



# Pharmacogenetics of antidepressants

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Up to 60% of depressed patients do not respond completely to antidepressants (ADs) and up to 30% do not respond at all. Genetic factors contribute for about 50% of the AD response. During the recent years the possible influence of a set of candidate genes as genetic predictors of AD response efficacy was investigated by us and others. They include the cytochrome P450 superfamily, the P-glycoprotein (ABCB1), the tryptophan hydroxylase, the catechol-*O*-methyltransferase, the monoamine oxidase A, the serotonin transporter (5-HTTLPR), the norepinephrine transporter, the dopamine transporter, variants in the 5-hydroxytryptamine receptors (5-HT1A, 5-HT2A, 5-HT3A, 5-HT3B, and 5-HT6), adrenoreceptor beta-1 and alpha-2, the dopamine receptors (D2), the G protein beta 3 subunit, the corticotropin releasing hormone receptors (CRHR1 and CRHR2), the glucocorticoid receptors, the c-AMP response-element binding, and the brain-derived neurotrophic factor. Marginal associations were reported for angiotensin I converting enzyme, circadian locomotor output cycles kaput protein, glutamatergic system, nitric oxide synthase, and interleukin 1-beta gene. In conclusion, gene variants seem to influence human behavior, liability to disorders and treatment response. Nonetheless, gene × environment interactions have been hypothesized to modulate several of these effects.

**Keywords:** pharmacogenetics, antidepressants, gene, SNP, depression

## INTRODUCTION

Depressive disorders constitute a major public health issue and have been estimated to be the fourth major cause of disability worldwide, and may become second only to cardiovascular diseases in the next two decades (Mathers et al., 2000), thus contributing heavily to the global burden of diseases in man, according to Murray and Lopez (1997), who conducted a study for the World Health Organization (WHO). Unfortunately, depressed patients are not totally satisfied with the current effectiveness and tolerance of available antidepressant (AD) medications. Less than 50% of all patients treated with the currently available ADs show full remission and despite the clear need for better therapies, recent efforts to develop novel ADs have been relatively unsuccessful (Agid et al., 2007). The recent Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial showed that even with systematic measurement-based treatment, approximately one-third of patients reach full remission after one treatment trial, with only two-thirds reaching remission after four treatment trials. Treatment-resistant depression (TRD) is therefore a common problem in the treatment of major depressive disorder (MDD), with 60–70% of all patients meeting the criteria for TRD (Rush et al., 2006a,b; Trivedi et al., 2006a,b). It becomes of great interest to the scientific community and to our patients to report, in future clinical trials, not response rates alone but also remission rates, in order to assess the real clinical AD efficacy. This is relevant in order to improve the still incomplete knowledge of the pathogenetic mechanisms of depression and to better understand the AD mechanisms of action, in order to develop new AD

drugs with a better efficacy and safety profiles. ADs currently available include first- and second-generation drugs. First-generation ADs (FGAs) include monoamine oxidase inhibitors (MAOIs) and tricyclic ADs (TCAs), which became available for therapy in the 1960s. The mechanism of MAOIs and TCAs represented the main evidence for the monoamine hypothesis of depression and major depression (MD), an intrinsically tautological hypothesis which, nevertheless, has driven pharmacological research on depression for over four decades (Blier and de Montigny, 1994; Stahl, 1998). Second-generation ADs (SGAs) include several different classes of drugs that were developed mainly in the 1980s and 1990s, starting with selective serotonin reuptake inhibitors (SSRIs) and including serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors (NARIs), noradrenergic and specific serotonergic ADs (NaSSAs), and 5-hydroxytryptamine 2A (5-HT2A) receptor antagonists/reuptake inhibitors (SARIs). All the SGAs are based on the monoamine hypothesis, with a primary mechanism consisting of monoamine reuptake inhibition and/or antagonism for selected monoamine receptor(s) (Stahl, 1998). Finally, there is a class of third-generation drugs (TGAs), novel compounds that are in most cases characterized by non-monoaminergic mechanisms (although some of these have been in development for quite a while). Most of these compounds are based on peptidergic, glutamatergic, or circadian rhythm-related mechanisms, but a few still relate to a monoaminergic mechanism (Racagni and Popoli, 2008). Nowadays one of the more promising approaches in psychiatric research is pharmacogenetics. The aim

of pharmacogenetics is to detect genetic factors that determine variations both in clinical response and in side effects under pharmacotherapy. It is well known that the large interpatient variability in clinical response to ADs is influenced by a variety of genetic as well as pathophysiological and environmental factors. The basis for such marked interindividual variations in the clinical response to AD treatments is not clear yet. However it seems that at least some of this variation has a genetic basis (Serretti et al., 2005a). Increasing evidence suggests that single nucleotide polymorphisms (SNPs) can be used in clinical association studies to determine the contribution of genetic variance in drugs response (Malhotra et al., 2004; Serretti et al., 2005a; Drago et al., 2009). In recent years, the development of pharmacogenetics has provided more opportunities for individualized pharmacotherapy of depressive disorders (Perlis, 2007; Horstmann and Binder, 2009). At present time, most pharmacogenetic studies investigated genes related to metabolism, genes coding for receptors and transporters and genes related to the second messenger system (Perlis, 2007). In this review, we summarize the major findings related to the pharmacogenetics of genes affecting response to ADs. To reach this target we reviewed the literature searching the MEDLINE and EMBASE (September 2010) using the search terms pharmacokinetics, pharmacodynamics, gene, variation, AD, efficacy, depression, mood disorder, genetic, candidate, cytochrome, P-glycoprotein (Pgp), tryptophan hydroxylase (TPH), catechol-O-methyltransferase (COMT), monoamine oxidase A (MAO-A), HTT, norepinephrine transporter (NET), dopamine transporter (DAT), 5-HT1A, 5-HT2A, 5-HT3A, 5-HT3B, 5-HT6, angiotensin converting enzyme (ACE), circadian locomotor output cycles kaput protein (CLOCK), nitric oxide synthase (NOS), interleukin 1-beta (IL-1B), brain-derived neurotrophic factor (BDNF), glycogen synthase kinase 3 beta (GSK-3 $\beta$ ), adrenoceptor beta-1 (ADRB1), adrenoceptor alpha-2 (ADRA2A), dopamine receptors, Gbeta3, corticotropin releasing hormone (CRH) receptor (CRHR1), glucocorticoid receptor (GR), glutamate receptor (also using extensive gene names; for overview see **Table 1**).

## PHARMACOKINETICS

### CYTOCHROME P450

Differences in AD plasma concentrations, and possibly safety, may be caused by polymorphisms in the genes that encode some of the cytochrome P450 (CYP) isoenzymes that metabolize ADs. The CYP superfamily is a class of proteins containing a heme cofactor that localize mainly to the liver. They represent the major enzymes responsible for the phase I oxidative reactions of many drugs and endogenous substances and over 50 isoenzymes are known so far (Ingelman-Sundberg et al., 2007). The most relevant cytochromes in humans are: CYP1A, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A.

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 2**, the isoenzymes CYP1A2, CYP2C9/19, CYP2D6, and CYP3A4 are the major enzymes that catalyze AD metabolic reactions (Spina et al., 2008).

With regards to CYP2D6 gene in particular, its polymorphisms were associated with the metabolism of most AD drugs (Lin and Lu, 1998). So far, more than 100 different alleles were reported

at different frequencies in different populations of the world (for information see <http://www.cypalleles.ki.se/>), with a considerable number of variants which encodes inactive isoforms or with decreased or negligible activity, while other variations consist of gene duplications (Bertilsson et al., 2002). Those gene variants are often associated with different drug metabolism rate. According to the inherited CYP2D6 alleles, individuals are classified as poor (PM), intermediate (IM), extensive (EM), or ultrarapid (UM) metabolizers. Individuals who are PMs have a combination of two partially or totally defective alleles and often, they complain of side effects and drug intolerance at low dosages of drugs for its accumulation. Occasionally, these individuals are labeled as non-compliant for treatment. IMs have in their allelic combination one wild type allele plus one a partially or totally defective allele. The expected phenotype is between the EM and the PM phenotypes. In the case of CYP2D6, there is good evidence for a linear relationship between gene copy number and metabolism of a drug (i.e., amitriptyline and nortriptyline; Grasmader et al., 2004; Steimer et al., 2004). It is reasonable to expect that those drugs predominately metabolized through CYP2D6 may also show an IM status due to the low hepatic content of CYP2D6 and limiting enzymatic capacity. Drugs with additional metabolic routes (i.e., CYP2C19 and CYP3A) may have IM or EM status due to the additional metabolic routes for drug elimination. Individuals who are EM, also called normal or "wild type" have two active alleles. This genotype serves as the reference genotype for other studies. The UM category exists for CYP2D6 and CYP1A2 enzymes. UM individuals usually have multiple copies of the allele on one or the other chromosome, this condition increased enzymatic activity due to an increased the amount of protein produced (Gaikovitch et al., 2003). Interesting and noteworthy the prevalence of different genotypes and phenotypes is notably different depending on ethnicity.

Pharmacogenetic studies which investigated the influence of CYP2D6 variants on AD outcome actually do not reach univocal results; this may at least partly be due to the heterogeneity of studied populations. Indeed, while some authors reported positive association with therapeutic effects (Rau et al., 2004; Tsai et al., 2010) or side effects (Rau et al., 2004; Shams et al., 2006; Suzuki et al., 2006), other authors found lack of association (Murphy Jr. et al., 2003; Grasmader et al., 2004; Serretti et al., 2009; Murata et al., 2010), both for therapeutic and side effects (Peters et al., 2008). Moreover, several authors found an association between CYP2D6 variants and AD serum levels (Charlier et al., 2003; Grasmader et al., 2004; Suzuki et al., 2010; Tsai et al., 2010), but without univocal results (Murphy Jr. et al., 2003; Ohara et al., 2003). In the case of CYP1A2, duplications do not occur, but polymorphisms affecting transcription and translation of the encoded protein in the presence of inducers, such as tobacco smoke, can produce a UM phenotype (Sachse et al., 1999; Pavanello et al., 2005). UMs often requires doses of a CYP2D6-metabolized drug above (e.g., fluoxetine) or below (e.g., codeine, which is a prodrug for morphine) than conventional dosing guidelines to achieve a therapeutic desired effect. The CYP2C19 gene is on another cytochrome gene active in the metabolism of several ADs (Liu et al., 2002b; Yin et al., 2006; Rudberg et al., 2008; Schenk et al., 2010), and largely investigated concerning AD response. Also in this case the different isoforms

**Table 1 | Overview of genetic association studies.**

Gene	Principal polymorphism investigated	Alleles	Amino acid change	Frequency*		Region	Antidepressants involved	Reference**
				Major allele	Minor allele			
P-glycoprotein	rs1045642	A/C/ G/T	1145 I/?	A (56%)	G (44%)	Coding exon	Paroxetine; citalopram; nortriptyline	Roberts et al. (2002), Gex-Fabry et al. (2008), Kato et al. (2008a), Mihaljevic Peles et al. (2008), Nikisch et al. (2008), Peters et al. (2008)
	rs1128503	A/C/ G/T	412 G/?	G (56%)	A (44%)	Coding exon		
	rs2032582	A/G/T	893 S/?	C (54%)	A (46%)	Coding exon		
	rs10280101	A/C	None	A (85%)	C (15%)	Intron		
	rs7787082	A/G	None	G (82%)	A (18%)	Intron		
	rs2032583	A/G	None	A (85%)	G (15%)	Intron (boundary)		
	rs2235040	C/T	None	C (85%)	T (15%)	Intron (boundary)		
TPH1	rs1800532	G/T	None	G (56%)	T (44%)	Intron	Fluvoxamine; paroxetine; citalopram; typical neuroleptics	Serretti et al. (2001b,c), Anttila et al. (2007), Ham et al. (2007), Viikki et al. (2010)
TPH2	rs1843809	G/T	None	T (89%)	G (11%)	Intron	Fluoxetine; citalopram	Peters et al. (2004), Tzvetkov et al. (2008), Tsai et al. (2009b)
	rs1386494	C/T	None	C (87%)	T (13%)	Intron		
	rs1487276	C/T	None	C (87%)	T (13%)	Intron		
	rs10897346	C/T	No data	No freq. data	No freq. data	No data		
	rs1487278	C/T	None	T (78%)	C (22%)	Intron		
COMT	rs2171363	A/G	None	G (64%)	A (36%)	Intron	Fluoxetine; paroxetine; citalopram	Benedetti et al. (2009), Tsai et al. (2009a), Kocabas et al. (2010)
	rs4680	A/G	158 V/M	G (51%)	A (49%)	Coding exon		
MAO-A	uVNTR	No data	No data	No freq. data	No freq. data	Promoter	Mirtazapine; fluoxetine	Peters et al. (2004), Tadic et al. (2007), Tzeng et al. (2009)
	rs6323	G/T	297 R/R	T (73%)	G (27%)	Coding exon		
	rs1465108	A/G	None	G (70%)	A (30%)	Intron		
	rs1799835	G/T	314 F/V			Coding exon		

(Continued)

Table 1 | Continued

5-HTTLPR	44 bp Del/Ins	long/ short	No data	I (51%)	s (49%)	Promoter	Fluvoxamine; paroxetine; citalopram; fluoxetine; nortriptyline; mirtazapine; sertraline	Zanardi et al. (2001), Rausch et al. (2002), Arias et al. (2003), Joyce et al. (2003), Durham et al. (2004), Murphy Jr. et al. (2004), Peters et al. (2004), Serretti et al. (2004c), Kraft et al. (2005), Kim et al. (2006), Smeraldi et al. (2006), Bozina et al. (2008), Huezo-Diaz et al. (2009), Mandelli et al. (2009), Min et al. (2009), Mrazek et al. (2009), Wilkie et al. (2009), Illi et al. (2010)
	Stin2	VNTR	No data	No freq. data	No freq. data	Intron		
	rs25531	A/G	None	No freq. data	No freq. data	Promoter		
NET	rs5566	C/G	369 A/P	G (100%)	C (0%)	Coding exon	Desipramine; paroxetine; sertraline; fluvoxamine; pindolol; nortriptyline; milnacipran; fluoxetine; venlafaxine	Yoshida et al. (2004), Hahn et al. (2005), Kim et al. (2006), Dong et al. (2009), Min et al. (2009), Uher et al. (2009)
	rs5563	A/C	292 N/T	A (100%)	C (0%)	Coding exon		
	rs5558	G/T	528 F/C	T (100%)	G (0%)	Coding exon		
	rs5569	A/G	429 T/T	G (57%)	A (43%)	Coding exon		
	rs2242446	C/T	None	T (73%)	C (27%)	5' UTR		
	rs1532701	A/G	None	A (53%)	G (47%)	Intron		
	rs5564	A/G	None	A (95%)	G (5%)	Intron (boundary)		
	rs1362621	A/G	None	A (76%)	G (24%)	Promoter		
DAT	40-bp in exon 15	VNTR	No data	No freq. data	No freq. data	3' UTR	Mirtazapine; venlafaxine; citalopram	Kirchheiner et al. (2006), Lavretsky et al. (2008)
5-HT1A receptor	rs6295	C/G	None	C (56%)	G (44%)	Promoter	Fluoxetine; nefazodone; fluvoxamine; citalopram	Perez et al. (1997), Lemondé et al. (2004), Serretti et al. (2004a), Arias et al. (2005), Hong et al. (2006), Parsey et al. (2006), Yu et al. (2006), Kato et al. (2009), Villafuerte et al. (2009)

(Continued)

Table 1 | Continued

Gene	Principal polymorphism investigated	Alleles	Amino acid change	Frequency*		Region	Antidepressants involved	Reference**
				Major allele	Minor allele			
5-HT2A receptor	rs1800042	A/G	273 G/D	No freq. data	No freq. data	Coding exon	Citalopram; paroxetine; fluvoxamine	Choi et al. (2005), Kato et al. (2006)
	rs1799921	A/G	28 I/V	A (99%)	G (1%)	Coding exon		
	rs1800044	G/T	220 R/L	No freq. data	No freq. data	Coding exon		
	rs1799920	A/G	22 G/S	No freq. data	No freq. data	Coding exon		
	rs10042486	C/T	None	C (50%)	T (50%)	Promoter		
	rs1364043	G/T	None	T (78%)	G (22%)	Downstream		
5-HT3A receptor	rs6311	C/T	None	C (53%)	T (47%)	Promoter	Paroxetine; fluvoxamine	Tremblay et al. (2003), Kato et al. (2006), Sugai et al. (2006), Tanaka et al. (2008)
	rs6313	A/G	34 S/S	G (53%)	A (47%)	Coding exon		
	rs6314	A/G	452 H/Y	G (94%)	A (6%)	Coding exon		
	rs1062613	C/T	None	C (78%)	T (22%)	5' UTR		
5-HT3B receptor	C195T	C/T	No data	No freq. data	No freq. data	No data	Venlafaxine; fluoxetine	Wu et al. (2001), Lee et al. (2005)
	(-100 -102) AAG del/ins	long/short	No data	No freq. data	No freq. data	No data		
	rs1176744	A/C	129 Y/S	A (71%)	C (29%)	Coding exon		
5-HT6 receptor	rs35312182	A/G	None	A (96%)	G (4%)	Intron	Various antidepressant; citalopram	Zill et al. (2003), Crowley et al. (2008)
	rs1805054	C/T	89 Y/Y	C (88%)	T (12%)	Coding exon		
ADRA2A	rs11195419	A/C	None	C (88%)	A (12%)	3' UTR	Nortriptyline	Perroud et al. (2009)
ADRB1	G1165C	C/G	No data	No freq. data	No freq. data	No data	Various antidepressant; citalopram	Zill et al. (2003), Crowley et al. (2008)
D2 receptor	rs1801028	C/G	311 S/C	C (98%)	G (2%)	Coding exon	Various antidepressant; lamotrigine; olanzapine; fluoxetine	Serretti et al. (2001a, 2004b), Benedetti et al. (2003b), Garriock et al. (2006), Perlis et al. (2010)
D3 receptor	rs4245147	C/T	None	C (51%)	T (49%)	Intron	Various antidepressant; lamotrigine; olanzapine; fluoxetine	Serretti et al. (2001a, 2004b), Benedetti et al. (2003b), Garriock et al. (2006), Perlis et al. (2010)
	rs167770	A/G	None	A (71%)	G (29%)	Intron		
	rs6280	C/T	9 G/S	T (65%)	C (35%)	Coding exon		
D4 receptor	rs2134655	C/T	None	C (72%)	T (28%)	Intron	Various antidepressant; lamotrigine; olanzapine; fluoxetine	Serretti et al. (2001a, 2004b), Benedetti et al. (2003b), Garriock et al. (2006), Perlis et al. (2010)
	rs936461	A/G	None	G (65%)	A (35%)	Promoter		
	VNTR in exon 3	VNTR	No data	No freq. data	No freq. data	Coding exon		

(Continued)

Table 1 | Continued

GNB3	rs5443	C/T	275 S/S	C (62%)	T (38%)	Coding exon	Fluoxetine; nortriptyline; paroxetine; escitalopram; mirtazapine	Zill et al. (2000), Joyce et al. (2003), Serretti et al. (2003b), Lee et al. (2004), Hong et al. (2006), Kang et al. (2007), Wilkie et al. (2007), Kato et al. (2008b), Lin et al. (2009), Keers et al. (2010a)
CRHR1	rs242941	G/T	None	G (69%)	T (31%)	Intron	Fluoxetine	Licinio et al. (2004), Liu et al. (2007)
	rs1876828	A/G	None	G (78%)	A (22%)	Intron		
	rs242939	A/G	None	A (93%)	G (7%)	Intron		
CRHR2	rs2270007	C/G	None	C (83%)	G (16%)	Intron	Citalopram	Papiol et al. (2007)
GR	ER22/23EK	No data	No data	No freq. data	No freq. data	No data	Various antidepressant	van Rossum et al. (2006), Uher et al. (2009)
	BclI	No data	No data	No freq. data	No freq. data	No data		
	rs852977	A/G	None	A (66%)	G (34%)	Intron		
	rs10482633	G/T	None	T (80%)	G (20%)	Intron		
BDNF	rs10052957	A/G	None	G (65%)	A (35%)	Promoter		
	rs6265	C/T	66 V/M	C (80%)	T (20%)	Coding exon	Various antidepressant; citalopram; fluoxetine	Choi et al. (2006), Gratacos et al. (2008), Licinio et al. (2009), Domschke et al. (2010), Zou et al. (2010a)
	rs61888800	G/T	None	G (70%)	T (30%)	5' UTR		
	rs7124442	C/T	None	T (66%)	C (34%)	3' UTR		
	rs11030104	A/G	None	A (77%)	G (23%)	Intron		
NTRK2	rs2289657	A/C	600 I/I	C (95%)	A (5%)	Coding exon	Various antidepressant	Dong et al. (2009)
	rs56142442	C/T	794 P/P	No freq. data	No freq. data	Coding exon		
	rs2289658	C/T	None	T (96%)	C (4%)	Intron (boundary)		
	rs2289657	A/C	600 I/I	C (95%)	A (5%)	Coding exon		
	rs2289656	A/G	None	G (82%)	A (18%)	Intron (boundary)		

\*\*The table indicates the main references.

\*The allele frequencies are referred to Caucasians.

of the gene allowed a classification in phenotypes, with a group of subjects labeled as EM, another one with impaired catalytic capacity, called PM (Smith et al., 1998a,b); and an UM group (Rudberg et al., 2008). In conclusion, the pharmacokinetics of ADs is significantly altered, in particular by CYP2D6 and more marginally by CYP2C19 polymorphisms. However, it is still controversial whether therapeutic efficacy may be improved and/or adverse effects could

be prevented by the use of genotyping procedures, particular considering that genotype often do not correspond to a well-defined phenotype as state above. With regard to this, the recent approval by the FDA of the pharmacogenetic test, the AmpliCyp CYP450 Test (Roche Molecular System Inc.), assessing both polymorphic genes CYP2D6 and CYP2C19, may be of help to validate studies on personalized therapy of depression.



**Table 2 | Cytochrome P450 isoforms responsible for the biotransformation of antidepressants.** Based on Spina et al. (2008).

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
Mirtazapine	CYP2D6, CYP1A2, CYP3A4
Reboxetine	CYP3A4
Trazodone	CYP3A4
Nefazodone	CYP3A4
Bupropion	CYP2B6
Agomelatine	CYP1A2

### P-GLYCOPROTEIN

P-glycoprotein is a member of the ATP-binding cassette superfamily of membrane transport proteins encoded by the ATP-binding cassette, subfamily B, member 1 (*ABCB1*) gene [alternate name multidrug resistance protein 1 (*MDR1*)], it is responsible for the efflux of many drugs. It represents a major component of the blood–brain barrier (Schinkel et al., 1994) and the intestinal barrier (Van Asperen et al., 1998), and it contributes to renal and biliary elimination of drugs (Kusuhara et al., 1998; Chiou et al., 2000). Because of its location at the blood–brain barrier, Pgp may regulate the concentration of ADs in the brain. For paroxetine, venlafaxine, and fluoxetine the data indicate that they might be Pgp substrates; for citalopram the data are conflicting (Rochat et al., 1999; Uhr et al., 2000). Several variants of *ABCB1* are known (Kioka et al., 1989; Mickley et al., 1998; Hoffmeyer et al., 2000; Ito et al., 2001), among these three – C3435T (rs1045642), C1236 (rs1128503), and G2677T (rs2032582) – have been associated with altered Pgp activity. Studies investigating the influence of these functional polymorphisms on ADs response have given contradictory results (Roberts et al., 2002; Laika et al., 2006; Fukui et al., 2007). Indeed, while some authors found positive associations between rs2032582 (Kato et al., 2008a; Nikisch et al., 2008) or rs1045642 (as well as haplotype with rs2032582 and rs1128503; (Kato et al., 2008a) and AD response or side effects (nortriptyline-induced postural hypotension; (Roberts et al., 2002), other authors failed to find positive association for rs2032582 and rs1045642 (Gex-Fabry et al., 2008; Mihajlevic Peles et al., 2008), also considering together with rs1128503 (Peters et al., 2008). Finally negative findings have been reported also for rs10280101, rs7787082, rs2032583, rs2235040 (Perlis et al., 2010), and rs2032582 (Laika et al., 2006).

## PHARMACODYNAMICS

### MONOAMINE METABOLIC ENZYMES

#### Tryptophan hydroxylase

Tryptophan hydroxylase is an enzyme involved in the synthesis of serotonin. There are two distinct *TPH* genes that encode two different homologous enzymes TPH1 and TPH2. TPH1 is mostly expressed in tissues that express serotonin in the skin, gut, and pineal gland but it is also expressed in the central nervous system (CNS). TPH2 is exclusively expressed in neuronal cell types and is the predominant isoform in the CNS. *TPH* gene has been considered one of the most promising genes concerning the genetic modulation of AD response. Several studies found an association between TPH1 polymorphisms and suicidal behavior and worse response to SSRIs (Serretti et al., 2001b,c; Ham et al., 2007). Unfortunately following studies found controversial results (Yoshida et al., 2002; Rujescu et al., 2003; Bellivier et al., 2004; Peters et al., 2004; Serretti et al., 2004c; Ham et al., 2005; Hong et al., 2006; Kato et al., 2007; Illi et al., 2009). Nevertheless recently studies have shown an association between rs1800532 and AD response, concerning both clinical response (Anttila et al., 2007; Viikki et al., 2010) and side effect profile (Secher et al., 2009), suggesting that the role of this polymorphisms is not yet deeply understood and needs further investigation, particularly considering also other polymorphisms in the same gene and/or in other correlated genes [like *5-HT2A*, *G protein beta 3 subunit (GNB3)*, and *COMT*; (Anttila et al., 2007; Secher et al., 2009)]. Also TPH2 polymorphisms have been associated with AD response: rs1843809, rs1386494, and rs1487276 (Peters et al., 2004), rs10897346 and rs1487278 (Tzvetkov et al., 2008), rs2171363 (Tsai et al., 2009b). Although these results need to be clearly replicated, overall these data suggested a role for TPH2 gene in AD pharmacogenetics.

#### Catechol-O-methyltransferase

Catechol-O-methyltransferase is one of several enzymes that degrade catecholamines such as dopamine, epinephrine, and norepinephrine (NE). COMT is an intracellular enzyme located in the postsynaptic neuron. The *COMT* gene have several allelic variants, among these the most well-studied is rs4680, results in a change in the enzyme structure [Val(108/158)Met], which influences activity (high activity in Val/Val, intermediate activity in Val/Met, and low activity in Met/Met genotype; (Lachman et al., 1996). This polymorphism was associated with AD treatment, in particular rs4680 seems to influence fluoxetine and paroxetine response (Benedetti et al., 2009; Tsai et al., 2009a). However, other studies showed contrasting results with other drugs (Szegeedi et al., 2005; Arias et al., 2006; Baune et al., 2008a; Yoshida et al., 2008; Benedetti et al., 2009). Particularly Met/Met genotype has been associated both with better (Baune et al., 2008a; Yoshida et al., 2008; Benedetti et al., 2009; Tsai et al., 2009a) and worse response (Szegeedi et al., 2005; Arias et al., 2006). On the other hand, Hilli et al. (2009) did not find any association between this variant and AD response. Moreover stressful life events do not seem to interact with rs4680 to predict treatment outcome (Bukh et al., 2010). Recently Perlis et al. (2009a) and Kocabas et al. (2010) investigated other SNPs within the *COMT* founding more or less association with citalopram or other AD response. Although so far no replication studies have been performed, this result supports the role of *COMT* gene variants on the AD response.

### **Monoamine oxidase A**

Monoamine oxidases are a family of enzymes that catalyze the oxidation of monoamines. In humans there are two types of MAO: MAO-A and MAO-B, and both are found in CNS, in particular in neurons and astroglia. The MAO-A, coded by the MAO-A gene, metabolizes several important amines and catecholamines including dopamine, serotonin, and NE. Polymorphism in the gene's promoter region is due to a repetitive sequence [variable number tandem repeat (VNTR)] located 1.2 kb upstream of the MAO-A gene, regulates the activity of the MAO-A gene and have been linked to variations in the biological activity and also influences the concentration of serotonin (Sabol et al., 1998). Because the activity of MAO-A influences neurotransmitter concentrations, polymorphisms in these genes may affect AD response. Researchers like Tadic et al. (2007) and more recently Tzeng et al. (2009) reported that the VNTR polymorphism in the MAO-A gene promoter region was associated with mirtazapine response. Nevertheless, as a matter of fact, several reports did not found any correlation between this polymorphism and the AD response (Cusin et al., 2002; Muller et al., 2002; Yoshida et al., 2002; Peters et al., 2004). Other polymorphisms within this gene were more marginally studied, with some positive but not replicated results. Particularly Peters et al. (2004) reported an association between rs1465108 and rs6323 and fluoxetine response whilst Tadic et al. (2007) found an association between rs1799835 and mirtazapine response only in the female sample). Finally an effect of the rs6323 genotype on the placebo response has been reported (Leuchter et al., 2009).

### **MONOAMINE TRANSPORTERS**

#### **Serotonin transporter (SLC6A4)**

The serotonin transporter (SERT or SLC6A4) regulates brain serotonin neurotransmission by transporting the neurotransmitter serotonin from synaptic space to presynaptic neurons. It is the principal site of action of many ADs (mainly SSRI, SNRI, TCA) and it represents a target of primary interest in the AD pharmacogenetics. The most investigated variant of this gene is located in the promoter region (5-HTTLPR) and it is able to impact the expression of the SERT. This polymorphism was firstly described in 1996 by Heils et al. (1996) as an insertion/deletion of 44 bp involving 2 U in a sequence of 16 repeated elements: the long (l) allele has twice the expression in the basal state than the short (s) form. 5-HTTLPR polymorphism has been studied in association with affective symptomatology (anxiety disorders, substance abuse, bipolar disorder, eating disorders, and depression) and with pathological behaviors and personality traits related to anxiety, impulsivity, and stress (Serretti et al., 2006). Moreover, several reports found an association with AD response, in particular, studies in Caucasians showed a positive association between L allele and better response (Smeraldi et al., 1998; Pollock et al., 2000; Zanardi et al., 2000, 2001; Rausch et al., 2002; Arias et al., 2003; Joyce et al., 2003; Durham et al., 2004; Murphy Jr. et al., 2004; Serretti et al., 2004c; Bozina et al., 2008; Huez-Diaz et al., 2009; Mandelli et al., 2009; Mrazek et al., 2009; Illi et al., 2010) although negative findings have been reported as well (Hu et al., 2007; Kraft et al., 2007; Dogan et al., 2008; Maron et al., 2009; Wilkie et al., 2009; Baffa et al., 2010; Reimherr et al., 2010). A meta-analysis performed by

Serretti et al. (2007b) showed a significant association between the s/s variant of 5-HTTLPR and remission rate and between both s/s and s/l variants and response rate. Nonetheless, a more recent meta-analysis performed by Taylor et al. (2010) failed to replicate this result, probably because they did not consider separately Caucasian and Asian samples. Other studies focused on the possible interaction between genetic and environment finding that stressful life events could interact with 5-HTTLPR genotype to determine AD response (Bukh et al., 2009; Mandelli et al., 2009; Keers et al., 2010b), although this topic is still controversial (Coventry et al., 2010). These findings were found to be more consistent in Caucasian than in Asian samples, probably for a different prevalence of this mutation in diverse ethnicities. Interestingly Murphy Jr. et al. (2004) showed an interaction between the HTTLPR genotype and the AD used on the side effect profile suggesting that the effect of this polymorphism on outcome may depend on the mechanism of AD action as well. Another polymorphism influencing SERT expression, described as a 17-bp VNTR polymorphism, was identified by Ogilvie et al. (1996) within intron 2 (STin2). Some evidences suggested this polymorphism as a risk factor for depressive disorder (Ogilvie et al., 1996; Gutierrez et al., 1998; MacKenzie and Quinn, 1999) and suicide behavior (Gaysina et al., 2006; Lopez de Lara et al., 2006), creating a synergistic effect with 5-HTTLPR (Hranilovic et al., 2004). Moreover, different authors reported an effect of STin2 on AD response (Kim et al., 2000, 2006; Peters et al., 2004; Bozina et al., 2008; Min et al., 2009; Mrazek et al., 2009; Wilkie et al., 2009), even though not consistently (Ito et al., 2002; Dogan et al., 2008; Huez-Diaz et al., 2009). More recently rs25531, a SNP located just upstream of the 5-HTTLPR, was found to impact the response to AD pharmacotreatment and, consistently, it was shown to modulate the effect of the other 5-HTTLPR alleles (Kraft et al., 2005; Smeraldi et al., 2006). Nevertheless the results are still controversial with both negative (Kraft et al., 2007; Maron et al., 2009; Baffa et al., 2010) and positive findings (Kraft et al., 2005; Mrazek et al., 2009; Bonvicini et al., 2010).

#### **Norepinephrine transporter (SLC6A2)**

The norepinephrine transporter or NET [or noradrenaline transporter (NAT)] is encoded by the SLC6A2 gene. It is a monoamine transporter that transports the neurotransmitters NE (noradrenaline) from the synapse back to cytosol, hence other transporters vesicular monoamine transporter (VMAT) sequester NE into vesicles for later storage and release. Several investigators have studied the relationship between NET genetic polymorphisms and susceptibility to psychiatric disorders, including MD, bipolar disorder, schizophrenia, and alcohol dependence (Owen et al., 1999; Leszczynska-Rodziewicz et al., 2002; Samochowiec et al., 2002; Zill et al., 2002), without observing major findings. Several genetic variants are known in the human NET gene: rs5566 (A369P), rs5563 (N292T), rs5558 (F528C), rs5569 (G1287A), and rs2242446 (T-182C) variants were proved to be functional and impact the AD effect (Yoshida et al., 2004; Hahn et al., 2005; Kim et al., 2006). With particular regard to AD response, rs5569, a silent mutation is associated with the cerebrospinal fluid concentration of 3-methoxy-4-hydroxyphenylglycol, a major NE metabolite (Jonsson et al., 1998), and with the response to methylphenidate,



a drug with noradrenergic action, in attention deficit hyperactivity disorder (ADHD; (Yang et al., 2004). The association between this polymorphism and the AD response was previously examined in Japanese patients by Yoshida et al. (2004): they reported that the NET G1287A polymorphism (A/A genotype) was associated with the onset of response but not the final clinical improvement. Moreover, Kim et al. (2006) showed a positive association between G/G rs5569 genotype and better response to nortriptyline, although no effect on SSRIs response has been detected. The NET T-182C polymorphism was first reported by Zill et al. (2002) and the presence of the T allele was associated with a superior response to milnacipran (Yoshida et al., 2004; for a review see Higuchi, 2010). Consistently one other study did not find any association between these polymorphisms and SSRIs (fluoxetine, paroxetine, or citalopram) or venlafaxine response in an Asiatic sample of depressed patients (Min et al., 2009). Recently other NET polymorphisms have been investigated: Uher et al. (2009) showed an association between rs60329 and rs1532701 polymorphism and favorable response to treatment with nortriptyline, and Dong et al. (2009) found that the rs5564 and rs1362621 were associated with remission with desipramine and fluoxetine treatment. Nevertheless, Baffa et al., 2010) did not find any association with seven polymorphisms in the promoter, intronic and exonic region of NET (rs35915, rs28386840, rs168924, rs2242446, rs36017, rs47958, rs171798). However, results are not unequivocal, and replication studies are warranted.

### **Dopamine transporter**

The DAT (SLC6A3) 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, including ADHD (Barr et al., 2000), schizophrenia (Prata et al., 2009), and alcoholism (Heinz et al., 2004). *SLC6A3* gene has a VNTR at the 3' end (rs28363170; Sano et al., 1993). This polymorphism has been studied in association with several diseases, including bipolar affective disorders (Waldman et al., 1997; Greenwood et al., 2001). AD drugs, in particular SSRIs, modulate availability of DAT, and dopaminergic mechanisms may play an important role in AD drug action (Ichikawa and Meltzer, 1995; Smith et al., 2000; Kugaya et al., 2003; Willner et al., 2005; Zhou et al., 2005). However, according to our best knowledge, the relationship between the DAT polymorphism and AD response has been weakly studied. Kirchheiner et al. (2006) showed an association between the 9/10 and 9/9 genotypes and a higher risk of poorer and slower response to various AD drugs than the 10/10 genotype. Moreover, the 10/10 genotype seems to be associated with an endophenotype (Gottesman and Gould, 2003) of late-life depression that responds preferentially to methylphenidate added to a SSRI (Lavretsky et al., 2008).

## **MONOAMINE RECEPTORS**

### **5-Hydroxytryptamine 1A or serotonin-1A receptors**

Serotonin-1A receptors is a Gprotein-coupled receptor 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

(Lesch and Gutknecht, 2004; Sharp et al., 2007). The 5-HT1A receptor also serves as the predominant (somatodendritic) autoreceptor of the raphe nuclei, reducing the firing rate of these neurons, 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 (Wang and Aghajanian, 1977; Verge et al., 1985; Sprouse and Aghajanian, 1986; Blier and de Montigny, 1987; Hutson et al., 1989; Meller et al., 1990; Hjorth and Sharp, 1991; Kreiss and Lucki, 1994). The 5-HT1A receptor is coded by the 5-hydroxytryptamine receptor 1A (*HTR1A*) gene. A role for this gene in the AD response has been postulated because several AD desensitize raphe 5-HT1A autoreceptors, leading to an enhancement of the serotonergic neurotransmission that could be associated with the AD effect of these drugs. Moreover there are some evidences that the block of the 5-HT1A autoreceptors may accelerate the AD action (Perez et al., 1997). The most investigated *HTR1A* variants are: C(-1019)G (rs6295); Gly272Asp (rs1800042); Ile28Val (rs1799921); Arg219Leu (rs1800044); and Gly22Ser (rs1799920). Among these, the most investigated one concerning AD response is rs6295, which is located in the promoter region of the gene. The rs6295 G allele has been associated with an up regulation of the expression of the receptor (Lemonde et al., 2003; Albert and Lemonde, 2004), moreover there are some evidences suggesting that G allele carriers have higher risks for depression and suicidal behavior and of being more resistant to AD treatment (Lemonde et al., 2003, 2004; Serretti et al., 2004a; Arias et al., 2005; Hong et al., 2006; Parsey et al., 2006; Yu et al., 2006; Kato et al., 2009; Villafuerte et al., 2009). In particular, Lemonde et al. (2004) reported that AD response to the SSRI fluoxetine, NARI nefazodone, and 5-HT1A agonist flibanserin, was associated with this polymorphism. Nonetheless other authors reported conflicting results (Peters et al., 2004; Serretti et al., 2004a; Mandelli et al., 2007; Noro et al., 2010). Noteworthy, Yu et al. (2006) found an association between rs6295 and AD response only in females, showing an interaction with gender, and Baune et al. (2008b) showed an association only in patients with melancholic depression. No interaction has been found between rs6295 and stressful life events with the AD response (Bukh et al., 2010). Another SNP associated with better AD response was rs1800042, although negative results are reported as well (Suzuki et al., 2004; Yu et al., 2006; Levin et al., 2007). With regard to drug related adverse events, neither rs1800042 nor rs6295 seem to be significantly associated to paroxetine discontinuation syndrome (Murata et al., 2010). Also other 5-HT1A polymorphisms were studied in association with AD response. A recent paper reported that rs10042486 C/C and rs1364043 T/T genotypes were strongly associated with a better response to AD drugs (Kato et al., 2009). All these data suggested that other 5-HT1A gene variants need to be considered in order to better elucidate the role of this gene on AD response (Drago et al., 2008).

### **5-HT2A receptor**

5-Hydroxytryptamine 1A receptor is a G protein-coupled receptor coded by the *HTR2A* gene; it is expressed widely throughout the CNS, near most of the serotonergic terminal rich areas, including neocortex (mainly prefrontal, parietal, and somatosensory

cortex) and the olfactory tubercle. An increasing number of studies suggested that HTR2A levels and activity are altered in psychiatric disorders like MDD (Yatham et al., 1999; Meyer et al., 2001; Yamauchi et al., 2005; Bhagwagar et al., 2006), evidence supported also by animal studies (Skrebuhhova et al., 1999). The most widely investigated polymorphisms of HTR2A gene are: A-1438G (rs6311), C102T (rs6313), and His452Tyr (rs6314). HTR2A variations have been investigated as functional candidates in several psychiatric disorders such as schizophrenia, ADHD, affective disorders, eating disorders, anxiety disorders, obsessive compulsive disorders, suicide, Alzheimer's disease. In particular, several studies have been shown an association between rs6311 polymorphism and mood disorders, bipolar disorder, and MDD (Chee et al., 2001; Choi et al., 2004), such as with AD response (Choi et al., 2005; Kato et al., 2006). A weak link has been found between the rs6313 SNP and schizophrenia, moreover, this polymorphism has been studied in relation to suicide attempts (Williams et al., 1996; Vaquero-Lorenzo et al., 2008). Consistently, Minov et al. (2001) showed an association between the 5-HT2A rs6313 SNP (102T/C) and AD response. These two variants (rs6311 and rs6313) are in linkage disequilibrium (LD) and they can be considered together (Spurlock et al., 1998), therefore studies by Choi et al. (2005) and Kato et al. (2006) may be considered replications of results from Minov et al. (2001). On the other side there are studies that failed to replicate positive results (Cusin et al., 2002; Sato et al., 2002; Peters et al., 2004; Yoshida et al., 2004; Hong et al., 2006; Suzuki et al., 2006; Illi et al., 2009). Several other variants have been reported to influence AD response (Cusin et al., 2002; Peters et al., 2004, 2009; McMahan et al., 2006; Perlis et al., 2009b; Uher et al., 2009; Wilkie et al., 2009; Horstmann et al., 2010; Kishi et al., 2010; Lucae et al., 2010). Overall data suggested a role for the 5-HT2A gene in the AD response, although a wider knowledge of this gene is needed in order to better disentangle this issue (Serretti et al., 2007a).

### **5-HT3A, 3B receptors**

The 5-HT3 receptor is expressed throughout the central and peripheral nervous systems and mediates a variety of physiological functions; it is the only ion channel subtype in the serotonin family. Five different subunits, A–E, of the 5-HT3 receptor have been identified. Association studies have been carried out to establish causal relationships between genetic variants within genes encoding 5-HT3A and 5-HT3B and side effects profile rather than clinical response. Yamada et al. (2006) showed an association between haplotype block in the 5-HT3B gene [that includes Y129S (rs1176744) polymorphism] and MD in women and in patients with bipolar affective disorder (Frank et al., 2004). Likewise, a common variation in the regulatory region of the 5-HT3A gene C178T has been associated with bipolar affective disorder in Caucasians (Niesler et al., 2001), although a recent study on Japanese patients did not confirm this result (Yamada et al., 2006). Consistently HTR3A rs1062613 (C178T) and two polymorphisms in HTR3B (–100–102 AAG deletion variant and rs1176744) have been found to be associated with chemotherapy and paroxetine treatment induced vomiting and nausea (Tremblay et al., 2003; Kato et al., 2006; Sugai et al., 2006; Tanaka et al., 2008). Nevertheless, studies on gastrointestinal side effects during

SSRIs treatment showed no association with HTR3B rs1176744 (Suzuki et al., 2006; Tanaka et al., 2008), HTR3A rs1062613 and C195T (Sugai et al., 2006), as well as no association has been found between HTR3A (rs1062613) and HTR3B (rs35312182 and rs1176744) polymorphisms and paroxetine discontinuation syndrome (Murata et al., 2010).

### **5-HT6 receptor**

The 5-HT6 receptor is a G protein-coupled receptor which is expressed almost exclusively in the brain. Genetic variants within this gene likely have an effect on brain and several studies have investigated whether 5-HT6 polymorphisms are associated with brain-related variables, such as neuropsychiatric disorders. In this regard, several studies showed an implication of this gene in some behavior trait (Ballaz et al., 2007; Mitchell et al., 2007). Moreover, it seems to be involved in AD mechanism (Svenningsson et al., 2007; Wesolowska and Nikiforuk, 2007). The C267T variant (rs1805054), in the first exon, may have a role in the modulation of AD response as well (Kohen et al., 1996; Lee et al., 2005). Indeed, this polymorphism (rs1805054) has been investigated for association with AD response in several studies. Despite preliminary negative results (Wu et al., 2001), a subsequent study reported that C/T carriers showed better AD response (Lee et al., 2005). Nevertheless, this finding has not been replicated by further studies (Illi et al., 2009; Wilkie et al., 2009).

### **Adrenoreceptor beta-1 and adrenoreceptor alpha-2**

The ADRB1 and ADRA2A are G protein associated receptor: ADRB1 stimulates adenylate cyclase while alpha 2 adrenoreceptor inactivates adenylate cyclase. A recently identified functional polymorphism in the ADRB1 G(1165)C leading to the amino acid variation Gly389Arg may play a functional role, and it was associated with an enhanced coupling to the stimulatory Gs protein and increased adenylate cyclase activation, resulting in a better and faster response to AD treatment (Zill et al., 2003). Nevertheless, Crowley et al. (2008) failed to confirm the relevance of this gene in modulating the response to citalopram treatment. ADRA2A gene, it seems to be related to the pretreatment hypothalamic–pituitary–adrenal (HPA) axis hyperactivity and increased adrenocorticotropin in male depressed patients (Haefner et al., 2008). Recently, Perroud et al. (2009) showed an association between rs11195419 ADRA2A polymorphism and suicidality ideation among nortriptyline treated patients.

### **Dopamine receptors**

Dopamine receptors are divided into D1-like family (D1 and D5, which are coupled to a Gs protein and activate adenylate cyclase), and D2-like family (D2, D3, and D4, which are coupled to a Gi protein and inhibit adenylate cyclase). Only the D2-like family was associated to depressive disorder. Focusing on AD response, we have some line of evidence suggesting a role for D2 receptor as well (Maj et al., 1989; Dzedzicka-Wasylewska and Solich, 2004; Willner et al., 2005). A functional polymorphism (S311C, rs1801028) within D2 receptor gene has been repeatedly investigated without finding any influence on AD response (Serretti et al., 2001a, 2004b; Benedetti et al., 2003b). However, a recent study showed an association between D2 rs4245147 SNP and

lamotrigine response in a sample of bipolar depressed patients (Perlis et al., 2010), suggesting a role of this gene in AD response as well. In the same study (Perlis et al., 2010) founded an association between three D3 receptor SNPs (rs167770, rs6280, and rs2134655) and olanzapine/fluoxetine combination response in a sample of bipolar I depressed patients. Moreover, they reported a marginal association between D4 receptor SNP rs936461 and lamotrigine response (Perlis et al., 2010). Several studies investigated VNTR polymorphism in exon 3 of D4 receptor gene, in relationship with AD response, unfortunately with negative results (Serretti et al., 1999, 2001a), except for Garriock et al. (2006) who found a significant modulation effect on various AD medications.

## INTRACELLULAR SIGNAL TRANSDUCTION PATHWAYS

### G protein beta 3 subunit

The  $\beta 3$  subunit of the G protein complex, encoded by *GNB3* gene, is present in all cells of the body and it has a key role in the downstream signaling cascade following monoamine receptors activation (Hamm, 1998). For this reason a possible involvement in the pharmacogenetic of AD response has been suggested as well. The C825T (rs5443) polymorphism is the most investigated variant within the *GNB3* gene in this field. It was associated with AD treatment response; particularly the T variant seems to predict better AD response. Nonetheless also in this case both opposite and negative results have been reported as well (Zill et al., 2000; Joyce et al., 2003; Serretti et al., 2003b; Lee et al., 2004; Hong et al., 2006; Kang et al., 2007; Wilkie et al., 2007; Kato et al., 2008b; Lin et al., 2009; Keers et al., 2010a). Finally, Anttila et al., (2007) failed to find any association between this polymorphism and ECT response in depressed patients.

## HYPOTHALAMIC–PITUITARY–ADRENAL AXIS AND STRESS HORMONE SYSTEM

### CRH receptors (CRHR1 and CRHR2)

The principal neuro-endocrine regulator of the HPA axis is the CRH, which plays an important role in coordinating the endocrine, autonomic, immune and behavioral responses to stress. Several studies showed a key role of CHR in depression (Nemeroff et al., 1984, 1988; Brady et al., 1992; Raadsheer et al., 1994; Michelson et al., 1997; Gold and Chrousos, 2002; Liu et al., 2002a). Consistently most AD treatment seems to attenuate or normalize HPA axis activity (De Bellis et al., 1993; Ising et al., 2005; Ising and Holsboer, 2007; Schule et al., 2009). In the CNS there are two fundamental subtypes of CRH receptors: CRHR1 and CRHR2. CRHR1 gene is considered to play a key role in mediating the CRH elicited effects in depression and anxiety (Van Pett et al., 2000). Moreover, CRHR1 antagonists have consistently demonstrated AD properties in experimental animals and humans (Seymour et al., 2003; Overstreet and Griebel, 2004; Kehne, 2007) even if this finding was not constantly replicated (Binneman et al., 2008). Several polymorphisms, in particular the rs242941 G/G genotype and one haplotype including two other SNPs beyond rs242941 (rs1876828 and rs242939), were found to be related to fluoxetine response (Licinio et al., 2004; Liu et al., 2007).

Moreover, Papiol et al., 2007 found an association between CRHR2 gene rs2270007 and citalopram response.

### Glucocorticoid receptor

Hyperactivity of HPA axis might be caused by impaired glucocorticoid signaling. Glucocorticoids act through the GR (or NR3C1). Within this gene several polymorphisms have been associated with MDD and AD response. In particular, the BclI and ER22/23EK polymorphisms were associated with susceptibility to develop MD (van Rossum et al., 2006). In addition, the ER22/23EK polymorphism was associated with a faster clinical response to AD treatment (van Rossum et al., 2006). Recently, these results were not repeated in Korean depressive patients (Lee et al., 2009). Brouwer et al. (2006) found that carriers of the BclI polymorphism have higher baseline ATCH values and they showed a trend toward lower decrease of Hamilton Rating Scale for Depression rates than non-carriers. Finally, the rs852977, rs10482633, rs10052957 polymorphisms were associated with AD response in the STAR\*D sample, although none of them survived after correction for hypothesis-wide effective number of comparisons (Uher et al., 2009).

### c-AMP RESPONSE-ELEMENT BINDING

An increasing number of studies recently focused on the role of the c-AMP response-element binding (CREB) protein in MDD. As a matter of fact, several studies found a role of CREB both in the etiology and pharmacotherapy of MDD (Sulser, 2002; Blendy, 2006). CREB1 has also been found to be associated with AD response in depressed patients (Wilkie et al., 2007) and with lithium response in patients with bipolar disorder (CREB1-1H and CREB1-7H SNPs; Mamdani et al., 2008). Further, rs4675690, a SNP located at the 5' of CREB1, was found to have a role in suicidal behaviors in patients with MD (Perlis et al., 2007b) and, along with rs7569963, to be associated with anger expression in men suffering from MD (Perlis et al., 2007a). Despite some negative results (Burcescu et al., 2005; Hettema et al., 2009), current evidence suggests that CREB1 could play an important role both in the development of MDD and related features as well as in the ADs response like showed in several studies on animal models (Thome et al., 2000; Kuipers et al., 2006; Tardito et al., 2006; Boer et al., 2010). The CREB1 polymorphisms are still poorly investigated in the field of pharmacogenetic of AD response, resistance and remission. Dong et al. (2009), like Wilkie et al. (2007), failed to find any association between several CREB polymorphisms and AD response, although they showed a significant association between one SNP (rs3730276) and MDD. Recently, Serretti et al. (2011) suggested that some alleles or haplotypes within CREB1 could be related to treatment resistance but not to response and remission to current AD treatment as well as to a diagnosis of MD. Finally, Perlis et al. (2007a) suggested a role of genetic variants within CREB gene on treatment-emergent suicidal ideation during citalopram treatment. Interestingly they found significant associations only in men, suggesting a significant gene  $\times$  sex interaction.

### BRAIN-DERIVED NEUROTROPHIC FACTOR

Brain-derived neurotrophic factor, a member of the neurotrophin family of survival-promoting molecules, plays an important role in the growth, development, maintenance, and function of several neuronal systems (Acheson et al., 1995). There is growing evidence that BDNF can be relevant in mood disorders and that modulation of its biosynthesis following prolonged AD treatment may



contribute to neuroplastic changes required for clinical response (Calabrese et al., 2007; Reagan et al., 2007). There are several studies that suggested a role of the BDNF in the mechanism of action of AD drugs (Conti et al., 2007; Rogoz et al., 2007). The reported increase in BDNF mRNA expression after AD treatment is a cornerstone of the BDNF hypothesis of AD action (Jacobsen and Mork, 2004). Several evidences support an influence of BDNF polymorphisms in AD response. In this regard, the most investigated SNP within this gene is rs6265 which results in a valine to methionine (V66M) substitution (Egan et al., 2003). Nonetheless results are still controversial (Wilkie et al., 2007; Rajewska-Rager et al., 2008; Kang et al., 2009). While some authors found a better outcome for the heterozygote genotype (Yoshida et al., 2007) or a trend in this direction (Tsai et al., 2003; Zou et al., 2010a), on the other hand other studies showed an association between Val/Val genotype and better outcome (Mandelli et al., 2010; Zou et al., 2010b). Moreover, several studies reported Met allele associated with better response (Choi et al., 2006; Licinio et al., 2009), and with lower fluoxetine side effects (Zou et al., 2010a). Rs6265 was also associated with the presence of stressful life events prior to the depression onset (Bukh et al., 2009), although this result was not confirmed in a further study by the same authors (Bukh et al., 2010). Also rs90887, rs61888800, rs7124442, and rs11030104 SNPs within BDNF gene have been associated with AD response (Gratacos et al., 2008; Licinio et al., 2009; Domschke et al., 2010; Mandelli et al., 2010). A strong association was found between rs962369 and an increase in suicidal ideation during AD treatment (Perroud et al., 2009). Finally, it is interesting to note that significant associations between some variants in neurotrophic tyrosine kinase, receptor, type 2 gene (NTRK2) – that encode the BDNF receptor – (rs2289657, rs56142442, rs2289658, rs2289657, and rs2289656) and AD response have been found in Mexican-Americans (Dong et al., 2009).

#### OTHER GENE VARIANTS

Besides those described, there are many genes that may influence both the onset and evolution of MDD, and the effects of AD pharmacotreatment, among these noteworthy are: the ACE (Baghai et al., 2001, 2003, 2004; Bondy et al., 2005), the CLOCK gene (Benedetti et al., 2003a; Serretti et al., 2003a, 2005b), the glutamatergic system (Laje et al., 2007, 2009; Paddock et al., 2007; Perlis et al., 2009b; Tsunoka et al.,

2009; Horstmann et al., 2010), NOS (Paul, 2001; Suzuki et al., 2003; Wegener et al., 2003; Okumura et al., 2010), and IL-1B (Yu et al., 2003; Tadic et al., 2008; Baune et al., 2010; Uher et al., 2010).

#### GENOME-WIDE ASSOCIATION STUDIES

A genome-wide association study (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 a particular disease. This innovative method seems particularly useful to study complex diseases, such as psychiatric disorders. One of the limits of this methodology is the risk of false positive results. Even if in AD pharmacogenetics, the number of GWAS performed is limited and results need replication, unbiased approaches using genome-wide gene expression or association results could lead to important advances in this field. Recently, GWAS were performed within the GENDEP project and the STAR\*D (Craddock et al., 2009; Garriock and Hamilton, 2009; Ising et al., 2009; Laje et al., 2009; Perroud et al., 2010). One of the major limits of GWAS is the incapacity to detect rare genetic variants (<1% of the population). Indeed, current GWAS technologies are able to detect only association for genetic variants present in 5% or more of the population (Craddock et al., 2009). The results reached by GWAS, to date, have been disappointing. For this reason large meta-analysis to reach genome-wide significance are often needed (McCarthy and Hirschhorn, 2008).

#### CONCLUSION

The synopsis of pharmacogenetic studies indicates several strong candidate genes involved in AD response. Nonetheless, the lack of standardized study design renders meta-analyses as well as comparisons across studies difficult. Several factors can influence the results that often are conflicting: inclusion criteria, medication, outcome and side effect measures, ethnicity, and genetic coverage. Given the complex nature of the biology of AD treatment response and the relevance of environmental factors, such as repeated treatment, number of episodes or the occurrence of life events, the addition of non-genetic markers for optimal treatment prediction will likely be necessary (Holsboer, 2008). There is great hope that the field of pharmacogenomics will offer personalized medicine treatments based on genetic profiles and in this way may have the potential to offer many benefits for further therapeutic approaches.

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