

Salud Mental

Instituto Nacional de Psiquiatría Ramón de la Fuente

perezrh@imp.edu.mx

ISSN (Versión impresa): 0185-3325

MÉXICO

2007

Alessandro Serretti

PHARMACOGENETICS OF ANTIDEPRESSANTS

*Salud Mental*, noviembre-diciembre, año/vol. 30, número 006

Instituto Nacional de Psiquiatría Ramón de la Fuente

Distrito Federal, México

pp. 1-12

Red de Revistas Científicas de América Latina y el Caribe, España y Portugal

Universidad Autónoma del Estado de México

<http://redalyc.uaemex.mx>



## PHARMACOGENETICS OF ANTIDEPRESSANTS

Alessandro Serretti\*

Since the serendipitous discovery of imipramine, in 1957, different classes of antidepressant drugs have been used to treat depressive syndromes. Although their efficacy is well established, still 30-40% of patients do not show a significant response (>50% reduction in baseline score on the Hamilton Rating Scale for Depression – HAMD) to therapeutic doses of antidepressant medications administered for 6-8 weeks of treatment, while 60-70% fail to achieve full remission (17-item HAMD<7) (Moncrieff and Kirsch, 2005). Partial remission has been associated with a higher recurrence, a greater functional impairment and a worse quality of life (Fava et al., 2002; Tranter et al., 2002). All antidepressants have a lag phase and it takes at least 3-4 weeks to observe the real effect of treatment administration (Quitkin et al., 1996). Such a delayed response may increase the patients' suffering and the risk of suicidal behavior and early discontinuation of treatment. Patients have to stay in hospital for longer periods and this results in higher costs. Therefore early identification of responders to a specific antidepressant treatment would be of great usefulness both from a clinical and economical point of view. Unfortunately, in spite of some evidence concerning the predictive power of demographic characteristics, illness features and social factors (Esposito and Goodnick, 2003; Goodnick, 1996; Nierenberg, 2003), none of such variables could unequivocally be linked to treatment outcome and antidepressant choice is still based on a trial and error procedure.

Inherited differences in drug response have been described for a variety of compounds supporting the influence of genetic factors on treatment outcome (Roden and George, 2002; Weinshilboum, 2003). This has been investigated in antidepressant short term treatment (O'Reilly et al., 1994; Orsini, 1987; Pare et al., 1962; Serretti et al., 1998).

Further, one important determinant in treatment decision making is the occurrence of side effects, which can negatively impact compliance. This was reported to be of 40% to 90% in different studies of antidepressant drugs with an average of 65% (Cramer and Rosenheck, 1998). As the prevalence and severity of side effects follow interindividual variations, it is reasonable to hypothesize a genetic basis for drug tolerability (Murphy et al., 2003a). The present paper will review the literature concerning genetic influence on the efficacy and tolerability of antidepressants. Traditional approaches based on the analysis of candidate genes which act throughout pharmacodynamic and pharmacokinetic mechanisms are now integrated by complementary genome-wide approaches (Brown and Botstein, 1999).

### Pharmacodynamic aspects

The monoamine hypothesis, which identifies the biological basis for depression in a deficiency of brain monoamine neurotransmitters (Schildkraut, 1965), is still considered a valid model to account for the mechanism of action of antidepressant drugs (Bondy, 2002). Increasing evidence demonstrates that monoaminergic systems and other biological systems implicated in the pathophysiology of depression such as the substance P and stress-hormone systems, have reciprocal interactions, and ultimately stimulate neurogenesis (Reul and Holsboer, 2002; Schwarz and Ackenheil, 2002). These pathways showed to be affected by several antidepressant treatments, thus they represent the main focus of pharmacogenetic research. Other lines of investigation have included inflammatory cytokines (Schiepers et al., 2005) and the endogenous clock system (Healy and Waterhouse, 2005).

### Brain monoamine systems

*Tryptophan hydroxylase.* Tryptophan hydroxylase (TPH) catalyzes the rate-limiting step in 5-HT biosynthesis.

\*Institute of Psychiatry, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy. Tel +39 051 6584237, Fax +39 051 521030 e.mail: alessandro.serretti@unibo.it

Its prominent role in the pathophysiology of depression is underscored by the fact that tryptophan depletion can induce a transient depressive state in individuals with a known history of depressive disorder (Booij et al., 2003). The gene encoding TPH has been cloned and mapped on 11p15.3-p14 (Craig et al., 1991). It includes two bi-allelic polymorphisms in position 218 (A218C) and 779 (A779C) of intron 7, which are in strong disequilibrium (Nielsen et al., 1997). The A218C polymorphism is located in a potential GATA transcription factor-binding site, therefore it may influence gene expression, and consequently antidepressant (AD) response. The rarer TPH\*A-allele of A218C polymorphism showed in fact to be associated with a decreased 5-HT synthesis (Jonsson et al., 1997), even if this finding has not been replicated.

The presence of this allele may predispose to suicidal behavior as emerged from two recent meta-analyses (Bellivier et al., 2004; Rujescu et al., 2003). The A-allele was also associated with a slower and less marked HAMD improvement in two double-blind trials with fluvoxamine and paroxetine we carried out in our center in Milan (Serretti et al., 2001b; Serretti et al., 2001c). Subsequent studies performed in Japan (Yoshida et al., 2002b) and Korea (Ham et al., 2005) failed to demonstrate a correlation between the TPH A218C polymorphism and response to Selective Serotonin Reuptake Inhibitors (SSRIs). Recently a new TPH isoform was discovered and called TPH-2 (Walther et al., 2003), while the original isoform is now TPH-1. The gene encoding TPH-2 (chromosome 12) is 150-fold more expressed in mouse brain than the TPH-1 gene (Malek et al., 2005), therefore it might represent a promising candidate for pharmacogenetic investigation. Peters et al. tested both TPH isoforms in 96 unipolar depressives patients treated with fluoxetine for 12 weeks (Peters et al., 2004). While the TPH-1 gene was associated with general response, TPH-2 variants were implicated in specific response to fluoxetine. These findings are in line with the latest published studies demonstrating that all TPH isoforms are expressed in the human brain, with different levels of each isoform between the brain areas (Zill et al., 2005). Two studies examined the relationship between TPH-2 polymorphisms and resistant depression (Garriock et al., 2005; Zhang et al., 2005): a marginal association emerged with the TPH-2 G1463A single-nucleotide polymorphism (Zhang et al., 2005).

*Serotonin transporter.* Extracellular monoamines are cleared from the synaptic cleft and carried into the synaptic terminal by plasma membrane proteins which are termed transporters. As these proteins are high-affinity targets for psychostimulants (cocaine,

amphetamine) and different classes of ADs, they are suitable candidates for pharmacogenetic research. To date, a large amount of studies have involved the serotonin transporter (SERT) gene. The brain SERT is the principal site of action of many antidepressant drugs (SSRI, TCA) and mediates the behavioral and toxic effects of cocaine and amphetamines. SERT knockout mice show robust phenotypic abnormalities when compared to normal mice, with increased anxiety and inhibited exploratory locomotion (Holmes et al., 2003a). The deletion of the SERT gene produces also a reduction in aggressive behavior and home cage activity of knockout mice; this effect is further enhanced by desensitization of 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors (Holmes et al., 2003b).

Ramamoorthy et al. (1993) identified and cloned a single gene encoding the human SERT (SLC6A4), localized to chromosome 17q11.1-q12. The gene spans 31 kb and consists of 14 exons (Lesch et al., 1994). Heils et al. (1996) reported a polymorphism in the transcriptional control region upstream of the SERT coding sequence. The polymorphism is located approximately 1000 bp upstream of the transcription initiation site within a region composed of 16 repeat units (5-HTTLPR). It consists of a 44-bp insertion/deletion involving units 6 to 8. It is known that the long (l) 5-HTTLPR allele has twice the SERT expression in the basal state than the short (s) form. As the 5-HTTLPR polymorphism can affect SERT expression and SERT is the main target of SSRIs, it is reasonable to hypothesize the influence of 5-HTTLPR variants on SSRI response. This has been tested in several studies (table 1): a better outcome in l-allele carriers (Arias et al., 2003; Joyce et al., 2003; Murphy et al., 2004; Pollock et al., 2000; Rausch et al., 2002; Smeraldi et al., 1998; Zanardi et al., 2000; Zanardi et al., 2001) has been a consistent finding among Caucasian patients. Instead, Asian studies produced conflicting results, with some samples showing the same genotype-response association pattern as Caucasians (Kato et al., 2005; Lee et al., 2004b; Yu et al., 2002) and others revealing a better response in 5-HTTLPR s-allele carriers (Kim et al., 2000; Yoshida et al., 2002a) or no effect of the 5-HTTLPR (Yoshida et al., 2004). Most likely the small sample sizes, different ethnicity and different definition of responders do not allow to draw a definite conclusion on the role of the 5-HTTLPR polymorphism. This appears to influence treatment outcome independently from other predictors, including antidepressant dose and SERT affinity (Rausch et al., 2002).

Recent studies suggest that the 5-HTTLPR polymorphism may also affect antidepressant tolerability. Thus in a double-blind trial of elderly

outpatients s-allele carriers treated with paroxetine were characterized by more severe adverse effects and higher discontinuation rates compared to l/l homozygotes, while in a subgroup on mirtazapine the s-allele was associated with a better tolerability and fewer discontinuations (Murphy et al., 2004). Still the s-allele was shown to identify patients at risk for developing insomnia and agitation with fluoxetine treatment (Perlis et al., 2003). However other studies reported no association between 5-HTTLPR variants and side effects occurring with SSRIs (Takahashi et al., 2002). Two studies demonstrated an increased risk for antidepressant-induced mania with carriage of the s-allele (Masoliver et al., 2006; Mundo et al., 2001), but negative findings were also reported (Rousseva et al., 2003; Serretti et al., 2004b).

Over the last few years new polymorphisms within the SERT gene have attracted attention as predictors of antidepressant response, their interaction with the 5-HTTLPR waiting to be elucidated. Ogilvie et al. identified a different variable number tandem repeat (VNTR) polymorphism in the second intron of the SERT gene (Stin2) which was related to susceptibility to major depression (Gutierrez et al., 1998; Ogilvie et al., 1996). Ito et al. (2002) reported no association of Stin2 with fluvoxamine response. A single nucleotide polymorphism (rs25531 SNP), located just upstream of the 5-HTTLPR, revealed a significant influence on antidepressant response to fluoxetine and, intriguingly, a moderation effect on 5-HTTLPR alleles. In the presence of the G-allele of this SNP, the l-allele of the 5-HTTLPR is associated with non-response, as the s-allele where it is expressed together with the A-allele of the rs25531 SNP (Kraft et al., 2005).

*Norepinephrine transporter.* One study determined whether NET gene variants could affect response to minalcipram (Yoshida et al., 2004). Significant associations were reported with the T-128C (T-allele predicting a better response) and A1287G polymorphisms (slower onset of response in A/A genotype carriers).

*Monoamine oxidase A.* MAO-A is a major degrading enzyme in the metabolic pathways of monoamine neurotransmitters (NE, DA, 5-HT). The gene encoding MAO-A - chromosome Xp11.23 (Sabol et al., 1998) - is supposed to influence the mechanism of action of SSRIs through an interaction with SERT (Maes and Meltzer, 1995). A polymorphism located 1.2 kb upstream the MAO-A coding sequences (VNTR) was reported to affect the transcription of the MAO-A promoter (Sabol et al., 1998). Its influence on AD treatment efficacy was investigated in three studies which yielded negative results (Cusin et al., 2002; Muller

et al., 2000; Yoshida et al., 2002b). More recently, in a sample of Chinese inpatients with major depressive disorder, the 3-repeat variant of the MAO-A VNTR was positively associated with antidepressant treatment outcome in females (Yu et al., 2005).

*Catechol-o-methyltransferase.* COMT is involved in the catabolic pathways of NE and DA. Moreover, this enzyme can indirectly affect brain 5-HT given reciprocal interactions between DA and 5-HT. Lachman et al. (1996) reported a functional polymorphism consisting on a transition of guanine to adenine at codon 158, leading a substitution of Val to Met in MB-COMT (and in position 108 in S-COMT). It has been shown that the Met allele results in a three to fourfold lower enzymatic activity than Val allele (Mannisto and Kaakkola, 2005; Weinshilboum et al., 1999). Two recent studies report that patients with Met-Met homozygosity are less likely to respond to mirtazapine (Szegedi et al., 2005) and citalopram (Arias et al., 2006).

*Beta 1 adrenoceptor.* These receptors serve as important regulators of Central Nervous System-mediated behavior and of several neural functions, including mood, memory, neuroendocrine control, and stimulation of autonomic function, and are involved in the mediation of AD effects (Crissman et al., 2001). This may also explain why beta-blocker medications are associated with side effects such as depression and lethargy (Kirigiti et al., 2000).

Beta1 adrenergic receptor gene ADRB1 was mapped on 10q24-q26 (Yang-Feng et al., 1990). A polymorphism in the intracellular cytoplasm tail, consisting of a G/C transversion at position 1165 of the ADRB1 gene, was shown to alter the receptor-Gs protein interaction, with functional consequences on signal transduction (Mason et al., 1999). This polymorphism was also found to affect response to "noradrenergic" antidepressant agents, even if the finding was only marginally significant (Zill et al., 2002).

*Dopamine receptors.* DA-containing neurons are located primarily in the midbrain and a number of experimental observations have suggested that a decreased dopaminergic neurotransmission might be associated with depression. Moreover, an interaction between the serotonergic and dopaminergic systems in the nucleus accumbens has been established, since motivation and hedonia have been associated with DA release in the nucleus accumbens (Zangen et al., 2001). In spite of these data suggesting a pathogenic role for the dopamine system in depressive disorders, no significant association of DRD2 and DRD4 variants with SSRI efficacy was observed in a large sample (N=364) of

depressed inpatients collected in our center in Milan (Serretti et al., 2001a).

**5-HT<sub>1A</sub> receptors.** These receptors are located on cortical and limbic neurons, both at postsynaptic and presynaptic levels where they act as autoreceptors, preventing the further release of 5HT with a negative feedback. Pindolol is thought to accelerate the onset of AD action by blocking 5-HT<sub>1A</sub> autoreceptors (Perez et al., 1997). A SNP in the promoter region of the 5-HT<sub>1A</sub> gene (G to C substitution at position -1019 [Wu and Comings, 1999]) was associated with the diagnosis of major depression in a case-control study (Lemondé et al., 2003) and, more recently, with antidepressant treatment outcome. Since 2004 five independent studies reported either a better response to SSRI drugs in 5-HT<sub>1A</sub> -1019C/C homozygotes (Hong et al., 2006) or a worse response in G-allele carriers (Arias et al., 2005; Lemondé et al., 2004; Serretti et al., 2004a). A different Gly272Asp polymorphism was explored in Japanese MDD outpatients treated with fluvoxamine. Asp allele carriers showed a more marked reduction in depressive symptomatology compared to Gly/Gly homozygotes (Suzuki et al., 2004). This finding was not confirmed by subsequent studies (Yu et al., 2006).

**5-HT<sub>2A</sub> receptors.** The activation of 5-HT<sub>2A</sub> receptors in medial prefrontal cortex and anterior cingulate cortex is thought to mediate the hallucinogenic properties of LSD, whereas in amygdala the 5-HT<sub>2A</sub> receptor activation is a component of antidepressant response. The 5-HT<sub>2A</sub> receptors may mediate some of the AD effects seen in experimental animal models of depression (Skrebuhhova et al., 1999). An antidepressant drug such as nefazodone was found to partially exert its therapeutic effect via a 5-HT<sub>2A</sub> receptor antagonism (Hemrick-Luecke et al., 1994). The gene coding for 5-HT<sub>2A</sub> receptor was mapped to chromosome 13q14-q21 (Campbell et al., 1997). A T to C substitution at position 102 was implicated in AD response (Minov et al., 2001), even if the finding could not be replicated in two independent samples (Cusin et al., 2002; Hong et al., 2006). In addition, more side effects were reported in patients with the 5-HT<sub>2A</sub>-102C/C genotype who were treated with either paroxetine or mirtazapine for eight weeks (Murphy et al., 2003b). Another polymorphism in the promoter region of the 5-HT<sub>2A</sub> gene (-1438 G/A SNP) was independently explored by three research groups (Choi et al., 2005; Sato et al., 2002; Yoshida et al., 2004): one study showed a greater improvement of “core” depressive symptomatology and somatic anxiety in 5-HT<sub>2A</sub>-1438G allele carriers (Choi et al., 2005). Finally, the T/T variant of the 5-HT<sub>2A</sub> -C1420T SNP revealed a

marginal association with a worse response to SSRI treatment (Cusin et al., 2002).

**5-HT<sub>6</sub> receptors.** This is a G-protein coupled receptor which stimulates adenylyl cyclase. In the rat it shows high affinity for ADs such as mianserin and clomipramine (Boess et al., 1997). 5HT<sub>6</sub> receptor antagonists seem to improve retention performance in experimental animals which has implicated a role for 5HT<sub>6</sub> in cognition enhancement (Meneses, 2001; Rogers and Hagan, 2001). Kohen et al. (1996) reported a silent polymorphism consisting of a thymidine to cytosine substitution at position 267 (TC 267) within the first exon of the 5-HT<sub>6</sub> receptor gene. This SNP was investigated for association with AD response in two studies. In the first one, 34 MDD patients receiving various ADs yielded negative results (Wu et al., 2001). More recently, in a study involving a larger MDD sample (N=71), 5-HT<sub>6</sub> receptor CT heterozygotes were found to have a better response to AD treatment than homozygotes (CC + TT genotypes) (Lee et al., 2005).

### **Intracellular signal transduction pathways**

**G-protein Beta-3 subunit.** G-proteins are key components of intracellular signal transduction in all cells of the body including neurons. Inactive G-proteins are trimers coupled with receptors on the cell-membrane. The active form is a GTP-bound alpha monomer resulting from the dissociation of a beta-gamma dimer (Neer, 1995). Chronic treatment with fluoxetine showed to attenuate GTP binding to gamma subunit in the dorsal raphe nucleus of rats, thus inducing desensitisation of 5HT<sub>1A</sub> receptors (Castro et al., 2003). Beta subunit is subdivided into three subtypes. The gene encoding beta3 subunit (GNB3) is located at human chromosome 12p13, in a region which harbours other five genes (Ansari-Lari et al., 1996). Its sequence spans 7.5 kb and includes 11 exons and 10 introns. A polymorphism in GNB3 exon 10 (C825T SNP) has been shown to modulate signal transduction and ion transport activity (Siffert et al., 1998). GNB3 825T variant is associated with the occurrence of the splice variant Gbeta3s, which, despite a deletion of 41 amino acids, is functionally active in reconstituted systems. To date, four independent studies have demonstrated a better antidepressant response in patients with one or two copies of the Gbeta3 T-allele (Joyce et al., 2003; Lee et al., 2004a; Serretti et al., 2003b; Zill et al., 2000). Hong et al. (2006) reported the only negative study in an Asian sample.

### **Stress hormone system**

Stressful or traumatic events occurring in early life significantly increase the risk for depression in adulthood (Nemeroff and Vale, 2005). To further underscore the

relationship between stress response and depressive disorder, genes coding for components of the stress hormone system have so far been associated with AD treatment outcome.

*CRH receptor 1.* A number of animal studies have displayed the antidepressant properties of CHR receptor I antagonists (Overstreet and Griebel, 2004; Seymour et al., 2003). A three SNP haplotype within the corticotrophin-releasing hormone receptor 1 (CRHR1) could be associated with response to desipramine or fluoxetine in a sample of Mexican-Americans (Licinio et al., 2004).

*Glucocorticoid receptor gene.* A research group in Munich, Germany, identified a functional polymorphism of the glucocorticoid receptor (GR) gene (ER22/23EK) and a series of SNPs within the gene encoding the hsp90 co-chaperone FKBP5 (a part of the mature GR hetero-complex that regulates GR sensitivity), which were shown to modulate the onset of response to various classes of antidepressant drugs (Binder et al., 2004). However no replication followed.

### **ACE-substance P system**

*Angiotensin converting enzyme.* There is increasing evidence pointing to the involvement of the substance P system in the pathophysiology of depression. NK1 receptor antagonists have shown preclinical activity in several paradigms of anxiety and depression (Czeh et al., 2005; Gentsch et al., 2002). Mutant mice lacking the NK1 receptor gene have an increased firing rate of dorsal raphe serotonergic neurons, an effect that can also be seen after the administration of substance P antagonists (Arranz-Estevez, 2005). When given chronically, NK1 antagonists promote an enhancement of serotonergic transmission in the hippocampus that seems to be mediated by interaction with other neurotransmission systems (Guiard et al., 2006). Clinical efficacy of such drugs has also been demonstrated among patients with major depression, although the results have been inconclusive (Kramer et al., 2004). In the Central Nervous System substance P is co-localized with the angiotensin converting enzyme (ACE) which is thought to participate in its degradation. An intronic insertion/deletion (I/D) polymorphism determines functional variants of the ACE gene with a secondary impact on substance P levels and antidepressant activity. Indeed, the D allele, which determines higher ACE plasma levels (Rigat et al., 1990), was recently associated with higher substance P levels (Arinami et al., 1996) and a faster response to antidepressant treatments (Baghai et al., 2001), including total sleep deprivation (Baghai et al., 2003), particularly among females (Baghai et al., 2004).

Interestingly, this polymorphism also influences HPA-axis reactivity in depressed patients, with patients carrying the D/D genotype having the highest cortisol response in the Dex-CRH test administered at admission (Baghai et al., 2002). More recently, another component of the ACE-substance P system, the angiotensin II receptor gene (ATI), was added to outcome predictors in major depression (Bondy et al., 2005).

### **Proinflammatory cytokines**

*Interleukin 1-Beta.* Interleukin-1 (IL-1), produced mainly by blood monocytes, mediates the host reactions of acute phase response. In female rats, IL-1 may induce a behavioral complex called sickness behavior, characterized by locomotor retardation, sleep disorders, soporific effects, anorexia, weight loss, hyperalgesia, decreased social exploration, and inhibition of sexual behavior (Dantzer et al., 1998). This animal behavior, which resembles human depression, can be inhibited by chronic antidepressant treatment (Dunn et al., 2005). Increased production of IL-1 has been reported in patients with major depression and dysthymia (Anisman et al., 2002; Anisman et al., 1999). IL-1, like other cytokines, may cause hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and reduction in 5-HT levels which ultimately result in the onset of depression (Dunn et al., 2005). The association of a biallelic polymorphism (-511C/T SNP) located in the promoter region of the IL-1beta gene to fluoxetine response was studied in 119 depressed patients who underwent a 4-week treatment with fluoxetine. Trial results showed a trend towards T/T homozygotes having milder depressive symptoms and a more favorable fluoxetine response compared to C-allele carriers (Yu et al., 2003).

### **Endogenous clock system**

*Circadian Locomotor Output Cycles Kaput (CLOCK).* The endogenous control of circadian rhythms is regulated by a central pacemaker localized in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. Several genes are thought to interact in rhythms control and they are called "clock" for their function of regulation of timing in biological functions (Reppert and Weaver, 2001). In particular, CLOCK gene was identified in mice (King et al., 1997) and in humans (Steeves et al., 1999). The mRNA of human CLOCK gene has been found in the SCN, hippocampus, piriform cortex and cerebellum (Steeves et al., 1999), all areas involved in biological rhythms. One polymorphism, named 3111 T/C located in the 3' flanking region, has been shown to affect mRNA stability and half-life (Mignone et al., 2002). The C allele has been associated with significantly higher "eveningness" in healthy subjects and with a delay in preferred timing for activity or sleep episodes, with no

changes in sleep architecture (Katzenberg et al., 1998). In mood disorders the same C variant was associated with higher recurrence rates in bipolar patients (Benedetti et al., 2003), increased lifetime sleep disturbances (Serretti et al., 2003a) and persistence of insomnia during antidepressant treatment (Serretti et al., 2005).

### Pharmacokinetic aspects

*Cytochrome P450 enzyme complex.* The cytochrome P450 (CYP) superfamily exists in over 50 isoenzymes that catalyze the oxidation of many drugs and chemicals. In humans, seven isoforms -CYP1A, CYP2A6, CYP2B6, CYP2C, CYP2D6, CYP2E1 and CYP3A enzymes- account for approximately 70% of the liver cytochromes. CYP2D6 has been implicated in the metabolism of most antidepressant drugs (Lin and Lu, 1998). So far, up to 75 different alleles have been reported for CYP2D6; more than 15 of these encode an inactive or no enzyme at all, while others consist of gene duplications (Bertilsson et al., 2002). Such gene variants have shown a clear influence on drug metabolism, and individuals are classified as poor (PM), intermediate (IM), extensive (EM) and ultra-rapid (UM) metabolizers according to their inherited genetic profile (Nebert and Dieter, 2002). However, their effect on AD response and tolerability is less consistent and still under investigation.

A direct correlation was observed between the number of functional CYP2D6 gene copies and plasma levels of some TCAs such as nortriptyline (Dalen et al., 1998). From these pharmacokinetic studies it has been extrapolated that starting doses of nortriptyline are probably enough to reach therapeutic plasma levels in subjects with no or only one functional copy of the CYP2D6 gene, among whom higher doses might increase toxicity. On the contrary, high-normal doses of the drug may be required for patients with 2-4 copies (Bertilsson et al., 2002). Dose adjustments according to CYP2D6 genotype have been proposed for TCAs in view of their small therapeutic “windows” (Kirchheiner et al., 2001).

Like TCAs, CYP2D6 variants have been shown to modify the plasma concentrations of the SSRI paroxetine (Ozdemir et al., 1999) and the SNRI venlafaxine (Veefkind et al., 2000). For the latter, a relationship between PM status and the increased occurrence of cardiovascular side effects or toxicity has been reported. On the contrary, no relationship between CYP2D6 genotype, tolerability and efficacy was observed in a sample of geriatric inpatients on paroxetine (Murphy et al., 2003b). So, even if dose recommendations based on CYP2D6 genotypes have been put forward for SSRIs too, the relevance of such dose adjustments is questionable given their flat dose response curve (Brosen

and Naranjo, 2001). The impact of CYP2D6 variants might be greater for SSRI + TCA combined treatments. Indeed, co-administration of paroxetine and desipramine in EM who had at least two functional copies of the CYP2D6 gene was found to result in a 5-fold decrease in desipramine clearance (Brosen et al., 1993).

*P-glycoprotein.* P-glycoprotein is a member of the highly conserved superfamily of ATP-binding cassette (ABC) transporter proteins. It acts as a pump that, in view of its localization –liver, kidney and small capillars of the blood-brain barrier (Thiebaut et al., 1987)–, appears to regulate the clearance of xenobiotics and access to the brain for psychotropic drugs (Schinkel et al., 1996). The gene encoding p-glycoprotein –formerly MDR1, now ABCB1– is localized to chromosome 16. An intronic ABCB1 polymorphism was found to be associated with remission to antidepressant therapy but not with drug plasma levels (Uhr, 2005). It is therefore likely that ABCB1 variants influence antidepressant response by affecting the transport of drugs across the blood-brain barrier, with a mechanism that does not imply modification of drug plasma concentration.

### Perspectives in psychopharmacogenetics

In spite of the popular claim that pharmacogenetics holds promises for an individualized approach to psychopharmacology, important shortcomings have so far hampered the use of research data in clinical practice:

1. Although the literature provides us with an increasing number of candidate genes, only a few of them could be consistently associated with drug efficacy or tolerability.
2. Even those genes with a proven influence on drug behavior could show opposite effects in different studies.
3. Only a small amount of variance in individual response to psychotropic drugs could be explained by genetic factors.

Accordingly, improving the consistence of results across studies and expanding the number of candidate genes appear to be priorities in the agenda of today’s psychopharmacogenetics.

In the study of clinical response, focus is classically decreasing in overall psychopathology. However, increasing evidence suggests that single candidate genes can have a selective impact on few clusters of symptoms rather than on the global clinical pictures of mood disorders. For instance, the therapeutic effect of 5-HTTLPR variants is principally directed to somatic anxiety (Kato et al., 2005; Yu et al., 2002). Similarly, the C/C genotype of the CLOCK gene was associated with persistence of insomnia during SSRI treatment, while it

had no effect on overall antidepressant response (Serretti et al., 2005). This may imply that a major cause of contrasting findings in published studies is the presence of different symptom profiles in their samples. So, future pharmacogenetic analyses should target symptom dimensions.

Each candidate gene may also be related to factors that independently affect treatment outcome. For example, as personality traits and disorders are known to worsen the outcome of treated mood disorders, genes that are associated with these factors should predict a poor drug response. Accordingly, recent studies demonstrate an excess of anxiety traits in the presence of the 5-HTTLPR s-allele (Lesch et al., 1996; Melke et al., 2001), which was already linked with a negative prognosis of antidepressant treatment (see above). Most findings in the field of pharmacogenetics could be obtained by exploring a relatively small number of candidate genes which encoded proteins involved in drug activity. In spite of some appreciable results, this hypothesis-driven approach is probably too restrictive and leaves out a large number of candidate polymorphisms. Indeed, all observed gene variants do not reach the putative 50% of variance explained by genetic factors in the complex trait of antidepressant response. *Pharmacogenomics* may then aid in identifying more candidates by discovering those genes that are activated or de-activated in response to treatment (Bailey et al., 1998). One popular method of experimental genomics is expression array (Brown and Botstein, 1999). This involves hybridization of fluorescent or radioactively labeled mRNA species to cDNA arrays. So, thousands of mRNA transcripts are analyzed simultaneously, and those that change after treatment are related to candidate genes. Alternatively, *proteomics* evaluates gene activity by detecting protein expression instead of mRNA transcripts (Kao, 1999). Both animal and human tissues have been used for these studies. Most literature has investigated antidepressant treatment-related genome-wide mRNA expression changes in rodent brain tissue (Chen et al., 2003; Drigues et al., 2003; Landgrebe et al., 2002; Yamada et al., 2005). A few studies have investigated the effects of antidepressant treatment on peripheral blood monocytes (Palotas et al., 2004). Overall results have been largely inconsistent. In fact, whole genome SNP analyses have an expected high number of false positive associations due to the high degree of multiple testing. To bypass this problem, the last few years have witnessed the development of new experimental designs that combine the methods of linkage analysis, pharmacogenomics and proteomics. Examples of such sequential approaches have already been published with promising results (Lachman et al., 1997; Niculescu et al., 2000).

Besides individualizing drug treatment, pharmacogenetics/pharmacogenomics would offer a good solution to the problem of biological diversity in psychiatric disorders. Thus, response to a given drug could be used to identify homogeneous forms within pathophysiologically heterogeneous syndromes, which may facilitate the discovery of new susceptibility genes for psychiatric conditions. This strategy has been proposed and successfully applied to lithium response in bipolar disorder (Alda, 1999). However, the emerging literature has extended the influence of single genes to a wide range of psychological and psychopathological phenomena in addition to drug response. The SERT gene is an emblematic example of such multiple effects. Indeed, the 5-HTTLPR polymorphism has been associated with different characteristics of mood disorders: age of onset (Bellivier et al., 2002; Nobile et al., 2004), illness recurrence (Cusin et al., 2001; Rousseva et al., 2003), drug response (see above), reactivity to stressful life events (Caspi et al., 2003), personality traits (Park et al., 2004) and several psychiatric diagnoses such as alcoholism (Feinn et al., 2005), smoking (Kremer et al., 2005), psychosomatic disorders (Yeo et al., 2004), eating disorders (Matsushita et al., 2004; Steiger et al., 2005), suicide (Courtet et al., 2001), autism (Bartlett et al., 2005) and attention deficit hyperactivity disorder (Bobb et al., 2005). Future studies will clarify whether such phenotypes are all simultaneously present or at different times in the same individuals. Complex phenotypic profiles will then be obtained by pooling together such different features on the basis of their linear association with gene variants (Serretti et al., in press). This is a simple methodology to resume solitary data in comprehensive models, and we suggest it as a starting-point for future research on the role of crucial genes in modulating human behaviors.

## REFERENCES

1. ALDA M: Pharmacogenetics of lithium response in bipolar disorder. *J Psychiatry Neurosci*, 24:154-158, 1999.
2. ANISMAN H, KOKKINIDIS L, MERALI Z: Further evidence for the depressive effects of cytokines: anhedonia and neurochemical changes. *Brain Behav Immun*, 16:544-56, 2002.
3. ANISMAN H, RAVINDRAN AV, GRIFFITHS J, MERALI Z: Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. *Mol Psychiatry*, 4:182-8, 1999.
4. ANSARI-LARI M, MUZNY D, LU J, LU F et al.: A gene-rich cluster between the CD4 and triosephosphate isomerase genes at human chromosome 12p13. *Genome Res*, 6:314-326, 1996.
5. ARIAS B, CATALAN R, GASTO C, GUTIERREZ B, FANANAS L: 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow up study. *J Clin Psychopharmacol*, 23:563-7, 2003.



6. ARIAS B, CATALAN R, GASTO C, GUTIERREZ B, FANANAS L: Evidence for a combined genetic effect of the 5-HT<sub>1A</sub> receptor and serotonin transporter genes in the clinical outcome of major depressive patients treated with citalopram. *J Psychopharmacol*, 19:166-172, 2005.
7. ARIAS B, SERRETT A, LORENZI C, GASTO C et al.: Analysis of COMT gene (Val 158 Met polymorphism) in the clinical response to SSRIs in depressive patients of European origin. *J Affect Disord*, 90:251-256, 2006.
8. ARINAMI T, LI L, MITSUSHIO H, ITOKAWA M et al.: An insertion/deletion polymorphism in the angiotensin converting enzyme gene is associated with both brain substance P contents and affective disorders. *Biol Psychiatry*, 40:1122-7, 1996.
9. ARRANZ ESTEVEZ FJ: The modulatory role of neurokinins in affective behaviors. *Actas Esp Psiquiatr*, 33:55-65, 2005.
10. BAGHAI T, SCHULE C, ZWANZGER P, MINOV C et al.: Hypothalamic-pituitary-adrenocortical axis dysregulation in patients with major depression is influenced by the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene. *Neurosci Lett*, 328:299-303, 2002.
11. BAGHAI T, SCHULE C, ZWANZGER P, ZILL P et al.: Influence of a functional polymorphism within the angiotensin I-converting enzyme gene on partial sleep deprivation in patients with major depression. *Neurosci Lett*, 339:223-226, 2003.
12. BAGHAI TC, SCHULE C, ZILL P, DEIML T et al.: The angiotensin I converting enzyme insertion/deletion polymorphism influences therapeutic outcome in major depressed women, but not in men. *Neurosci Lett*, 363:38-42, 2004.
13. BAGHAI TC, SCHULE C, ZWANZGER P, MINOV C et al.: Possible influence of the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene on therapeutic outcome in affective disorders. *Mol Psychiatry*, 6:258-9, 2001.
14. BAILEY D, BONDAR A, FURNESS L: Pharmacogenomics-it's not just pharmacogenetics. *Curr Opin Biotechnol*, 9:596-601, 1998.
15. BARTLETT CW, GHARANI N, MILLONIG JH, BRZUSTOWICZ LM: Three autism candidate genes: a synthesis of human genetic analysis with other disciplines. *Int J Dev Neurosci*, 23:221-34, 2005.
16. BELLIVIER F, CHASTE P, MALAFOSSE A: Association between the TPH gene A218C polymorphism and suicidal behavior: a meta-analysis. *Am J Med Genet B Neuropsychiatr Genet*, 124:87-91, 2004.
17. BELLIVIER F, LEROUX M, HENRY C, RAYAH F et al.: Serotonin transporter gene polymorphism influences age at onset in patients with bipolar affective disorder. *Neuroscience Letters*, 334:17-20, 2002.
18. BENEDETTI F, SERRETTI A, COLOMBO C, BARBINI B et al.: Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet*, 123B:23-6, 2003.
19. BERTILSSON L, DAHL M, DALEN P, AL-SHURBAJI A: Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *Br J Clin Pharmacol*, 53:111-122, 2002.
20. BINDER E, SALYAKINA D, LICHTNER P, WOCHNIK G et al.: Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet*, 36:1319-1325, 2004.
21. BOBB AJ, CASTELLANOS FX, ADDINGTON AM, RAPOPORT JL: Molecular genetic studies of ADHD: 1991 to 2004. *Am J Med Genet B Neuropsychiatr Genet*, 132:109-25, 2005.
22. BOESS F, MONSMA FJ, CAROLO C, MEYER V et al.: Functional and radioligand binding characterization of rat 5-HT<sub>6</sub> receptors stably expressed in HEK293 cells. *Neuropharmacology*, 36:713-720, 1997.
23. BONDY B, BAGHAI T, ZILL P, SCHULE C et al.: Genetic variants in the angiotensin I-converting-enzyme (ACE) and angiotensin II receptor (AT1) gene and clinical outcome in depression. *Prog Neuropsychopharmacol Biol Psychiatry*, 29:1094-99, 2005.
24. BONDY M: Pathophysiology of depression and mechanisms of treatment. *Dialogues Clinical Neuroscience*, 4:21-29, 2002.
25. BOOIJ L, VAN DER DOES A, RIEDEL W: Monoamine depletion in psychiatric and healthy populations: review. *Mol Psychiatry*, 8:951-973, 2003.
26. BROSEN K, HANSEN J, NIELSEN K: Inhibition by paroxetine of desipramine metabolism in extensive but not in poor metabolizers of sparteine. *Eur J Clin Pharmacol*, 44:344-355, 1993.
27. BROSEN K, NARANJO C: Review of pharmacokinetic and pharmacodynamic interaction studies with citalopram. *Eur Neuropsychopharmacol*, 11:275-283, 2001.
28. BROWN PO, BOTSTEIN D: Exploring the new world of the genome with DNA microarrays. *Nat Genet*, 21:33-7, 1999.
29. CAMPBELL D, SUNDARAMURTHY D, MARKHAM A, PIERI L: Fine mapping of the human 5-HT<sub>2A</sub> gene to chromosome 13q14 and identification of two highly polymorphic linked markers suitable for association studies in psychiatric disorders. *Genet Test*, 1:297-299, 1997.
30. CASPI A, SUGDEN K, MOFFITT TE, TAYLOR A et al.: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*, 301:386-9, 2003.
31. CASTRO ME, DIAZ A, DEL OLMO E, PAZOS A: Chronic fluoxetine induces opposite changes in G protein coupling at pre and postsynaptic 5-HT<sub>1A</sub> receptors in rat brain. *Neuropharmacology*, 44:93-101, 2003.
32. CHEN B, WANG J, SUN X, YOUNG L: Regulation of GAP-43 expression by chronic desipramine treatment in rat cultured hippocampal cells. *Biol Psychiatry*, 53:530-537, 2003.
33. CHOI M, KANG R, HAM B, JEONG H, LEE M: Serotonin receptor 2A gene polymorphism (-1438A/G) and short-term treatment response to citalopram. *Neuropsychobiology*, 52:155-162, 2005.
34. COURTET P, BAUD P, ABBAR M, BOULENGER JP et al.: Association between violent suicidal behavior and the low activity allele of the serotonin transporter gene. *Mol Psychiatry*, 6:338-41, 2001.
35. CRAIG SP, BOULARAND S, DARMON MC, MALLETT J, CRAIG IW: Localization of human tryptophan hydroxylase (TPH) to chromosome 11p15.3-p14 by in situ hybridization. *Cytogenetics Cell Genetics*, 56:157-9, 1991.
36. CRAMER JA, ROSENHECK R: Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv*, 49:196-201, 1998.
37. CRISSMAN AM, MAKHAY MM, O'DONNELL JM: Discriminative stimulus effects of centrally administered isoproterenol in rats: mediation by beta-1 adrenergic receptors. *Psychopharmacology (Berl)*, 154:70-5, 2001.
38. CUSIN C, SERRETTI A, LATTUADA E, LILLI R et al.: Influence of 5-HTTLPR and TPH Variants on Illness Time Course in Mood Disorders. *J Psychiatric Research*, 35:217-223, 2001.
39. CUSIN C, SERRETTI A, ZANARDI R, LATTUADA E et al.: Influence of monoamine oxidase A and serotonin receptor 2A polymorphisms in SSRIs antidepressant activity. *International J Neuropsychopharmacology*, 5:27-35, 2002.
40. CZECH B, PUDOVKINA O, VAN DER HART M, SIMON M et al.: Examining SLV-323, a novel NK1 receptor antagonist, in a chronic psychosocial stress model for depression. *Psychopharmacology (Berl)*, 180:548-557, 2005.
41. DALEN P, DAHL M, RUIZ M et al.: 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther*, 63:444-452, 1998.

42. DANTZER R, BLUTHE R, GHEUSI G, CREMONA S et al.: Molecular basis of sickness behavior. *Ann N Y Acad Sci*, 856: 132-138, 1998.
43. DRIGUES N, POLTYREV T, BEJAR C, WEINSTOCK M, YODIM M: cDNA gene expression profile of rat hippocampus after chronic treatment with antidepressant drugs. *J Neural Transm*, 110:1413-1436, 2003.
44. DUNN A, SWIERGIEL A, DE BEAUREPAIRE R: Cytokines as mediators of depression: what can we learn from animal studies? *Neurosci Biobehav Rev*, 29:891-909, 2005.
45. ESPOSITO K, GOODNICK P: Predictors of response in depression. *Psychiatr Clin North Am*, 26:353-365, 2003.
46. FAVA GA, FABBRI S, SONINO N: Residual symptoms in depression: an emerging therapeutic target. *Prog Neuropsychopharmacol Biol Psychiatry*, 26:1019-1027, 2002.
47. FEINN R, NELLISSERY M, KRANZLER HR: Meta-analysis of the association of a functional serotonin transporter promoter polymorphism with alcohol dependence. *Am J Med Genet B Neuropsychiatr Genet*, 133:79-84, 2005.
48. GARRIOCK H, ALLEN J, DELGADO P, NAHAZ Z et al.: Lack of association of TPH2 exon XI polymorphisms with major depression and treatment resistance. *Mol Psychiatry*, 10:976-977, 2005.
49. GENTSCH C, CUTLER M, VASSOUT A, VEENSTRA S, BRUGGER F: Anxiolytic effect of NKP608, a NK1-receptor antagonist, in the social investigation test in gerbils. *Behav Brain Res*, 133:363-368, 2002.
50. GOODNICK PJ: *Predictors of Treatment Response in Mood Disorders. Clinical Practice*. American Psychiatric Press, Washington, 1996.
51. GUIARD B, LANFUMEY L, GARDIER A: Microdialysis approach to study serotonin outflow in mice following selective serotonin reuptake inhibitors and substance P (neurokinin 1) receptor antagonist administration: a review. *Curr Drug Targets*, 7:187-201, 2006.
52. GUTIERREZ B, PINTOR L, GASTO C, ROSA A et al.: Variability in the serotonin transporter gene and increased risk for major depression with melancholia. *Hum Gen*, 103:319-322, 1998.
53. HAM B, LEE M, LEE H, KANG R et al.: No association between the tryptophan hydroxylase gene polymorphism and major depressive disorders and antidepressant response in a Korean population. *Psychiatr Genet*, 15:229-301, 2005.
54. HEALY D, WATERHOUSE J: The circadian system and the therapeutics of the affective disorders. *Pharmacol Ther*, 65:241-263, 2005.
55. HEILS A, TEUFEL A, PETRI S, STÖBER G et al.: Allelic variation of human serotonin transporter gene expression. *J Neurochem*, 66:2621-2624, 1996.
56. HEMRICK-LUECKE SK, SNODDY HD, FULLER RW: Evaluation of nefazodone as a serotonin uptake inhibitor and a serotonin antagonist in vivo. *Life Sci*, 55:479-83, 1994.
57. HOLMES A, MURPHY DL, CRAWLEY JN: Abnormal behavioral phenotypes of serotonin transporter knockout mice: parallels with human anxiety and depression. *Biol Psychiatry*, 54:953-9, 2003a.
58. HOLMES A, YANG RJ, LESCH KP, CRAWLEY JN, MURPHY DL: Mice lacking the serotonin transporter exhibit 5-HT(1A) receptor-mediated abnormalities in tests for anxiety-like behavior. *Neuropsychopharmacology*, 28:2077-88, 2003b.
59. HONG C, CHEN T, YU Y, TSAI S: Response to fluoxetine and serotonin 1A receptor (C-1019G) polymorphism in Taiwan Chinese major depressive disorder. *Pharmacogenomics J*, 6:27-33, 2006.
60. ITO K, YOSHIDA K, SATO K, TAKAHASHI H et al.: A variable number of tandem repeats in the serotonin transporter gene does not affect the antidepressant response to fluvoxamine. *Psychiatr Res*, 111:235-9, 2002.
61. JONSSON EG, GOLDMAN D, SPURLOCK G, GUSTAVSSON JP et al.: Tryptophan hydroxylase and catechol-O-methyltransferase gene polymorphisms: relationships to monoamine metabolite concentrations in CSF of healthy volunteers. *European Archives Psychiatry Clinical Neuroscience*, 247:297-302, 1997.
62. JOYCE PR, MULDER RT, LUTY SE, MCKENZIE JM et al.: Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein beta3 subunit as predictors of response to fluoxetine and nortriptyline. *Int J Neuropsychopharmacol*, 6:339-46, 2003.
63. KAO C: Functional genomic technologies: creating new paradigms for fundamental and applied biology. *Biotechnol Prog*, 15:304-311, 1999.
64. KATO M, IKENAGA Y, WAKENO M, OKUGAWA G et al.: Controlled clinical comparison of paroxetine and fluvoxamine considering the serotonin transporter promoter polymorphism. *Int Clin Psychopharmacol*, 20:151-156, 2005.
65. KATZENBERG D, YOUNG T, FINN L, LIN L et al.: A Clock polymorphism associated with human diurnal preference. *Sleep*, 21:569-576, 1998.
66. KIM DK, LIM SW, LEE S, SOHN SE et al.: Serotonin transporter gene polymorphism and antidepressant response. *Neuroreport*, 11:215-9, 2000.
67. KING DP, VITATERNA MH, CHANG AM, DOVE WF et al.: The mouse Clock mutation behaves as an antimorph and maps within the W19H deletion, distal of Kit. *Genetics*, 146: 1049-1060, 1997.
68. KIRCHHEINER J, BROSEN K, DAHL ML, GRAM LF et al.: CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr Scand*, 104:173-92, 2001.
69. KIRIGITI P, YANG YF, LI X, LI B et al.: Rat beta 1-adrenergic receptor regulatory region containing consensus AP-2 elements recognizes novel transactivator proteins. *Mol Cell Biol Res Commun*, 3:181-92, 2000.
70. KOHEN R, METCALF MA, KHAN N, DRUCK T et al.: Cloning, characterization, and chromosomal localization of a human 5-HT6 serotonin receptor. *J Neurochem*, 66:47-56, 1996.
71. KRAFT J, SLAGER S, MCGRATH P, HAMILTON S: Sequence analysis of the serotonin transporter and associations with antidepressant response. *Biol Psychiatry*, 58:58, 2005.
72. KRAMER M, WINOKUR A, KELSEY J, PRESKORN S et al.: Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. *Neuropsychopharmacology*, 29:2, 2004.
73. KREMER I, BACHNER-MELMAN R, RESHEF A, BROUDE L et al.: Association of the serotonin transporter gene with smoking behavior. *Am J Psychiatry*, 162:924-30, 2005.
74. LACHMAN HM, KELSOE JR, REMICK RA, SADOVNICK AD et al.: Linkage studies suggest a possible locus for bipolar disorder near the velo-cardio-facial syndrome region on chromosome 22. *American J Medical Genetics*, 74:121-128, 1997.
75. LACHMAN HM, MORROW B, SHPRINTZEN R, VEIT S et al.: Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. *Am J Med Genet*, 67:468-72, 1996.
76. LANDGREBE J, WELZL G, METZ T, VAN GAALLEN MM et al.: Molecular characterisation of antidepressant effects in the mouse brain using gene expression profiling. *J Psychiatry Res*, 36:119-29, 2002.
77. LEE HJ, CHA JH, HAM BJ, HAN CS et al.: Association between a G-protein beta3 subunit gene polymorphism and the symptomatology and treatment responses of major depressive disorders. *Pharmacogenomics J*, 4:29-33, 2004.
78. LEE MS, LEE HY, LEE HJ, RYU SH: Serotonin transporter promoter gene polymorphism and long-term outcome of antidepressant treatment. *Psychiatr Genet*, 14:111-5, 2004b.

79. LEE S, LEE K, LEE H, HAM B et al.: Association between the 5-HT<sub>6</sub> receptor C267T polymorphism and response to antidepressant treatment in major depressive disorder. *Psychiatry Clin Neurosci*, 59:140-145, 2005.
80. LEMONDE S, DU L, BAKISH D, HRDINA P, ALBERT PR: Association of the C(1019)G 5-HT<sub>1A</sub> functional promoter polymorphism with antidepressant response. *Psychopharmacology (Berl)*, 24:24, 2004.
81. LEMONDE S, TURECKI G, BAKISH D, DU L et al.: Impaired trans-repression at a 5-HT<sub>1A</sub> receptor gene polymorphism associated with major depression and suicide. *J Neurosci*, 23:8788-99, 2003.
82. LESCH KP, BALLING U, GROSS J, STRAUSS K et al.: Organization of the human serotonin transporter gene. *J Neural Transm Gen Sect*, 95:157-62, 1994.
83. LESCH KP, BENGEL D, HEILS A, SABOL SZ et al.: Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, 274:1527-31, 1996.
84. ICINIO J, O'KIRWAN F, IRIZARRY K, MERRIMAN B et al.: Association of a corticotropin-releasing hormone receptor 1 haplotype and antidepressant treatment response in Mexican-Americans. *Mol Psychiatry*, 9:1075-1082, 2004.
85. LIN JH, LU AY: Inhibition and induction of cytochrome P450 and the clinical implications. *Clin Pharmacokinet*, 35:361-90, 1998.
86. MAES M, MELTZER HY: The serotonin hypothesis of major depression. In: Bloom FE, Kupfer DJ (eds). *Psychopharmacology: The Fourth Generation of Progress*. Raven Press, 933-944, New York, 1995.
87. MALEK Z, DARDENTE H, PEVET P, RAISON S: Tissue-specific expression of tryptophan hydroxylase mRNAs in the rat midbrain: anatomical evidence and daily profiles. *Eur J Neurosci*, 22:895-901, 2005.
88. MANNISTO P, KAAKKOLA S: Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. *Pharmacol Rev*, 51:593-628, 2005.
89. MASOLIVER E, MENOYO A, PEREZ V, VOLPINI V et al.: Serotonin transporter linked promoter (polymorphism) in the serotonin transporter gene may be associated with antidepressant-induced mania in bipolar disorder. *Psychiatr Genet*, 16:25-29, 2006.
90. MASON DA, MOORE JD, GREEN SA, LIGGETT SB: A gain-of-function polymorphism in a G-protein coupling domain of the human beta<sub>1</sub>-adrenergic receptor. *J Biol Chem*, 274:12670-4, 1999.
91. MATSUSHITA S, SUZUKI K, MURAYAMA M, NISHIGUCHI N et al.: Serotonin transporter regulatory region polymorphism is associated with anorexia nervosa. *Am J Med Genet B Neuropsychiatr Genet*, 128:114-7, 2004.
92. MELKE J, LANDEN M, BAGHEI F, ROSMOND R et al.: Serotonin transporter gene polymorphisms are associated with anxiety-related personality traits in women. *Am J Med Genet*, 105:458-63, 2001.
93. MENESES A: Role of 5-HT<sub>6</sub> receptors in memory formation. *Drug News Perspect*, 14:396-400, 2001.
94. MIGNONE F, GISSI C, LIUNI S, PESOLE G: Untranslated regions of mRNAs. *Genome Biol*, 3:REVIEWS0004, 2002.
95. MINOV C, BAGHAI TC, SCHULE C, ZWANZGER P et al.: Serotonin-2A-receptor and -transporter polymorphisms: lack of association in patients with major depression. *Neurosci Lett*, 303:119-22, 2001.
96. MONCRIEFF J, KIRSCH I: Efficacy of antidepressants in adults. *BMJ*, 331:551-557, 2005.
97. MULLER DJ, SCHULZE TG, MACCIARDI F, OHLRAUN S et al.: Moclobemide response in depressed patients: association study with a functional polymorphism in the monoamine oxidase-A promoter Eighth World Congress on Psychiatric Genetics. Vol. 96 (4). *Neuropsychiatric Genetics*, Wiley-Liss, pp 537 Versailles, 2000.
98. MUNDO E, WALKER M, CATE T, MACCIARDI F, KENNEDY JL: The Role of Serotonin Transporter Protein Gene in Antidepressant-Induced Mania in Bipolar Disorder. *Arch Gen Psychiatry*, 58:539-544, 2001.
99. MURPHY G, HOLLANDER S, RODRIGUES H, SCHATZBERG A: Effects of the serotonin transporter promoter polymorphism on paroxetine and mirtazapine efficacy and side effects in geriatric major depression. In: Hospital TZH (ed). *Pharmacogenetics in Psychiatry Meeting*. Vol. 1, pp green tab. New York, 2003a.
100. MURPHY GM Jr, HOLLANDER SB, RODRIGUES HE, KREMER C, SCHATZBERG AF: Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. *Arch Gen Psychiatry*, 61:1163-9, 2004.
101. MURPHY GM Jr, KREMER C, RODRIGUES HE, SCHATZBERG AF: Pharmacogenetics of Antidepressant Medication Intolerance. *Am J Psychiatry*, 160:1830-1835, 2003b.
102. NEBERT D, DIETER M: The evolution of drug metabolism. *Pharmacology*, 61:124-135, 2002.
103. NEER EJ: Heterotrimeric G proteins: organizers of transmembrane signals. *Cell*, 80:249-57, 1995.
104. NEMEROFF C, VALE W: The neurobiology of depression: inroads to treatment and new drug discovery. *J Clin Psychiatry*, 66:5-13, 2005.
105. NICULESCU AB 3rd, SEGAL DS, KUCZENSKI R, BARRETT T et al.: Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. *Physiol Genomics*, 4:83-91, 2000.
106. NIELSEN DA, JENKINS GL, STEFANISKO KM, JEFFERSON KK, GOLDMAN D: Sequence, splice site and population frequency distribution analyses of the polymorphic human tryptophan hydroxylase intron 7. *Brain Research. Molecular Brain Research*, 45:145-8, 1997.
107. NIERENBERG AA: Predictors of response to antidepressants general principals and clinical implications. *Psychiatr Clin North Am*, 26:345-352, 2003.
108. NOBILE M, CATALDO MG, GIORDA R, BATTAGLIA M et al.: A case-control and family-based association study of the 5-HT<sub>1LPR</sub> in pediatric-onset depressive disorders. *Biol Psychiatry*, 56:292-5, 2004.
109. OGILVIE AD, BATTERSBY S, BUBB VJ, FINK G et al.: Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet*, 347:731-733, 1996.
110. O'REILLY RL, BOGUE L, SINGH SM: Pharmacogenetic response to antidepressants in a multicase family with affective disorder. *Biol Psychiatry*, 36:467-71, 1994.
111. ORSINI A: Antidepressant responses and segregation analyses in affective families. In: Racagni G, Smeraldi E (eds). *Anxious Depression: Assessment and Treatment*. Raven Press, New York, 1987.
112. OVERSTREET D, GRIEBEL G: Antidepressant-like effects of CRF1 receptor antagonist SSR125543 in an animal model of depression. *Eur J Pharmacol*, 497:49-53, 2004.
113. OZDEMIR V, TYNDALE R, REED K: Paroxetine steady-state plasma concentration in relation to CYP2D6 genotype in extensive metabolizers. *J Clin Psychopharmacol*, 19:472-475, 1999.
114. PALOTAS A, PUSKAS L, KITAJKA K, PALOTAS M et al.: The effect of citalopram on gene expression profile of Alzheimer lymphocytes. *Neurochem Res*, 29:1563-1570, 2004.
115. PARE CM, REES L, SAINSBURY MJ: Differentiation of two genetically specific types of depression by the response to anti-depressants. *Lancet*, 2:1340-3, 1962.
116. PARK JW, KIM JS, LEE HK, KIM YI, LEE KS: Serotonin transporter polymorphism and harm avoidance personality in chronic tension-type headache. *Headache*, 44:1005-9, 2004.

117. PEREZ V, GILABERTE I, FARIES D, ALVAREZ E, ARTIGAS F: Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. *Lancet*, 349:1594-7, 1997.
118. PERLIS RH, MISCHOULON D, SMOLLER JW, WAN YJ et al.: Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. *Biol Psychiatry*, 54:879-83, 2003.
119. PETERS EJ, SLAGER SL, MCGRATH PJ, KNOWLES JA, HAMILTON SP: Investigation of serotonin-related genes in antidepressant response. *Mol Psychiatry*, 9:879-889, 2004.
120. POLLOCK BG, FERRELL RE, MULSANT BH, MAZUMDAR S et al.: Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. *Neuropsychopharmacology*, 23:587-590, 2000.
121. QUITKIN F, MCGRATH P, STEWART J, TAYLOR B, DF K: Can the effects of antidepressants be observed in the first two weeks of treatment? *Neuropsychopharmacology*, 15:390-394, 1996.
122. RAMAMOORTHY S, BAUMAN AL, MOORE KR, HAN H et al.: Antidepressant- and cocaine-sensitive human serotonin transporter: molecular cloning, expression, and chromosomal localization. *Proc Natl Acad Sci USA*, 90:2542-6, 1993.
123. RAUSCH JL, JOHNSON ME, FEI Y-J, LI JQ et al.: Initial conditions of serotonin transporter kinetics and genotype: influence on ssri treatment trial outcome. *Biological Psychiatry*, 51:723-732, 2002.
124. REPPERT S, WEAVER D: Molecular analysis of mammalian circadian rhythms. *Annu Rev Physiol*, 63:647-76, 2001.
125. REUL J, HOLSBOER F: Pathophysiology of depression and mechanisms of treatment. *Dialogues Clinical Neuroscience*, 4:31-46, 2002.
126. RIGAT B, HUBERT C, ALHENC-GELAS F, CAMBIEN F et al.: An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest*, 86:1343-6, 1990.
127. RODEN D, GEORGE AJ: The genetic basis of variability in drug responses. *Nat Rev Drug Discov*, 1:37-44, 2002.
128. ROGERS D, HAGAN J: 5-HT<sub>2</sub>A receptor antagonists enhance retention of a water maze task in the rat. *Psychopharmacology (Berl)*, 158:114-119, 2001.
129. ROUSSEVA A, HENRY C, Van den BULKE D, FOURNIER G et al.: Antidepressant-induced mania, rapid cycling and the serotonin transporter gene polymorphism. *Pharmacogenomics J*, 3:101-4, 2003.
130. RUJESCU D, GIEGLING I, SATO T, HARTMANN A, MOLLER H: Genetic variations in tryptophan hydroxylase in suicidal behavior: analysis and meta-analysis. *Biol Psychiatry*, 54:465-473, 2003.
131. SABOL SZ, HU S, HAMER D: A functional polymorphism in the monoamine oxidase A gene promoter. *Human Genetic*, 103:273-279, 1998.
132. SATO K, YOSHIDA K, TAKAHASHI H, ITO K et al.: Association between -1438G/A promoter polymorphism in the 5-HT<sub>2A</sub> receptor gene and fluvoxamine response in Japanese patients with major depressive disorder. *Neuropsychobiology*, 46:136-40, 2002.
133. SCHIEPERS O, WICHERS M, MAES M: Cytokines and major depression. *Prog Neuropsychopharmacol Biol Psychiatry*, 29:201-217, 2005.
134. SCHILDKRAUT JJ: The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry*, 122:509-22, 1965.
135. SCHINKEL A, WAGENAAR E, MOL C, van DEEMTER L: P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs. *J Clin Invest*, 97:2517-2524, 1996.
136. SCHWARZ M, ACKENHEIL M: The role of substance P in depression: therapeutic implications. *Dialogues Clinical Neuroscience*, 4:21-29, 2002.
137. SERRETTI A, ARTIOLI P, LORENZI C, PIROVANO A et al.: The C(-1019)G polymorphism of the 5-HT<sub>1A</sub> gene promoter and antidepressant response in mood disorders: preliminary findings. *Int J Neuropsychopharmacol*, 7:453-460, 2004a.
138. SERRETTI A, ARTIOLI P, ZANARDI R, LORENZI C et al.: Genetic features of antidepressant induced mania and hypo-mania in bipolar disorder. *Psychopharmacology (Berl)*, 174:504-511, 2004b.
139. SERRETTI A, BENEDETTI F, MANDELLI L, LORENZI C et al.: Genetic dissection of psychopathological symptoms: Insomnia in mood disorders and CLOCK gene polymorphism. *Am J Med Genet*, 121B:39-43, 2003a.
140. SERRETTI A, CALATI R, MANDELLI L, De RONCHI D: Serotonin transporter gene variants and behaviour: a comprehensive review. *Current Drug Target*, 7:1659-1669, 2006.
141. SERRETTI A, CUSIN C, BENEDETTI F, MANDELLI L et al.: Insomnia improvement during antidepressant treatment and CLOCK gene polymorphism. *Am J Med Genet B Neuropsychiatr Genet*, 10:10, 2005.
142. SERRETTI A, FRANCHINI L, GASPERINI M, RAMPOLDI R et al.: Smeraldi E. Mode of inheritance in mood disorders families according to fluvoxamine response. *Acta Psychiatrica Scandinavica*, 98:443-450, 1998.
143. SERRETTI A, LORENZI C, CUSIN C, ZANARDI R et al.: SSRIs antidepressant activity is influenced by Gbeta3 variants. *Eur Neuropsychopharmacol*, 13:117-22, 2003b.
144. SERRETTI A, ZANARDI R, CUSIN C, ROSSINI D et al.: No association between dopamine D2 and D4 receptor gene variants and antidepressant activity of two selective serotonin reuptake inhibitors. *Psychiatry Research*, 104:195-203, 2001a.
145. SERRETTI A, ZANARDI R, CUSIN C, ROSSINI D et al.: Tryptophan hydroxylase gene associated with paroxetine antidepressant activity. *European Neuropsychopharmacology*, 11:375-380, 2001b.
146. SERRETTI A, ZANARDI R, ROSSINI D, CUSIN C et al.: Influence of tryptophan hydroxylase and serotonin transporter genes on fluvoxamine antidepressant activity. *Molecular Psychiatry*, 6:586-592, 2001c.
147. SEYMOUR P, SCHMIDT A, SCHULZ D: The pharmacology of CP-154,526, a non-peptide antagonist of the CRH1 receptor: a review. *CNS Drug Rev*, 9:57-96, 2003.
148. SIFFERT W, ROSSKOPF D, SIFFERT G, BUSCH S et al.: Association of a human G-protein beta3 subunit variant with hypertension. *Nature Genetics*, 18:45-8, 1998.
149. SKREBUHHOVA T, ALLIKMETS L, MATTO V. Effects of anxiogenic drugs in rat forced swimming test. *Methods Find Exp Clin Pharmacol*, 21:173-8, 1999.
150. SMERALDI E, ZANARDI R, BENEDETTI F, DIBELLA D et al.: Polymorphism Within the Promoter of the Serotonin Transporter Gene and Antidepressant Efficacy of Fluvoxamine. *Molecular Psychiatry*, 3:508-511, 1998.
151. STEEVES TD, ZHAO Y, SANGORAM AM, DU F et al.: Molecular cloning and characterization of the human clock gene: mexpression in the suprachiasmatic nuclei. *Genomics*, 57:198-200, 1999.
152. STEIGER H, JOOBER R, ISRAEL M, YOUNG SN et al.: The 5HT<sub>1LPR</sub> polymorphism, psychopathologic symptoms, and platelet [3H]-paroxetine binding in bulimic syndromes. *Int J Eat Disord*, 37:57-60, 2005.
153. SUZUKI Y, SAWAMURA K, SOMEYA T: The effects of a 5-hydroxytryptamine 1A receptor gene polymorphism on the clinical response to fluvoxamine in depressed patients. *Pharmacoeconomics J*, 4:283-286, 2004.
154. SZEGEDI A, RUJESCU D, TADIC A, MULLER MJ et al.: The catechol-O-methyltransferase Val108/158Met polymorphism affects short-term treatment response to mirtazapine, but not to paroxetine in major depression. *Pharmacogenomics J*, 5:49-53, 2005.

155. TAKAHASHI H, YOSHIDA K, ITO K, SATO K et al.: No association between the serotonergic polymorphisms and incidence of nausea induced by fluvoxamine treatment. *Eur Neuropsychopharmacol*, 12:477-81, 2002.
156. THIEBAUT F, TSURUO T, HAMADA H: Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. *Proc Natl Acad Sci USA*, 84:7735-7738, 1987.
157. TRANTER R, O'DONOVAN C, CHANDARANA P, KENNEDY S: Prevalence and outcome of partial remission in depression. *J Psychiatry Neurosci*, 27:241-247, 2002.
158. UHR M: ABCB1 genotyping is crucial for treatment with drugs that are P-glycoprotein substrates. *Biol Psychiatry*, 57:785, 2005.
159. VEEFKIND A, HAFFMANS P, HOENCAMP E: Venlafaxine serum levels and CYP2D6 genotype. *Ther Drug Monit*, 22:202-208, 2000.
160. WALTHER DJ, PETER JU, BASHAMMAKH S, HORTNAGL H et al.: Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science*, 299:76, 2003.
161. WEINSHILBOUM R: Inheritance and drug response. *N Engl J Med*, 348:529-537, 2003.
162. WEINSHILBOUM RM, OTTERNESS DM, SZUMLANSKI CL: Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annu Rev Pharmacol Toxicol*, 39:19-52, 1999.
163. WU S, COMINGS DE: A common C-1018G polymorphism in the human 5-HT1A receptor gene. *Psychiatr Genet*, 9:105-6, 1999.
164. WU WH, HUO SJ, CHENG CY, HONG CJ, TSAI SJ: Association Study of the 5-HT(6) Receptor polymorphism (C267T) and symptomatology and antidepressant response in major depressive disorders. *Neuropsychobiology*, 44:172-5, 2001.
165. YAMADA M, YAMADA M, HIGUCHI T: Antidepressant-elicited changes in gene expression: remodeling of neuronal circuits as a new hypothesis for drug efficacy. *Prog Neuropsychopharmacol Biol Psychiatry*, 29:999-1009, 2005.
166. YANG-FENG TL, XUE FY, ZHONG WW, COTECCHIA S et al.: Chromosomal organization of adrenergic receptor genes. *Proc Natl Acad Sci USA*, 87:1516-20, 1990.
167. YEO A, BOYD P, LUMSDEN S, SAUNDERS T et al.: Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut*, 53:1452-8, 2004.
168. YOSHIDA K, ITO K, SATO K, TAKAHASHI H et al.: Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*, 26:383-6, 2002a.
169. YOSHIDA K, NAITO S, TAKAHASHI H, SATO K et al.: Monoamine oxidase: A gene polymorphism, tryptophan hydroxylase gene polymorphism and antidepressant response to fluvoxamine in Japanese patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*, 26:1279-83, 2002b.
170. YOSHIDA K, TAKAHASHI H, HIGUCHI H, KAMATA M et al.: Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. *Am J Psychiatry*, 161:1575-80, 2004.
171. YU Y, TSAI S, HONG C, CHEN T, CHEN M, YANG C: Association study of a monoamine oxidase a gene promoter polymorphism with major depressive disorder and antidepressant response. *Neuropsychopharmacology*, 30:1719-23, 2005.
172. YU Y, TSAI S, LIOU Y, HONG C, CHEN T: Association study of two serotonin 1A receptor gene polymorphisms and fluoxetine treatment response in Chinese major depressive disorders. *Eur J Neuropsychopharmacol*, 16:498-503, 2006.
173. YU YW, CHEN TJ, HONG CJ, CHEN HM, TSAI SJ: Association Study of the Interleukin-1beta (C-511T) Genetic Polymorphism with Major Depressive Disorder, Associated Symptomatology, and Antidepressant Response. *Neuropsychopharmacology*, 28:1182-5, 2003.
174. YU YW, TSAI SJ, CHEN TJ, LIN CH, HONG CJ: Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. *Mol Psychiatry*, 7:1115-9, 2002.
175. ZANARDI R, BENEDETTI F, DIBELLA D, CATALANO M, SMERALDI E: Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of serotonin transporter gene. *J Clinical Psychopharmacology*, 20:105-107, 2000.
176. ZANARDI R, SERRETTI A, ROSSINI D, FRANCHINI L et al.: Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and nondelusional depression. *Biological Psychiatry*, 50:323-330, 2001.
177. ZANGEN A, NAKASHI R, OVERSTREET DH, YADID G: Association between depressive behavior and absence of serotonin-dopamine interaction in the nucleus accumbens. *Psychopharmacology (Berl)*, 155:434-9, 2001.
178. ZHANG X, GAINETDINOV R, BEAULIEU J-M, SOTNIKOVA T et al.: Loss-of-Function Mutation in Tryptophan Hydroxylase-2 Identified in Unipolar Major Depression. *Neuron*, 45:45, 2005.
179. ZILL P, BAGHAI TC, ENGEL R, ZWANZGER P et al.: *The Beta-1-Adrenergic Receptor Gene in Major Depression: Influence on Antidepressant Treatment*. In: Tsuang M (ed). Xth World Congress of Psychiatric Genetics. Vol. 114. Wiley-Liss New York, pp 777, Brussels, 2002.
180. ZILL P, BAGHAI TC, ZWANZGER P, SCHULE C et al.: Evidence for an association between a G-protein beta3-gene variant with depression and response to antidepressant treatment. *Neuroreport*, 11:1893-7, 2000.
181. ZILL P, BUTTNER A, EISENMENGER W, MOLLER H et al.: Analysis of tryptophan hydroxylase I and II mRNA expression in the human brain: A post-mortem study. *J Psychiatr Res*, [Epub ahead of print], 2005.