransmitter in the mammalian CNS and several hints suggest that glutamatergic signaling is involved in the pathophysiology of depression, including altered glutamate levels reported in the blood and CSF of patients with mood disorders, and several agents exerting their effect through different types of glutamate receptors possessing antidepressant properties (Hashimoto, 2011).

According to results of the STAR*D study an SNP (rs1954787) of the GRIK4 gene encoding kainate receptor subunit 1 (KA1; a.k.a. GluK4) was associated with treatment response to citalopram (Mayer, 2007; Stawski et al., 2010; Narasimhan and Lohoff, 2012; Horstmann and Binder, 2009). This result was confirmed by a preliminary study by Horstmann et al. (Horstmann et al., 2008) in the "Munich Antidepressant Response Signature" project (MARS) (Horstmann et al., 2008; Horstmann et al., 2010; Porcelli et al., 2011a). At the same time, a study did not find an effect of this SNP on response to duloxetine and a later analysis of the MARS study was also not able to corroborate the relevance of this SNP in AD response (Porcelli et al., 2011a; Perlis et al., 2010; Horstmann et al., 2010). Horstmann et al. (Horstmann et al., 2010)

have identified another SNP (rs12800734) in the GRIK4 gene that is more strongly associated with response to treatment. Furthermore, the predictive value of rs12800734 regarding treatment response was better when combined with variations of the 5HTR2A (rs17288723) and FKBP5 (rs1360780) genes (Horstmann et al., 2010).

The influencing role of some genetic polymorphisms of GRIA3 encoding AMPA receptor 3 subunit (GluA3 or GluR3) and GRIK2 encoding kainate receptor subunit 2 (GluK2 or GluR6) in AD-treatment associated suicidality has also emerged in some studies, but results are inconsistent (Perroud, 2011; Stawski et al., 2010; Narasimhan and Lohoff, 2012).

LIMITATIONS IN APPLICATION OF PHARMACOGENETIC ACHIEVEMENTS IN CLINICAL PRACTICE

Despite the impressive potential of pharmacogenetics and the great progress in the understanding of the pathomechanism of MDD and the genetic influence both on emergence of depression and on response to AD treatment, the use of pharmacogenetics in current clinical practice is still very limited, in part due to inconsistent results and failure to replicate several associations. Another problematic issue is the complexity and multifactorial nature of the genetics underlying psychiatric disorders and medication response. Since the therapeutic mechanism of ADs is not well understood, it is difficult for pharmacogenetic researchers to select "candidate" genes.

One challenge faced by pharmacogenetics is that the inter-individual variations in drug metabolism cannot be explained simply by genetic differences and a wide range of non-genetic factors influence drug metabolism. It has been estimated that an individual's drug level dynamically varies as much as 15% over time in response to the individuals' ever-changing environmental exposures from usual activities and lifestyle habits (Alvares, 1984).

The biggest advances concerning the pharmacogenetic prediction of ADRs concern the CYP 450 polymorphisms. However, it is still controversial whether therapeutic efficacy may be improved and/or ADRs could be prevented by the use of genotyping, particular considering that genotype often do not correspond to a well-defined phenotype. The recent approval by the FDA of the AmpliChip® CYP450 Test (Roche Molecular System Inc.), assessing polymorphic variants of CYP2D6 and CYP2C19 may help validate studies on personalized treatment of depression.

CONCLUSION

This review of pharmacogenetic studies encompasses a panel of candidate genes and their association with AD response and ADRs. The studies clearly demonstrate that genetic variation contributes to variability in medication response, with an impact on both efficacy and ADRs. The results of the various meta-analyses indicate a better treatment response to ADs with TPH2 T/T, BDNF 66Met and 5-HTTLPR L allele. 5-HTTLPR L and HTR2A-1438A (102T) were also associated with less AD (particularly SSRI)-induced side effects. Unfortunately, much remains to be done before the field of pharmacogenetics achieves its full potential. According to current findings, the explained variance of single gene polymorphisms seems to be minor, so that only the combination of various gene polymorphisms can realize the idea of individualizing/personalizing therapeutic decisions in individual cases. Clinical research has not yet produced large, replicable findings concerning the impact of genetic variations. This situation will hopefully be remedied as large, multicenter trials begin to collect pharmacogenetic data routinely (Evans and McLeod, 2003). In the most optimistic vision, a single blood test will test for thousands of important drug-metabolizing polymorphisms, making possible selection of a personally tailored ideal drug regimen and dosage for each individual according to the patients' specific genetic makeup. This will hopefully lead to a new era in which unintended consequences and ADRs will be problems of the past, and success will bring a reduction in the burden of MDD for both patients and society (Laje and McMahon, 2011).

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Az antidepresszívumok farmakogenetikája: a major depresszív zavar személyre szabott kezelése felé

A major depresszív zavar az egyik leggyakoribb pszichiátriai betegség, és a kiterjedt kutatások ellenére sem etiopatológiai hátterét nem értjük teljességében, sem olyan megfelelő farmakoterápiás eszközökkel nem rendelkezünk, melyek valamennyi beteg esetében képesek remissziót eredményezni. A depresszió heterogén jelenség mind manifesztációja, mind pedig biokémiai és genetikai háttere tekintetében, és számos rendszer szerepe feltételezhető. Ehhez hasonlóan a depresszió kezelése során alkalmazott farmakoterápiás szerek szintén több neurotranszmitter rendszer funkcióját befolyásolják. Jelenleg azonban nem állnak rendelkezésünkre olyan eszközök, melyek segítségével személyre szabottan választhatnánk ki azt a gyógyszert, mellyel egy adott beteg esetében a terápiás hatások maximalizálhatók a nemkívánatos mellékhatások minimális szinten tartása mellett. Jelen cikkben a szerzők áttekintik azokat a genetikai polimorfizmusokat, melyek szerepet játszhatnak az antidepresszívumok hatásainak és mellékhatásainak kialakulásában, és amelyek a jövőben irányvonalul szolgálhatnak a farmakoterápiás kezelés személyre szabott összeállításában major depresszióban szenvedő betegek esetében.

Kulcsszavak: farmakogenetika, antidepresszívumok, major depresszív zavar, polimorfizmus