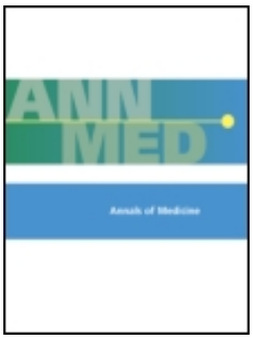

Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: informahealthcare.com/journals/iann20

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**To cite this article:** Elisabeth B. Binder & Florian Holsboer (2006) Pharmacogenomics and antidepressant drugs, Annals of Medicine, 38:2, 82-94, DOI: 10.1080/07853890600551045

**To link to this article:** https://doi.org/10.1080/07853890600551045

*Annals of Medicine*. 2006; 38: 82–94

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**REVIEW ARTICLE**

# Pharmacogenomics and antidepressant drugs

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**Abstract**
While antidepressant pharmacotherapy is an effective treatment of depression, it still is hampered by a delayed time of onset of clinical improvement and a series of side effects. Moreover, a substantial group of patients has only limited response or fails to respond at all. One source accounting for these variations are genetic differences as currently analysed by single nucleotide polymorphisms (SNP) mapping. In recent years a number of pharmacogenetic studies on antidepressant drugs have been published. So far they mostly focused on metabolizing enzymes of the cytochrome P450 (CYP) families and genes within the monoaminergic system with compelling evidence for an effect of CYP2D6 polymorphisms on antidepressant drug plasma levels and of a serotonin transporter promoter polymorphism on clinical response to a specific class of antidepressants, the selective serotonin reuptake inhibitors. It is clear, however, that other candidate systems have to be considered in the pharmacogenetics of antidepressant drugs, such as neuropeptidergic systems, the hypothalamus-pituitary adrenal (HPA) axis and neurotrophic systems. There is recent evidence that polymorphisms in genes regulating the HPA axis have an important impact on response to antidepressants. These studies mark the beginning of an emerging standard SNP profiling system that ultimately allows identifying the right drug for the right patient at the right time.

**Key words:** *Antidepressants, depression, pharmacodynamics, pharmacogenetics, pharmacokinetics*

## Introduction

Pharmacotherapy is an effective treatment of depression and since the serendipitous discovery of the first antidepressant drug, imipramine, a vast number of antidepressant drugs is now available. Despite intensive efforts in the development of antidepressant drugs, major breakthroughs have only been achieved on the side effect profile of these drugs. Even though antidepressants are the most effective treatment for depressive disorders, there is still substantial need for improvement. Adequate therapy response, i.e. full remission, to a single antidepressant drug is observed in only 40%–70% of patients, even when given in sufficiently high dose for up to 6 weeks. Reliable prediction of the clinical response of a patient to a specific antidepressant is not possible yet, and treatment is still governed by doctor's experience. Still one important factor in the decision-making process is the occurrence of side effects some of which are desired, such as enhancement of sleep, while others are not, e.g. weight gain. Another disadvantage shared by all antidepressants is a substantial lag between the onset of treatment and clinical improvement that can last up to several weeks or months, even though therapeutical plasma concentrations can now be reached in a shorter period of time because of lower cardiotropic side effects of newer drugs. Furthermore, there is a percentage of patients that is unresponsive to multiple treatment trials. Some of these patients are refractory to treatment from the beginning of their disease, but most of them become treatment refractory only after multiple episodes.

Drug response can be influenced by a variety of factors, including environmental (for example, nutrition and co-administered drugs) and genetic factors. Since the 1950s inherited differences in drug response have been described (1,2) for a variety of different compounds, establishing the field of pharmacogenetics and later pharmacogenomics. While pharmacogenetics refers to effects of single

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ISSN 0785-3890 print/ISSN 1365-2060 online 
DOI: 10.1080/07853890600551045

genes, pharmacogenomics describes the use of genome-wide approaches to elucidating individual differences in the outcome of drug therapy, including both adverse events and drug response.

Since the completion of the sequence of the human genome (3,4) in 2001, the number of pharmacogenetic/pharmacogenomic studies in psychiatry has surged and in this article we will focus upon several particularly promising candidates.

## Evidence from family studies

There is some evidence from family studies that suggests an important contribution of genetic factors in antidepressant response. Already in the early 1960s, studies on the effects of tricyclic antidepressants (TCAs) have been conducted in families (5,6). O'Reilly et al., 1994, report a familial aggregation of response to tranylcypromine, a monoamine oxidase inhibitor in a large family with major depression (7). These initial case reports were followed by only few systematic studies. Franchini et al., 1998, indicate a possible genetic basis of response to the selective serotonin reuptake inhibitor (SSRI) fluvoxamine in 45 pairs of relatives (8). In light of these data, some groups have used response to a certain antidepressant drug or mood stabilizer as an additional phenotype in classical linkage analyses for mood disorders in the hope of identifying genetically more homogenous families (9,10). Nonetheless, family studies supporting a genetic basis of response to antidepressant drugs are sparse, certainly due to difficulties in collecting such samples.

The genetic basis of differences in drug response likely lies in variants affecting the function of genes involved in the pharmacokinetics as well as the pharmacodynamics of these compounds.

## Pharmacokinetic aspects

Pharmacokinetics refers to processes influencing the delivery of a drug to the target, including absorption, distribution, metabolism and elimination. Several genetic polymorphisms in key genes of this pathway, such as the cytochrome P450 (CYP) gene family (hydroxylation and demethylation of compounds), N-acetyl transferase (N-acetylation), thiopurine methyltransferase (conjugation), and drug transporter molecules like genes from the multidrug resistance (MDR) gene family, have been reported to influence the pharmacokinetics of drugs (for review, see (2)).

**Key messages**

- So far the most of compelling evidence in pharmacogenetics of antidepressants is for an effect of CYP2D6 polymorphisms on antidepressant drug plasma levels and of a serotonin transporter promoter polymorphism on clinical response to selective serotonin reuptake inhibitors.
- Considering our lack of knowledge of the mechanism of action of antidepressant drugs, genome-wide strategies hold great promise in detecting novel candidate genes, which may serve as predictors of response, as targets of drug discovery, or both.

### *The cytochrome P450 gene family*

So far, approximately 50 CYP enzymes, which are haem proteins, have been identified. In humans there are about ten important drug-metabolizing CYP genes. These are mainly expressed in the smooth endoplasmic reticulum of hepatocytes, but can also be found in gut mucosa, kidney, lung tissue, skin and in the brain. Of these, CYP2D6, CYP2C19, CYP3A4 and CYP1A2 are important in the metabolism of antidepressant drugs (11,12). Most studies so far have focused on the role of CYP2D6 in the pharmacokinetics of antidepressant drugs that catalyses hydroxylation reactions. Over 70 functionally 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 (13). According to the inherited alleles, individuals can thus be grouped into poor (PM), intermediate (IM), extensive (EM) and ultra-rapid metabolizers (UM) (14). An increased risk of toxic reactions has been reported in PM while certain drugs may not reach therapeutic plasma concentrations in UM. The proportion of different metabolizers in a population varies with ethnicity, so that 7% of Caucasians but only 1% of Asians are PM, while certain African populations have higher proportions of UM (up to 29%). In addition there are several population specific alleles only encountered in certain ethnicities (13).

Dalen et al., 1998, reported a close correlation between the number of functional CYP2D6 gene copies and plasma levels of the TCA nortriptyline (15). From these single dose experiments, Bertilsson et al., 2002, extrapolated that patients with no or only one functional copy of the gene would already reach therapeutic plasma levels with starting doses for nortriptyline and would easily reach potentially

toxic concentrations with high-normal doses. Patients with two to four copies on the other hand would require high-normal doses to even reach therapeutic plasma-levels. In the case of the one reported patient with 13 gene copies, even high-normal doses would not be sufficient for clinically relevant plasma concentrations. Similar polymorphism/plasma concentration correlations have been reported for the SSRI paroxetine (16,17) and the combined serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine (18,19). For the latter a relationship between PM status and the increased occurrence of cardiovascular side effects or toxicity has been reported (20). In summary, knowledge of the CYP2D6 metabolizer status could be helpful in individualizing dose escalation schemes for certain antidepressants. This could be especially helpful in the case of TCAs, were relatively small dose/response windows have been reported for their antidepressant effect (21,22). For SSRIs on the other hand no clear dose-response relationship has been reported, at least for the treatment of depressive symptoms, and so far no threshold toxic concentrations have been defined (23,24). Specific dose recommendations based on CYP2D6 genotypes have already been put forward (25,26) with doses of TCA halved for PM. The proposed dose adjustments for SSRIs were significantly smaller, and some authors even question the relevance of genotype-adjusted dosing for SSRIs, given their flat dose-response curve (27). Indeed a recent paper by Murphy et al., 2003, did not find any relationship between CYP2D6 genotype and paroxetine-induced side effect or response in geriatric patients (28). Nonetheless, an identification of PM may prevent overdosing and the occurrence of specific side effects with SSRIs or SNRIs. In addition, knowledge of the metabolizer status of a patient may also be helpful in predicting problems with drug interactions. Brosen et al., 1993, report that pharmacokinetic interactions of paroxetine (an inhibitor of CYP2D6) and the TCA desipramine (extensively metabolized by CYP2D6) are dependent on the metabolizer status (29). Co-administration of the two drugs in EM who have at least two functional copies of the CYP2D6 gene leads to a five-fold decrease in desipramine clearance. In PM who lack functional CYP2D6 genes, desipramine clearance was not influenced by paroxetine, suggesting alternate metabolic pathways in PM.

In summary, most data are available on the influence of CYP2D6 polymorphisms on the pharmacokinetics of antidepressants. Genotype-adjusted dose escalation schemes have already been put forward and may be especially useful in TCA treatment. It has to be noted though that so far no prospective study has proven a superior clinical outcome or less side effect when drug and dosing choices were guided by genetic information of drug metabolizer status.

### *P-glycoprotein*

P-glycoprotein is a member of the highly conserved superfamily of adenosine tri-phosphate (ATP)-binding cassette (ABC) transporter proteins. This 170-kDa glycoprotein is encoded by the MDR1 gene (now termed ABCB1) on chromosome 16. It is a plasma membrane protein with two transmembrane domains each containing six membrane-spanning helices and an ATP-binding site that actively transports its substrates against a concentration gradient. P-glycoprotein is expressed in the apical membrane of the intestinal epithelial cells, the biliary canalicular membrane of hepatocytes and the luminal membrane of proximal tubular epithelial cells in the kidney. In addition, it is also found in high levels in the luminal membranes of the endothelial cells that line the small blood capillaries which form the blood-brain and blood-testis barrier (30,31). The MDR1 gene was first discovered as one of the causes of resistance of tumour cells against chemotherapy. Subsequent studies have discovered that its function is not limited to tumour cells but that P-glycoprotein protects cells throughout the healthy organism against many drugs by acting as an efflux pump for xenobiotics. Substrates besides antineoplastic drugs include certain antibiotics, analgesics, cardiotropic drugs and immunosuppressants. Because of its location at the blood brain barrier, P-glycoprotein is in a unique position to also regulate the concentration of psychotropic drugs in the brain and may limit the brain accumulation of many drugs (32). Experiments in transgenic mice lacking mdr1a or mdr1a and mdr1b, both homologues of the human MDR1 gene, show that also intracerebral concentrations of antidepressant drugs are regulated by this molecule (33–35). These studies conclude that the central nervous system (CNS) bioavailability of the SSRIs citalopram and paroxetine, the TCAs trimipramine, amitriptyline, nortriptyline and doxepine and the SNRI venlafaxin is regulated by these molecules, while this may not be true for the SSRI fluoxetine or mirtazapine. Since P-glycoprotein appears to regulate access to the brain for some antidepressants, it is perceivable that functional polymorphisms in this gene may influence intracerebral antidepressant concentration. While effects of P-glycoprotein polymorphisms have been reported for intestinal uptake, no such studies exist

for effects on blood-brain barrier penetration (36). Results from our group suggest that common polymorphisms within ABCB1 may alter the intracerebral concentration of antidepressants that are substrates of this transporter. We could show an association of an intronic ABCB1 single nucleotide polymorphism (SNP) with remission to antidepressant therapy but not to plasma drug levels ($n=286$). This association was only seen in patients treated with antidepressants that proved to be substrates of P-glycoprotein in the mouse knock-out model ($n=105$) (37). It is therefore possible that certain ABCB1 polymorphisms alter the efficiency with which P-glycoprotein transports substrate antidepressants at the blood-brain barrier and thus intracerebral concentrations of specific antidepressants. Prior knowledge of the patients' relevant ABCB1 genotypes could therefore prevent the administration of a drug that might never reach therapeutic intracerebral levels despite a plasma concentration believed to be sufficient.

## Pharmacodynamic aspects

The term pharmacodynamics encompasses all processes influencing the relationship between the drug concentration and the resulting effect. The genetics of pharmacodynamic aspects of antidepressant drugs covers both genes that code for drug targets, such as the serotonin (5-hydroxytryptamine (5-HT)) reuptake transporter, 5-HT receptors, and genes that are indirectly involved in drug action, such as genes downstream of monoaminergic activation or indirectly influenced by monoaminergic modulation, e.g. neuropeptides or ion channels. Even though the primary drug targets of antidepressants are known, it is still unclear which neurotransmitter systems are ultimately targeted that lead to clinical effects. A concatenation of data indicates that altering monoaminergic transmission alone is not sufficient to elicit an amelioration of depressive symptoms. This implies that the majority of candidate genes relevant for response to these drugs are still unknown. So far mostly candidate genes from the monoaminergic system have been investigated in pharmacogenetic studies for antidepressant response.

### *Monoaminergic candidate genes*

Most pharmacogenetic studies for antidepressants have been conducted on candidate genes from monoaminergic pathways. Within this system, the most thoroughly studied gene is the serotonin transporter (SLC6A4) located on chromosome 17q (38,39). Several polymorphisms have been described for this gene. A common functional polymorphism in the 5' promoter region of *SLC6A4*, referred to as the 5-HT transporter gene-linked polymorphic region (5-HTTLPR), consists of a repetitive region containing 16 imperfect repeat units of 22bp, located ~1,000 bp upstream of the transcriptional start site (40,41). The 5-HTTLPR is polymorphic because of the insertion/deletion of units 6–8, which produces a short (S) allele that is 44 bp shorter than the long (L) allele. Although the 5-HTTLPR was originally described as bi-allelic, rare ($<<5\%$) very-long and extra-long alleles have been described in Japanese and African Americans (42). Numerous additional variants within the repetitive region also occur (43). Thus, although most studies continue to treat this complex region as bi-allelic, this is an oversimplification that may be hiding additional genetic information. The 5-HTTLPR has been associated with different basal activity of the transporter, most likely related to differential transcriptional activity (40,41). The long variant (L-allele) of this polymorphism has been shown to lead to a higher serotonin reuptake by the transporter. Other potentially functional polymorphisms include a variable tandem repeat (VNTR) polymorphism in intron 3 as well as several non-synonymous SNPs in the coding region (for review, see (44)). The latter polymorphisms have, however, been less studied with regards to pharmacogenetic aspects than 5-HTTLPR. So far over 20 studies have investigated the effects of this polymorphism on response to antidepressant treatment, with most studies focusing on SSRI treatment (see Table I). In Caucasians all studies investigating the effects of the 5-HTTLPR on response to SSRIs in unipolar or bipolar depressed patients have shown at least nominally significant associations of the long variant (L-allele) of the 5-HTTLPR with better treatment outcome (45–54). In studies in Asian patients, the picture is less homogenous (55–60) and several of those studies suggest association of the S-allele with better outcome. To some extent these contrary findings between Asian and Caucasian patients may result from ethnically different allele frequencies, the S-allele being present in 50% of Caucasians but in 75% of Asians (42). The group of patients homozygous for the L-allele is thus smaller in Asian samples, possibly hampering the detection of a positive association of this genotype with response. It is also possible that different polymorphisms in SLC6A4 are relevant for response in different ethnic groups. Further studies addressing this issue are certainly warranted.

Associations with response to other types of antidepressants than SSRIs have been mostly

Table I. The influence of 5-HTTLPR genotype and response to antidepressant drugs. MP=mono/unipolar depression; BP=bipolar disorder.

| Type of antidepressant drug | Study (reference) | Positive association with response | Ethnicity |
|---|---|---|---|
| Fluvoxamine | $n$=99 (BP+MP) Smeraldi et al., 1998 (45) | L-allele $P$=0.017 | Caucasian |
| Fluvoxamine | $n$=155 (BP+MP) Zanardi et al., 2001 (49) | L-allele $P$=0.029 | Caucasian |
| Paroxetine | $n$=64 (BP+MP) Zanardi et al., 2000 (46) | L-allele (S-allele slower) $P<0.001$ | Caucasian |
| Paroxetine | $n$=95 (late life depression) Pollock et al., 2000 (47) | L-allele (S-allele slower) $P$=0.028 | Caucasian |
| Various antidepressants and ECT | $n$=104 (MP) Minov et al., 2001 (61) | No association | Caucasian |
| Citalopram | $n$=131 (MP) Arias et al., 2003 (48) | L-allele (S-allele more no remission) $P$=0.006 | Caucasian |
| Fluoxetine or Nortriptyline | $n$=169 (MP) Joyce et al., 2003 (51) | L-allele (SS slower response in patients > 25 years) | Caucasian |
| Sertraline or placebo | $n$=206 (MP, elderly) Durham et al., 2004 (52) | L-allele Only in sertraline group | Mostly Caucasian |
| Fluvoxamine or Paroxetine | $n$=221 (MP+BP) Serretti et al., 2004 (54) | L-allele (SS poor response) | Caucasian |
| Fluoxetine | $n$=96 (MP) Kraft et al., 2005 (67) | L-allele if rs25531=A S-allele if rs25531=G | Mostly Caucasian |
| Paroxetine | $n$=122 (MP geriatric) Murphy et al., 2004 (53) | L-allele $P<0.05$ | Mostly Caucasian |
| Mirtazapine | $n$=124 (MP geriatric) Murphy et al., 2004 (53) | No association | Mostly Caucasian |
| Fluoxetine or Paroxetine | $n$=120 (MP/Korean) Kim et al., 2000 (55) | S-allele $P$=0.007 | Asian |
| Fluvoxamine | $n$=66 (MP/Japanese) Yoshida et al., 2002 (57) | S-allele | Asian |
| Fluoxetine | $n$=121 (MP/Chinese) Yu et al., 2002 (58) | L-allele $P$=0.013 | Asian |
| Fluvoxamine | $n$=66 (MP/Japanese) Ito et al., 2002 (56) | No association | Asian |
| Various antidepressants | $n$=128 (MP/Korean) Lee et al., 2004 (59) | L-allele; SS genotype poor long-term (1–3 yrs) prognosis | Asian |
| Paroxetine or Fluvoxamine | $n$=81 (MP/Japanese) Kato et al., 2005 (60) | L-allele | Asian |

negative (53,57,61) but some positive findings were also reported (51,59). It is also of note that most of the SSRIs, which specifically target the 5-HTTLPR after prolonged treatment, not only affect the 5-HT system but also elicit increased norepinephrine (NE) release into the synaptic cleft. The 5-HTTLPR may also be involved in response to non-medication treatments for major depression, such as sleep deprivation. Two studies reported a similar effect of the 5-HTTLPR on response to sleep deprivation, with patients homozygous for the LL genotype profiting more from this treatment (62,63) while one study did not show such an effect (64). An enhancement of serotonergic transmission has been proposed as one possible mechanism of action of sleep deprivation (65).

While the 5-HTTLPR is a potentially functional polymorphism, it is possible that other polymorphisms within the SLC6A4 locus also influence serotonin transporter function and response to antidepressant treatment. Hamilton and colleagues have investigated the association of a series of single nucleotide polymorphisms (SNPs) in the SLC6A4 locus and response to antidepressants (66,67), the second study including a comprehensive re-sequencing of the gene. They found a nominally significant association of an SNP (rs25531), located just upstream of the 5-HTTLPR with antidepressant response to fluoxetine treatment. This SNP may be functionally relevant as it disrupts the consensus sequence of activator protein 2 transcription factor, believed to be relevant in regulating neural genes. Being associated with response and in linkage disequilibrium (LD) with 5-HTTLP5 ($r^2$=0.75), this SNP may influence associations with 5-HTTLPR. In the presence of the G-allele of this SNP, the L-allele of 5-HTTLPR seems to be associated with non-response, while this is the case for the S-allele in presence of the A-allele of the SNP (67). Hu et al., 2005, (68), also reported an SNP

within the L-allele that appears to alter the functional effects of this 5-HTTLPR allele.

Influences of these additional SNPs, as well as additional 5-HTTLPR alleles, should all be considered when interpreting 5-HTTLPR data and might explain some of the inconsistencies observed with this polymorphism.

Pharmacogenetic studies on antidepressants also exist for several other genes of the monoaminergic systems, including tryptophan hydroxylase 1 and 2 (TPH1, TPH2), monoamine oxidase A (MAOA), cathechol-O methyl transferase (COMT), 5-HT receptors (1a, 2a and 6), norepinephrine transporter, dopamine receptors and the G-protein $\beta$3 subunit (for review, see (69)). Only two of these genes, however, show positive associations that have been replicated: the G-protein $\beta$3 subunit (51,70–72) and tryptophan hydroxylase type 1 (TPH1) (66,73,74). Serretti and colleagues detected an association of an intronic SNP in TPH1 with response to fluvoxamine and paroxetine in two separate samples ($n$=217 and 121) (73,74). This association was replicated in a Caucasian ($n$=96) but not in a Japanese sample ($n$=66) (66,75). Three separate studies found no association of a VNTR polymorphism in MAOA, affecting gene transcription, with response to monoamine oxidase inhibitors and SSRIs ($n$=66–443) (75–77). Three different SNPs in 5HT2a have been investigated in three different studies, with two of the studies reporting an association with response to antidepressant treatment ($n$=104, 443 and 66, respectively) (61,77,78). No association was shown for a synonymous SNP in exon 1 of 5HT6 ($n$=34) (79). Also no association was found between two SNPs causing amino acid exchanges in the dopamine receptor type 2 and 4, respectively, and response to fluvoxamine and paroxetine ($n$=364) (80). As most monoaminergic receptors belong to the class of G-protein coupled receptors, G-protein subunits, such as the $\beta$3 subunit, are candidate genes for the pharmacogenetics of antidepressant drugs. A SNP within the G-protein $\beta$3 subunit leading to altered signal transduction, most likely via alternative splicing (81), was found to be associated with response to antidepressant treatment in four independent studies ($n$=169, 106, 490 and 88, respectively) (51,70–72).

Genes tested for associations with antidepressant response are summarized in Table II. At the present time association results with these other studies are far less convincing than those with SLC6A4. For some studies the numbers of investigated patients are small (the smallest sample size being 34) (79). For others, different polymorphisms have been investigated for the same genes, rendering it more difficult to compare the results across studies (e.g. 5HT2a). Replications of these results in different ethnic groups with large sample size are needed for a

Table II. Table of genes tested for association with antidepressant response. Y: one positive association reported. YR: positive associations replicated in independent studies. N: so far no positive associations reported.

| Gene symbol | Gene name | Reference ID | Chromosomal position | Association with antidepressant response |
|---|---|---|---|---|
| *ABCB1* | ATP-binding cassette sub-family B member 1 (p-glycoprotein) | NM_000927 | 7q21.12 | Y |
| *ACE* | Angiotensin converting enzyme | NM_000789 | 17q23.3 | Y |
| *COMT* | Catechol-O-methyltransferase | NM_000754 | 22q11.21-q11.23 | Y |
| *CRHR1* | Corticotropin releasing hormone receptor 1 | NM_004382 | 17q12-q22 | Y |
| *CYP2D6* | Cytochrome P450, family 2, subfamily D | NM_000106 | 22q13.2 | YR |
| *DRD2* | Dopamine receptor D2 | NM_000795 | 11q23.2 | N |
| *DRD4* | Dopamine receptor D4 | NM_000797 | 11p15.5 | N |
| *FKBP5* | FK506 binding protein 5 | NM_004117 | 6p21.3-21.2 | YR |
| *GNB3* | G-protein beta 3 | NM_002075 | 12p13.31 | YR |
| *HTR1A* | 5-hydroxytryptamine (serotonin) receptor 1A | NM_000524 | 5q11.2-q13 | Y |
| *HTR2A* | 5-hydroxytryptamine (serotonin) receptor 2A | NM_000621 | 13q14-q21 | YR |
| *HTR6* | 5-hydroxytryptamine (serotonin) receptor 6 | NM_000871 | 1p36.13 | N |
| *MAOA* | Monoamine oxidase A | NM_000240 | Yp11.4-p11.3 | N |
| *NR3C1* | Glucocorticoid receptor | NM_000176 | 5q31 | Y |
| *SLC6A2* | Norepinephrine transporter | NM_001043 | 16q12.2 | Y |
| *SLC6A4* | Serotonin transporter | NM_001045 | 17q11.1-q12 | YR |
| *TPH1* | Tryptophan hydroxylase 1 | NM_004179 | 11p15.3-p14 | YR |
| *TPH2* | Tryptophan hydroxylase 2 | NM_173353 | 12q21.1 | Y |

conclusive evaluation of the importance of these genes in the pharmacogenetics of antidepressant drugs.

Finally, two recent papers suggest that variants in monoaminergic genes may also modulate side effect profiles of antidepressant drugs ($n$=246). The C/C genotype of a SNP in the 5-HT2a receptor and the S-allele of the 5-HTTLPR were both associated with increase in discontinuation of paroxetine due to adverse events (28,52). The same association was not found for a group of patients treated with mirtazapine in the same study, suggesting an effect specific for SSRIs. These findings have to be considered when interpreting pharmacogenetic studies, as genetically determined differences in drug tolerability may confound differences in therapeutic response if side effects are not assessed separately.

*Stress hormone system*

Many basic and clinical research reports have underscored that adaptation to stressors or the failure to achieve this determines whether an individual carrying a genetic risk for depression will develop the clinical condition (82). Several studies suggest that a normalization of the hypothalamic-pituitary adrenal (HPA) axis hyperactivity and glucocorticoid receptor resistance that is observed in depression may be required for clinical response to antidepressive treatment (83). Indeed, three genes within the stress hormone system have so far been associated with antidepressant response. Licinio et al., 2004, reported an association of a 3 SNP haplotype within the corticotrophin releasing hormone receptor 1 (CRHR1) with response to desipramine or fluoxetine ($n$=80) (84). Our group has investigated the influence of polymorphism in genes regulating the HPA axis on response to antidepressant drugs in the Munich Antidepressant Response Signature (MARS) sample (85). In this sample, we recently detected an association of a functional polymorphism of the glucocorticoid receptor gene leading to two amino acid substitutions in codons 22 and 23 (ER22/23EK) that results in partial glucocorticoid receptor (GR) resistance in non-depressed subjects, with faster response to antidepressant treatment ($n$=367) (86). We also linked polymorphisms within the locus of *FKBP5,* encoding the GR-regulating co-chaperone of hsp90, FKBP5, to response to antidepressant treatment (87). We found a strong association ($P$=0.00003) between polymorphisms in FKBP5 and response to antidepressant drugs ($n$=280). A series of *in vivo* and *in vitro* studies have implicated FKBP5 as important regulator of GR sensitivity. The hsp90 co-chaperone FKBP5 is part of the mature GR heterocomplex (88). Upon hormone binding, FKBP5 is replaced by FKBP4, which then recruits dynein into the complex, allowing its nuclear translocation and transcriptional activity (89). Patients homozygous for the rare allele of the associated SNPs responded over ten days earlier to antidepressant treatment than patients with the other genotypes. This was observed in groups of patients treated with TCA, SSRI or mirtazapine, suggesting that this effect is independent of the class of antidepressant. This result could be replicated in a second sample of patients recruited at three different hospitals in Bavaria ($n$=80). The same genotypes were also associated with increased intracellular FKBP5 protein expression which triggers adaptive changes in GR (90) and thereby HPA axis regulation. Patients carrying the associated genotypes displayed less HPA axis hyperactivity during the depressive episode, as measured by the combined dexamethasone (Dex) suppression/CRH stimulation test (Dex-CRH test). It is therefore possible that even though homozygotes for these SNPs are as severely depressed as the other patients at the time point of hospitalization, their HPA axis regulation is less impaired due to compensatory mechanisms elicited by increased intracellular FKBP5 levels, allowing a faster restoration of normal HPA axis function. Because of the lack of a placebo-treated group it is, however, not possible to rule out the possibility that these patients have an inherently shorter duration of their depressive episodes, independent of antidepressant treatment. The polymorphisms associated with faster response are located from the promoter region to the 3' end of the gene and all in very strong linkage disequilibrium forming one risk haplotype. It is therefore difficult to pinpoint one of the polymorphisms as the causal variant. Nonetheless, rs1360780 located in intron 2 seems a promising candidate as it is only 400 bp downstream of a glucocorticoid responsive element (GRE) that has been shown to be functionally relevant (91). We have observed a much steeper correlation between FKBP5 mRNA expression in peripheral lymphocytes and serum cortisol levels in individuals carrying the genotypes associated with fast response to antidepressant than the two other genotypes, indicating an altered GR/FKBP5 feedback mechanism associated with these genotypes (87,92). Further studies replicating this finding in different populations are, however, necessary to judge its overall importance. If corroborated, phase III drug studies designed to evaluate drug efficacy, i.e. equal or superior response of a newly developed antidepressant compared with a standard drug, will

need to care for equal distribution of FKBP5 polymorphisms across the different comparison groups.

*Other candidate systems*

Besides the HPA axis, the substance P system is a candidate system for antidepressant efficacy. Enhanced substance P signalling via its neurokinin 1 (NK1) receptor has also been implicated in the pathophysiology of depression. Although a first report suggested clinical antidepressant activity of a NK1 receptor antagonist (93) a more recent phase III drug trial failed to support NK1 antagonism as a promising strategy, at least as long as no other neurotransmitter systems are simultaneously modulated. The angiotensin-converting enzyme (ACE) is also expressed in the central nervous system where it is colocalized with substance P, and it is postulated that one of its important functions in the CNS is the degradation of neuropeptides including substance P (94). An intronic insertion (I)/deletion (D) polymorphism determines functional variants of the ACE gene with major impact on ACE plasma concentrations (95,96). The D allele has been associated with higher ACE plasma levels (96), and also higher CNS substance P levels (97) and a faster response to antidepressant treatments (98). The latter finding seems to be predominantly carried by female patients ($n$=313) (99). 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 (100). These studies must be viewed as exploratory and warrant replication in larger populations.

## Genes as differential or overall predictors of antidepressant treatment response

The results just reviewed suggest that some genes specifically alter response to selected treatments, while others may generally modulate response to diverse antidepressant treatments, including non-pharmacologic interventions. As a class, pharmacokinetic candidate genes are likely to have specific effects. For example, polymorphisms in CYP2D6 or ABCB1 appear only to influence response to drugs that are substrates for their respective gene products. Genes influencing pharmacodynamics present a mixed picture. Thus, polymorphisms in the SLC6A4 seem to consistently influence response to SSRIs but not other types of antidepressants (for review, see (69)) or placebo (52). On the other hand, positive associations with sleep deprivation have been reported (62,63), so that this polymorphism may influence the response to any kind of treatment that enhances serotonergic neurotransmission. In contrast to those transmitter-specific effects, the association of polymorphisms in CRHR1, the glucocorticoid receptor and FKBP5 did not appear to be restricted to any specific class of antidepressant, as the same results were observed for patients treated with various classes of antidepressants (84,86,87). Candidate genes such as FKBP5 and other loci regulating the HPA axis, neurogenesis or other putative final common pathways of multiple antidepressant treatments, could therefore be common genetic modulators of response to treatment regardless of modality.

## Genome-wide approaches

So far, genome-wide pharmacogenetic association studies have not been performed. Genome-wide genetic association analyses using SNPs as markers are already technically possible and will become increasingly affordable. Both Affymetrix and Illumina have developed commercially available genome-wide SNP arrays. It will be more challenging to collect pharmacogenetic samples sufficiently large to have enough power for this type of analysis. Genome-wide analyses of mRNA (expression arrays) or protein expression (proteomics) on the other hand are performed at increasing numbers to study the genetics of treatment response. Both animal and human tissues have been used. Several studies have investigated antidepressant treatment-related genome-wide mRNA expression changes in rodent brain tissue (101–107). A few studies have investigated the effects of antidepressant treatment on peripheral blood monocytes (108,109). While a series of candidate genes have been identified using this approach, none so far have been validated. Overall, all whole genome-based approaches are hampered by the large number of false-positive results. So far each expression array study has yielded a large number of regulated genes, of which only a few, if any, will actually be true positives. Whole genome SNP analyses have an expected high number of false-positive associations due to the high degree of multiple testing. The use of convergent evidence from a series of genomic and functional approaches may be a promising alternative to identify potential true positives. In recent years, an increasing number of investigators have come to rely on not only one type of whole-genome approach, but on combining several of these approaches in order to identify the most promising candidates. A common approach to limit the number of candidate genes

from a large set of genes from proteomics and expression analysis as well genetic linkage studies has been to rely on previous data of a gene's potential pathophysiological involvement in the disorder of interest. With more novel candidate genes being confirmed for psychiatric disorders (e.g. (110)), it becomes increasingly clear that relying solely on hypothesis-driven selection strategies may miss the most important genes. Strategies combining several hypothesis-free approaches may be more promising but have so far not been applied to the pharmacogenomics of antidepressant response. John Kelsoe and his colleagues, for example, used an approach that combined microarray analysis of animal models of mania and linkage analysis in families with bipolar disorder to identify G-protein coupled receptor kinase 3 (GRK3) as a promising candidate gene for this disorder. This gene is involved in the homologous desensitization of G-protein coupled receptors. The group had initially identified a linkage peak for bipolar disorder on chromosome 22q (111,112). That linked region did, however, span 32 cM, making it a challenging task to identify the causal gene by fine-mapping strategies. The group then used microarray analysis of different brain regions in methamphetamine-treated rats and identified several genes that were regulated by this treatment that also mapped to previous linkage peaks with bipolar disorder (113). One of these was GRK3 which maps to 22q. In addition to being regulated in the animal model, protein levels for this gene were also found to be decreased in a subset of patient lymphoblastoid cell lines, and the magnitude of the decrease correlated with disease severity. By using resequencing and SNP genotyping strategies, the group confirmed the association of 5'UTR and promoter variants of this gene with bipolar disorder (114).

A recent collaboration between the University Laval in Quebec and the Max Planck Institute of Psychiatry in Munich provided strong evidence that a mutation in P2RX7, a gene coding for a purinergic ligand-gated ion channel, confers susceptibility for mood disorders. Genome-wide scans from a bipolar population in Quebec revealed the presence of a susceptibility locus on chromosome 12q24. Subsequent fine-mapping efforts identified the P2RX7 gene as the potential candidate gene in this region. Genotyping of SNPs in this gene in case control studies resulted in a significant association of a functional SNP in P2RX7 with bipolar disorder (115). This polymorphism results in an amino acid exchange in the intracellular loop of the ion channel, and functional studies indicate that this change decreases the efficiency of the channels' coupling to intracellular signalling cascades. Since this finding has recently been replicated (116) it is now tempting to speculate that carriers of this polymorphism might benefit from a drug that compensates for the surmised loss of function. The gene under consideration codes for an ion channel which when targeted by a drug elicits a much faster physiological response. Therefore, a new generation of antidepressants that acts faster and may have a better clinical profile can now be envisaged. This is just one example how unbiased human genetic approaches may ultimately translate into better drugs. It remains open whether such more specific genotype-based medicines will work only in those patients carrying the specific alleles.

## Conclusions

Despite all the shortcomings of the currently available pharmacogenetic studies, including small sample size, insufficient independent replication, a 'one polymorphism at a time' approach or an inundation with positive but not validated genes from expression arrays, this field holds great promise for the treatment of depression by facilitating, genetic prediction to response and identification of drug targets.

Pharmacogenetics may allow to develop sets of polymorphisms or mRNA markers (in peripheral lymphocytes, for example) that could be combined into easily used assays that will rapidly classify patients according to their likely response to pharmacotherapy. First steps toward this goal have been taken in the prediction of clozapine response using the combined information of polymorphisms from several candidate genes (117). In the future, psychiatrists may thus be able to base the clinical decision on the type and dose of a prescribed drug on more objective parameters than the ones used so far. This could limit unwanted side effects, adverse drug reactions, could reduce time to response and may ultimately lead to personalized medicines. New discoveries in the field of pharmacogenetics might also lead to a better understanding of the mechanism of action of antidepressant drugs. The identification of novel candidate genes will allow the development of novel drug targets and compounds. One might also identify subgroups of patients in which different pathophysiological changes lead to the development of depression. Here an individual targeting of the pathological pathway may become reality, again shortening time to response and reducing side effects.

## Acknowledgements

Part of the work from the Max Planck Institute of Psychiatry was supported by the Bavarian Ministry of Commerce (Bayerische Staatsministerium für Wirtschaft).

The authors declare that they do not have any potential financial conflict of interest.

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