

# Pharmacogenetics of antidepressant response

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Personalized medicine — the adaptation of therapies based on an individual's genetic and molecular profile — is one of the most promising aspects of modern medicine. The identification of the relation between genotype and drug response, including both the therapeutic effect and side effect profile, is expected to deeply affect medical practice. In this paper, we review the current knowledge about the genes related to antidepressant treatment response and provide methodologic proposals for future studies. We have mainly focused on genes associated with pharmacodynamics, for which a list of promising genes has been identified despite some inconsistency across studies. We have also synthesized the main results for pharmacokinetic genes, although so far they seem less relevant than those for pharmacodynamic genes. We discuss possible reasons for these inconsistent findings and propose new study designs.

## Introduction

Personalized medicine is one of the most promising aspects of contemporary medicine, and it may be achieved by the adaptation of therapies to individual patients by means of genetic and other molecular tools.<sup>1</sup> Currently, drugs are administered by trial and error. A substantial proportion of patients do not benefit from treatment, and those who do may incur serious side effects. Antidepressant response is usually associated with a 2–4 week lag before improvement is seen, and even though improvement may occur during the first 2 weeks of treatment, it is difficult to distinguish true improvement from a placebo effect.<sup>2</sup> During this period, patients may experience worsening clinical conditions, discontinue treatment prematurely<sup>3</sup> and feel hopeless. To reduce suffering and minimize costs, it is desirable to know in advance whether a drug is likely to be effective and tolerable. Unfortunately, clinical and anamnestic variants have not been found to be helpful in this respect,<sup>4</sup> while the genetically determined investigation of pharmacological responses could be more promising.<sup>5–7</sup> Pharmacogenetics is the study of how an individual's genetics affects his or her response to drugs, combining traditional pharmaceutical sciences, such as biochemistry, with annotated knowledge of genes, proteins and single-nucleotide polymorphisms (SNPs).

One of the first steps in pharmacogenetics is to detect candidate polymorphisms. There are millions of SNPs in the human genome, and even though they usually cosegregate in small groups, the identification of key variations is difficult. In contrast, when a genome-wide screen approach is performed, the results may be contradictory and poorly replicated, probably because of the presence of a wide range of stratification factors<sup>8</sup> and the enormous amount of DNA sequence variability in target sites, metabolizing enzymes and drug transport proteins.<sup>9</sup>

Most pharmacogenetic studies investigate genes related to metabolism, those that code for receptors and transporters and those related to second-messenger systems.<sup>5</sup> The most promising results in the pharmacokinetic field have been reported for genetic variations of genes coding for CYP2D6 and P-glycoprotein, although relative evidence is present only for the CYP2D6 gene variants. Furthermore, the number of interesting pharmacodynamic targets appears to be quite large, the most important of which appear to be genes coding for tryptophan hydroxylase, catechol-O-methyltransferase (COMT), monoamine oxidase A (MAOA), serotonin transporter (5-HTT), norepinephrine transporter (NET), dopamine transporter (DAT), monoamine receptors (5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>6</sub>, 5-HT<sub>3A</sub>, 5-HT<sub>3B</sub>,  $\beta$ 1 adrenoceptor), dopamine (DA) receptors, G protein  $\beta$ 3 subunit, corticotropin-releasing hormone (CRH) receptor I

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*J Psychiatry Neurosci* 2011;36(2):87–113.

Submitted Apr. 1, 2010; Revised May 19, June 12, 2010; Accepted June 14, 2010.

DOI: 10.1503/jpn.100059

(CRHR1), glucocorticoid receptor, angiotensin-converting enzyme, circadian locomotor output cycles kaput (CLOCK), nitric oxide synthase, interleukin (IL)-1 $\beta$  and brain-derived neurotrophic factor (BDNF).

We recently performed a review and meta-analysis of the pharmacogenetics of antidepressant response. Our review was mainly focused on the monoamine receptors *5-HTT* and *BDNF* genes.<sup>10</sup> We concluded that genetic variants in *5-HTT* (*5-HTTLPR* and *STin2*), *STin2*, *HTR1A*, *HTR2A*, *TPH1* and *BDNF* may modulate antidepressant response. Several other genes have also been reported to be involved in the pharmacogenetics of antidepressants. In this review, we focus on all of the genes that have been reported to be associated with antidepressant response. We also update previously reported results because of the large number of recently published papers and review the results for other relevant genes involved in the pharmacogenetics of antidepressants. We highlight the main results for each gene, summarizing the strongest findings and reporting the most promising new results. Furthermore, we comprehensively summarize the studies for each gene by reporting the main results, sample sizes and evaluating the quality of the studies. Finally, we debate the possible reasons for the controversial findings in the literature and suggest some methodologic issues that can increase the possibility of detecting true positive and replicable results.

There is growing interest in the potential role of pharmacogenetics in the application for the approval of new drugs and the review of existing ones. The US Food and Drug Administration (FDA) has begun to focus on the short-term benefits of pharmacogenetics.<sup>5</sup>

## Literature review

We reviewed the literature by searching MEDLINE and EMBASE (published prior to and including November 2009) using the terms "pharmacokinetics," "pharmacodynamics," "gene," "variation," "antidepressant," "efficacy," "cytochrome," "P-glycoprotein," "tryptophan hydroxylase," "catechol-O-methyl transferase," "monoamine oxidase A," "serotonin transporter," "norepinephrine transporter," "dopamine transporter," "5HT1A," "5HT2A," "5HT3A," "5HT3B," "5HT6," " $\beta$ 1 adrenoceptor," "dopamine receptors," "G protein  $\beta$ 3 subunit," "CRH receptor 1," "glucocorticoid receptor," "angiotensin converting enzyme," "CLOCK," "nitric oxide synthase," "interleukin-1 $\beta$ ," "BDNF" and "candidate." Our search yielded 926 articles; of these, we included 226 pharmacogenetic studies of antidepressant response in our review.

### Assessment of study quality

Quality of studies was defined according to criteria proposed by Serretti and colleagues<sup>8</sup> in a review on methodologic guidelines for pharmacogenetic studies. The authors proposed a scale of 31 methodological criteria against which to assess pharmacogenetic studies.<sup>8</sup> We evaluated the presence of these criteria in all studies selected, and we assigned 1 point for any reach criteria. Scores between 0 and 10 indi-

cated a poorly designed study, between 10 and 20 indicated a fair study and between 20 and 31 indicated an excellent study.

## Pharmacokinetics

### Cytochrome P450

Cytochrome P450 (CYP) describes a class of heme-containing proteins that represent the major enzymes responsible for the oxidation and reduction of numerous endogenous substrates and drugs. More than 50 isoenzymes that catalyze the oxidation of diverse drugs and chemicals are known so far. In humans, the most relevant cytochromes are CYP1A, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. More than 400 individual forms of cytochromes have been found in humans, and further studies may identify other relevant ones. A comprehensive list of CYP allele nomenclature can be found at [www.cypalleles.ki.se](http://www.cypalleles.ki.se).

Variation of DNA within coding genes can affect the rates of metabolism of certain drugs, possibly leading to overdose.<sup>1</sup> The genes *CYP2D6*, *CYP2B6* and *CYP2C19* have been widely investigated as candidate genes. Kirchheiner and colleagues<sup>11</sup> performed an exhaustive review about *CYP2D6* and *CYP2C19* and concluded that it is not yet possible to translate pharmacogenetic parameters fully into therapeutic recommendations, although a combination of polymorphisms in the pharmacokinetic and pharmacodynamic pathways might contribute to identifying the response patterns as well as patients at higher risk of side effects. In the present review, we update the results from Kirchheiner and colleagues,<sup>11</sup> summarizing past findings and adding recent results on these genes.

Variations in *CYP2D6* have been associated with a vast list of diseases (e.g., arterial hypertension,<sup>12</sup> leukemia,<sup>13</sup> childhood apnea,<sup>13</sup> thyroid cancer,<sup>14</sup> Alzheimer disease and Parkinson disease,<sup>15-19</sup> hepatic disease,<sup>20</sup> pulmonary disease,<sup>21,22</sup> breast cancer,<sup>23</sup> porphyrias<sup>24</sup>) and with people's ability to metabolize antidepressants.<sup>25</sup> To date, up to 75 different alleles have been reported for *CYP2D6* (descriptions available at [www.imm.ki.se/cypalleles](http://www.imm.ki.se/cypalleles)); more than 15 of these encode an inactive isoform or no enzyme, whereas other variations consist of gene duplications.<sup>26</sup> These gene variants are often associated with different rates of metabolizing drugs. Thus, individuals can be classified as poor, intermediate, extensive and ultrarapid metabolizers on the basis of their inherited genetic profiles.<sup>27,28</sup> The *CYP2D6* poor metabolizer phenotype is present in 5%–10% of the white population but is more rare in black and Asian populations. It has been recently reported that the frequency of poor and ultrarapid metabolizers were 0.22% and 1.25%, respectively, in a Korean sample.<sup>29</sup> Nevertheless, the 10 alleles causing decreased, but not absent, *CYP2D6* activity are frequently present in these populations.<sup>30-34</sup> The prevalence of poor metabolizers in nonwhite populations has been recently estimated to be as high as 3%.<sup>35</sup> The genetic background that differentiates poor metabolizers from intermediate and ultrarapid metabolizers seems to be associated with the number of gene copies: those with the ultrarapid metabolizer phenotype have been found to have multiple copies of *CYP2D6* with a direct influence on plasma drug

concentration, and 97% of all poor metabolizer phenotypes can be explained by the presence of 4 deficient activity *CYP2D6* alleles (3, 4, 5, 6).<sup>36</sup> In addition, it has been shown that genetic background affects the rate of enzymatic inhibition in a substance-specific manner.<sup>37</sup>

In addition, *CYP2C19* has an interesting set of genetic polymorphisms, and the detection of different alleles of the gene has allowed a classification of phenotypes similar to that for *CYP2D6*, making it possible to distinguish between extensive metabolizers and individuals with impaired catalytic capacity (poor metabolizers).<sup>37,38</sup> Moreover, the existence of an ultrarapid metabolizer isoform, named *CYP2C19\*17* (rs12248560), has recently been reported. This isoform has been shown to be associated with a reduced concentration of escitalopram to about half, whereas deletion of this gene is associated with an almost 6-fold increase of escitalopram concentration.<sup>39</sup> The frequency of the *CYP2C19* poor metabolizer phenotype in Asian populations is about 20%, whereas in white populations it is about 2%–5%.<sup>37,38</sup> Not surprisingly, it has recently been shown that the efficacy and side effects of citalopram treatment are influenced by *CYP2C19* in Chinese patients<sup>40</sup> and that the side effect profile associated with the amitriptyline treatment is partially dependent on the combination of a number of alleles coding for *CYP2D6* and *CYP2C19*.<sup>41</sup>

The *CYP2B6* cytochrome metabolizes bupropion, and it has recently been shown that the homozygous T allele (T/T) or heterozygous C and T allele (C/T) at position 1459 of *CYP2B6* (rs3211371) are associated with higher odds of abstinence from smoking in people who are also carriers of the *DRD2-Taq1* A2/A2 (rs1800497) genotype.<sup>42</sup> Moreover, the common allele with a G-to-T substitution at nucleotide 516

(516G>T; rs3745274) is associated with lower expression via aberrant splicing events,<sup>43</sup> and the amino acid substitution of leucine to phehenylalanine at position 264 (Leu264Phe) has been reported to have functional consequences on *CYP2B6* activity.<sup>44</sup> This is quite interesting because *CYP2B6* and *CYP3A4* are the main isoforms involved in metabolizing methadone and sibutramine (*CYP2B6* only), and it is thought that part of the individual response to these drugs depends on genetic variants of these cytochromes.<sup>45–47</sup> The recent results of genetic association tests for *CYP2D6*, *CYP2B6* and *CYP2C19* variations are presented in Table 1.

### *P-glycoprotein*

Antidepressants must enter the brain to have an effect. The blood–brain barrier regulates this event, and one of its active effectors is the P-glycoprotein. P-glycoprotein, an ATP-binding transporter protein, is a product of the *ABCB1* gene. It is a plasma membrane transporter that exports certain drugs and endogenous substances against a concentration gradient. P-glycoprotein is found in various human tissues, including the apical membranes of the gastrointestinal tract, the biliary canalicular membranes of hepatocytes, the luminal membranes of proximal tubular epithelial cells in the kidney, the testes, the placenta and the luminal membranes of endothelial cells of the blood–brain barrier.<sup>48</sup> Intuitively, the inhibition and induction of P-glycoprotein function can result in important drug–drug interactions. Because of its role in the blood–brain barrier, which limits drug intake to the brain, variations in its function are associated with drug treatment response and side effect profiles. Animal studies have shown that a wide variety of structurally unrelated drugs are

**Table 1: Relevant pharmacogenetic association studies that focused on cytochrome P450 (CYP)**

Study	Gene	Drug	Results	Quality (0–31)	Sample size
Zackrisson et al. <sup>48</sup>	<i>CYP2D6</i> <i>CYP2C19</i>	Various antidepressants	UM genotype ↑ suicide cases	8	504
Serretti et al. <sup>49</sup>	<i>CYP1A2</i> <i>CYP2C9</i> <i>CYP2C19</i> <i>CYP2D6</i>	Various antidepressants	No association between metabolic profiles and either response or remission rates	13	278
Peters et al. <sup>50</sup>	<i>CYP2D6</i> <i>CYP2C19</i> <i>CYP3A4</i> <i>CYP3A5</i>	Citalopram	No association with response or tolerance phenotypes	25	1953
David et al. <sup>42</sup>	<i>CYP2B6</i>	Bupropion	<i>DRD2</i> rs1800497 A2/A2 subject with rs3211371 T/T or C/T genotype ↑ abstinence	15	233
Shams et al. <sup>51</sup>	<i>CYP2D6</i>	Venlafaxine	PM phenotype ↑ side effects	11	25
Yin et al. <sup>40</sup>	<i>CYP2C19</i>	Citalopram	PM phenotype ↑ drug plasma concentrations and side effects	15	53
Suzuki et al. <sup>52</sup>	<i>CYP2D6</i>	Fluvoxamine	<i>CYP2D6</i> IM with 5-HT <sub>2A</sub> rs63311 G/G or A/G ↑↑ gastrointestinal side effects	18	96
Grasmader et al. <sup>53</sup>	<i>CYP2C9</i> <i>CYP2C19</i> <i>CYP2D6</i>	Various	<i>CYP2D6</i> ↑↑, <i>CYP2C19</i> ↑, <i>CYP2C9</i> – antidepressant plasma concentrations	14	112
Rau et al. <sup>54</sup>	<i>CYP2D6</i>	Various	PM ↑ side effects	5	28
Charlier et al. <sup>55</sup>	<i>CYP2D6</i>	Fluoxetine, paroxetine	PM ↑ plasma concentrations	9	49
Ohara et al. <sup>56</sup>	<i>CYP2D6</i>	Fluvoxamine	No association with fluvoxamine concentration	12	46
Murphy et al. <sup>57</sup>	<i>CYP2D6</i>	Paroxetine, mirtazapine	No association	18	122

↑ = positive association; ↓ = negative association; IM = intermediate metabolizer; PM = poor metabolizer; UM = ultrarapid metabolizer.

removed from the brain because of P-glycoprotein activity: most antidepressants have been shown to be substrates of this transporter (e.g., amitriptyline, nortriptyline, citalopram, venlafaxine, sertraline and trimipramine),<sup>59–63</sup> although there are some exceptions (i.e., fluoxetine, bupropion).<sup>61,62</sup> In addition, some antidepressants (e.g., nefazodone) have been reported to inhibit P-glycoprotein function,<sup>64</sup> whereas St. John's wort has been reported to enhance its activity.<sup>65</sup> So far, several *MDR1* SNPs have been identified, and mutations at positions 2677 (rs2032582) and 3435 (rs1045642) have been reported to be associated with altered P-glycoprotein expression, function or both.<sup>66</sup> Table 2 presents a list of studies that examined associations between P-glycoprotein variations and antidepressant response.

## Pharmacodynamics

### Monoamine metabolic enzymes

#### Tryptophan hydroxylase

Tryptophan hydroxylase (TPH) catalyzes the rate-limiting step in 5-HT biosynthesis. Long-term treatment of rats with selective serotonin reuptake inhibitors (SSRIs) has been shown to upregulate the mRNA and protein levels of TPH,<sup>74</sup> which supports the involvement of TPH in the pharmacologic action of antidepressants. Tryptophan hydroxylase has 2 isoforms: TPH1 and TPH2. The gene of the TPH1 isoform seems to be widely expressed in human tissues, particularly in peripheral organs such as the gut, pineal gland, spleen and thymus, and less frequently in the brain. A biallelic SNP at position 218 of *TPH1* (218A>C; rs1800532) is located in a potential GATA-transcription factor binding site; this SNP has been reported to influence gene transcription, with the rare TPH1\*a allele being associated with decreased 5-HT synthesis.<sup>75</sup> Consistent with the monoaminergic theory of depression, the presence of the TPH1\*a allele was found to be associated with suicidal behaviour and to worsen the response to SSRI therapy.<sup>76–78</sup> Conflicting results have been reported, especially in nonwhite populations.<sup>79–83</sup> Independent studies have reported no effects of the *TPH1* 218A>C SNP on the efficacy of SSRI therapy or related side effects.<sup>84,85</sup>

The *TPH2* gene seems to be more selectively expressed than

*TPH1* in the brain stem.<sup>86,87</sup> Animal experiments have shown that mice with a mutation in *Tph2* have reduced 5-HT tone in the central nervous system (CNS), whereas *Tph1* knockout mice do not have altered 5-HT tone.<sup>88–90</sup> Moreover, long-term treatment with fluoxetine was found to be associated with upregulation of *Tph2* mRNA expression, which seems to occur simultaneously with the antidepressant effect.<sup>91</sup> A similar reaction affecting the genetic expression machinery of cells was reported for citalopram and fluoxetine.<sup>92</sup> In contrast, Abumaria and colleagues<sup>93</sup> reported that citalopram did not enhance, but rather decreased, *Tph2* mRNA expression in the dorsal raphe nucleus of stressed and nonstressed animals. The same result was reported by Dygalo and colleagues.<sup>94</sup> Interestingly, Abumaria and colleagues<sup>93</sup> also reported that stress did not affect *Tph2* expression, but instead enhanced *Tph1* expression in the brains of rats, an event that was counteracted by treatment with citalopram in animal models of stress. In contrast, long-term administration of citalopram was associated with enhanced *Tph1* expression in controls. This suggests a more blunted differentiation between *TPH1* and *TPH2* in terms of expression specificity for the CNS or peripheral organs. It has been shown that *TPH1* may play a relevant role in the developing brain,<sup>95</sup> and this evidence could reasonably support further research focused on *TPH1*.

The *TPH2* gene is located at 12q21.1, and its variants have been associated with major depression,<sup>96</sup> suicidal behaviour,<sup>96,97</sup> attention-deficit/hyperactivity disorder and obsessive-compulsive disorder.<sup>98–100</sup> Zhang and colleagues<sup>89</sup> reported that 5-HT levels from cells expressing arginine at position 447 were reduced by about 55% compared with cells expressing proline at position 447. Moreover, in individuals with unipolar major depression, Zhang and colleagues<sup>101</sup> identified a 1463G>A transition in the *TPH2* gene. This functional SNP in *TPH2* replaces the highly conserved arginine at position 447 with histidine, which results in about an 80% loss of function in 5-HT production.<sup>101</sup> Analysis of SNPs in a cohort of 87 patients with unipolar major depression revealed that 9 patients carried the mutant allele, whereas only 3 of 219 controls carried this mutation. In addition, this functional SNP was not found in a cohort of 60 patients with bipolar disorder. A positive association was found by Peters and colleagues<sup>85</sup> in 2004, although those results were not

**Table 2: Relevant pharmacogenetic association studies that focused on P-glycoprotein**

Study	Gene	Drug	Results	Quality (0–31)	Sample size
Gex-Fabry et al. <sup>67</sup>	P-glycoprotein	Paroxetine	<i>ABCB1</i> genotype ↑ response (61A>G)	18	71
Kato et al. <sup>68</sup>	P-glycoprotein	Paroxetine	rs1045642, rs2032582, rs1128503 ↓ response rs2032582 ↑ response (T/T, T/A or A/A)	20	68
Mihaljevic Peles et al. <sup>69</sup>	P-glycoprotein	Paroxetine	No association	22	127
Nikisch et al. <sup>70</sup>	P-glycoprotein	Citalopram	rs2032582 GG/GT genotype ↑ response	5	15
Peters et al. <sup>50</sup>	P-glycoprotein	Citalopram	No association with response or tolerance	25	1953
Uhr et al. <sup>59</sup>	P-glycoprotein	Various	C allele (rs2032583) and T allele (rs2235015) ↑ response when antidepressant used a target of the P-glycoprotein	16	297
Fukui et al. <sup>71</sup>	P-glycoprotein	Fluvoxamine	rs1045642 T allele ↑ fluvoxamine plasma levels	13	62
Laika et al. <sup>72</sup>	P-glycoprotein	Amitriptyline	No association	14	50
Roberts et al. <sup>73</sup>	P-glycoprotein	Nortriptyline	rs1045642 C allele ↑ postural hypotension	17	160

↑ = positive association; ↓ = negative association.

replicated by other studies.<sup>102–104</sup> Further lack of replication can be found regarding suicide and major depressive disorder (MDD), even though most of the studies originate from a single group of investigators.<sup>105,106</sup>

Other recently studied polymorphisms (rs11178997 in the promoter region of *TPH2*;<sup>107</sup> rs7305115 and rs4290270;<sup>108</sup> rs4448731 and rs4641527;<sup>109</sup> rs4570625<sup>110</sup>) have been associated with different expression or function and impact on depressive or suicidal history, with possible interesting advantages in pharmacogenetic investigations. Lim and colleagues<sup>108</sup> reported that low levels of *TPH2* mRNA expression are associated with the CTGTG combination of alleles and high levels of expression with the TAAGA combination of alleles for the SNPs rs2171363, rs4760815, rs7305115, rs6582078 and rs9325202. Of these, rs7305115 is the only coding variation, although a further analysis suggested a minor role of this mutation, and the diminished concentration of *TPH2* mRNA was hypothesized to be associated with a cis-acting factor. The most relevant mutation appears to be the rs7305115, whose A allele increases and G allele decreases the levels of *TPH2* mRNA. The G allele appears to be the ancestral one, so that the high prevalence in the white population may be related to a bottleneck effect and may be associated with some advantages in selection, possibly through an effect on mood or mental activity. The rs4570625 variation is located in the promoter region of the *TPH2* gene and has been associated with amygdala reaction to fearful stimuli, which was greater in patients carrying the T allele,<sup>111–113</sup> an association that has been thought to mask, via linkage disequilibrium, a more strong association with rs7305115.<sup>108</sup> Consistent with the findings from imaging studies, rs4570625 was found to be associated with personality traits related to emotional instability and with cluster B and cluster C personality disorders.<sup>110</sup> Interestingly, Clark and colleagues<sup>114</sup> suggested that a glucocorticoid-mediated reduction of *TPH2* mRNA may be relevant to the etiology of

major depression in cases where glucocorticoids are elevated, since *TPH2* mRNA is regulated by glucocorticoids but not estradiol. Table 3 reports the results of some investigations that focused on the pharmacogenetics of *TPH1*- and *TPH2*-related antidepressant response.

#### Catechol-O-methyl transferase

Catechol-O-methyl transferase (COMT) is involved in the catabolic pathways of noradrenaline (NE) and DA and can indirectly affect brain 5-HT tone because of the interactions between DA and 5-HT. There is convincing evidence that interactions between the serotonergic and the dopaminergic systems occur. An increase in DA concentration has been hypothesized to be detrimental for depression and to delay final antidepressant response.<sup>122,123</sup> Consistently, an imaging study involving healthy participants reported the opposite effect on 5-HTT and DAT after 5 days of venlafaxine administration: the 5-HTT binding profile was lowered whereas the DAT binding profile was found to be higher.<sup>124</sup> Similar results were reported for citalopram and paroxetine,<sup>124</sup> but not for bupropion, which consistently does not show a direct serotonergic profile. Lachman and colleagues<sup>125</sup> reported a functional polymorphism consisting of a transition of guanine to adenine at codon 158, leading to a valine-to-methionine substitution in MBCOMT (and in position 108 in SCOMT). The polymorphism (rs4680) consists of a valine to methionine amino acid substitution at codon 158 in the membrane bound form and in position 108 in the soluble form of COMT, which results in a valine to methionine amino acid substitution in the corresponding enzyme. The valine homozygote is 4 times more active in metabolizing DA than the methionine homozygote.<sup>126</sup> This polymorphism has been associated with higher risk of suicidal behaviour and personality disorder traits,<sup>127</sup> and with a worse response to mirtazapine (but not paroxetine)<sup>128</sup> and citalopram.<sup>122</sup> Nevertheless, a better

**Table 3: Relevant pharmacogenetic association studies that focused on *TPH1* and *TPH2***

Study	Gene	Drug	Results	Quality (0–31)	Sample size
Tsai et al. <sup>115</sup>	<i>TPH2</i>	Fluoxetine, citalopram	rs2171363 heterozygote ↑ response	20	508
Illi et al. <sup>116</sup>	<i>TPH1</i> <i>TPH2</i>	Fluoxetine, paroxetine, citalopram	No association for rs1800532 ( <i>TPH1</i> ) and rs1386494 ( <i>TPH2</i> )	13	86
Peters et al. <sup>117</sup>	<i>TPH1</i> <i>TPH2</i>	Fluoxetine, citalopram	No association with citalopram response	17	2049
Tzvetkov et al. <sup>118</sup>	<i>TPH2</i>	Various antidepressants	rs10897346 and rs1487278 ↑ response	13	253
Kato et al. <sup>84</sup>	<i>TPH1</i>	Paroxetine, fluvoxamine	No association with treatment response and side effects	22	100
Hong et al. <sup>83</sup>	<i>TPH1</i>	Fluoxetine	No association	15	224
Ham et al. <sup>78</sup>	<i>TPH1</i>	Citalopram	rs1800532 A allele ↓ remission	18	105
Ham et al. <sup>82</sup>	<i>TPH1</i>	Various	No association	18	93
Serretti et al. <sup>119</sup>	<i>TPH1</i>	Various	No association	22	185
Serretti et al. <sup>120</sup>	<i>TPH1</i>	Fluvoxamine, paroxetine	No association	22	221
Peters et al. <sup>85</sup>	<i>TPH1</i> <i>TPH2</i>	Fluoxetine	7180T/G, -7065T/C, -5806T/G ( <i>TPH1</i> ) and rs1386492, rs1487276 ( <i>TPH2</i> ) ↑ response	19	96
Takahashi et al. <sup>121</sup>	<i>TPH1</i>	Fluvoxamine	No association with iatrogenic nausea	21	66
Yoshida et al. <sup>81</sup>	<i>TPH1</i>	Fluvoxamine	No association	15	66
Serretti et al. <sup>77</sup>	<i>TPH1</i>	Fluvoxamine	rs1800532 A/A genotype ↓ response	22	217
Serretti et al. <sup>78</sup>	<i>TPH1</i>	Paroxetine	rs1800532 A/A and A/C genotypes ↓ response	23	119

↑ = positive association; ↓ = negative association.

response to milnacipram in the homozygous methionine genotype carriers was found in Asian<sup>129,130</sup> and white populations.<sup>131,132</sup> A significant association has also been reported in placebo response.<sup>133</sup> Other SNPs associated with antidepressant response have been recently described, but no replications have been produced.<sup>134</sup> Increased weight gain after smoking cessation in patients treated with bupropion has been reported when *COMT* variation was considered together with variation within the DA receptor 2 (*DAT2*) coding gene.<sup>135</sup> Consistently, rs737865 and rs165599 were found to be associated with the efficacy of bupropion therapy in smoking cessation protocols.<sup>136</sup> Lack of association was reported for patients with bipolar 1 disorder.<sup>137</sup> Table 4 reports the main association studies that dealt with the effect of *COMT* variations on antidepressant response.

### Monoamine oxidase A

Monoamine oxidase A is a major degrading enzyme in the metabolic pathways of monoamine neurotransmitters (NE, DA, 5-HT). Interestingly, its absence in humans has been found to be life-compatible<sup>138</sup> and associated with a psychiatric-like syndrome characterized by borderline mental retardation and abnormal behaviours, such as impulsive aggression, attempted rape and exhibitionism. This syndrome was found to be associated with a punctual nonsense mutation in the *MAOA* gene.<sup>139</sup> Moreover, *MAOA* genetic variations may influence the mechanism of action of SSRIs through an interaction with 5-HT transporters.<sup>140</sup> A polymorphism located 1.2 kb upstream of the *MAOA* coding sequences (variable number tandem repeat; VNTR) was reported to affect the transcription of the *MAOA* promoter: alleles with 3.5 or 4 copies of the repeat sequence are transcribed 210 times more efficiently than those with 3 or 5 copies of the repeat, suggesting an optimal length for the regulatory region.<sup>141</sup> In contrast, a recent study reported that the genotype is not associated with *MAOA* activity, as measured by imaging techniques;<sup>142</sup> however, we suggest that this is not sufficient to rule out a role of the *MAOA* variations in psychiatric disorders. It can be hypothesized that a disrupted variation of a single enzyme is counteracted by the modulation of the signalling cascades that are associated with its activity. Nonetheless, this

modulation may have a limited balancing ability, which can be overwhelmed as far as adjunctive risk factors occur.

Bipolar disorder as well as suicidality, personality features, aggressive behaviour, alcoholism and antidepressant response in women have been associated with this and other polymorphisms in the *MAOA* gene sequence.<sup>133,143-151</sup> No association findings with antidepressant response can also be found in the literature.<sup>81,152,153</sup> Moreover, it has been reported that the 941T>G polymorphism (rs6323) in the *MAOA* gene is associated with mirtazapine response in girls and women.<sup>154</sup> Finally, a significant association with response has also been reported for rs1465 108G>A and rs6323A>C of *MAOA*.<sup>85</sup> Table 5 reports the most relevant association findings between the *MAOA* gene variations and the antidepressant response.

### Monoamine transporters

#### Serotonin transporter

The 5-HTT (encoded by *SLC6A4*) regulates 5-HT neurotransmission in the brain by removing it from the intercellular cleft. It is a target of primary interest in the pharmacogenetics of antidepressants because it is the principal site of action of many antidepressant drugs (e.g., SSRIs, tricyclic antidepressants). Moreover, 5-HTT is thought to mediate the behavioural and toxic effects of cocaine and amphetamines. In studies involving 5-HTT knockout mice,<sup>156,157</sup> animals showed increased anxiety and inhibited exploratory locomotion together with a reduction in aggressive behaviour and home cage activity, a behavioural phenotype that is similar to some of the symptoms associated with depressive episodes. This behaviour was found to be further stimulated after desensitization of 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors,<sup>156,157</sup> and it was found to be reduced in wild-type mice receiving serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs, in association with a decrease of 5-HT receptor density in the cortex.<sup>158</sup>

The most promising variations within the 5-HTT gene seem to be those located in the promoter zone, especially the 5-HTTLPR polymorphism: Heils and colleagues<sup>159</sup> described this polymorphism as a 44bp insertion/deletion involving 2 units in a sequence of 16 repeated elements. The presence of

**Table 4: Relevant pharmacogenetic association studies that focused on *COMT***

Study	Gene	Drug	Results	Quality (0-31)	Sample size
Benedetti et al. <sup>132</sup>	<i>COMT</i>	Paroxetine	Rs4680 Met/Met ↑ response, Met/Val ↑↓ response, Val/Val ↓ response	17	55
Leuchter et al. <sup>133</sup>	<i>COMT</i>	Placebo	Rs4680 Met/Met ↓ placebo response	15	132
Tsai et al. <sup>130</sup>	<i>COMT</i>	Fluoxetine	Males rs4680 Met carriers ↑ response	16	334
Perlis et al. <sup>134</sup>	<i>COMT</i>	Duloxetine	rs165599 GG, rs165774 GG, rs174696 CC ↑ response	13	102
Baune et al. <sup>131</sup>	<i>COMT</i>	Various	Rs4680 Met/Met ↑ response	18	256
Yoshida et al. <sup>129</sup>	<i>COMT</i>	Milnacipram	Rs4680 Met/Met ↑ faster therapeutic effect	18	81
Hu et al. <sup>135</sup>	<i>COMT</i>	Bupropion	rs6277 TC genotype ↑ weight gain No association with body mass index or weight change	16	283
Arias et al. <sup>122</sup>	<i>COMT</i>	Various	Small effect on citalopram treatment result	18	346
Szegedi et al. <sup>128</sup>	<i>COMT</i>	Mirtazapine, paroxetine	Rs4680 ↑ mirtazapine response	13	102

↑ = positive association; ↓ = negative association.

different alleles could affect 5-HTT expression: the long (l) 5-HTTLPR allele has twice the 5-HTT expression in the basal state than the short (s) allele. It has been consistently reported that this functional variation influences the antidepressant effect of different classes of antidepressant drugs. Moreover, a growing body of evidence links 5-HTTLPR genotypes to a variety of psychiatric disorders with affective symptomatology (e.g., depression, bipolar disorder, anxiety disorders, eating disorders, substance abuse) and to pathological behaviours and personality traits related to anxiety, impulsivity and stress.<sup>160</sup> A recent meta-analysis<sup>161</sup> confirmed the role of 5-HTTLPR in antidepressant response, showing that patients homozygous for the short allele have a selective and slower improvement of depressive "core" and somatic anxiety symptoms.<sup>162</sup> The short/long genotype was recently found to be associated with an odds ratio (OR) of 2.37 concerning adverse effects during treatment with SSRIs (dermatologic reactions, weight change and fatigue above all), and the homozygous short genotype showed an OR of 1.77.<sup>163</sup> These findings are generally well replicated in studies involving white populations,<sup>120,164-175</sup> although opposite or inconsistent findings have also been reported.<sup>176-180</sup> On the other hand, studies involving Asian populations usually report conflicting results: some studies reported that the short 5-HTTLPR allele was associated with better outcomes,<sup>181-184</sup> some found no effect of 5-HTTLPR genotype on treatment efficacy<sup>121,185,186</sup> and some reported that the long 5-HTTLPR allele was associated with better outcomes.<sup>83,187-191</sup> Interestingly, Lotrich and colleagues<sup>192</sup> recently reported that paroxetine blood concentration was positively associated with HAM-D response in a sample of elderly patients, but this association was found to be significant only in carriers of the short allele. In contrast, when augmentation strategies have been investigated, the short allele has been associated with a better response in patients prescribed pindolol or lithium.<sup>193,194</sup> This finding may be difficult to explain, and to make this challenge even more complex it has been reported that women are more sensitive to mood imbalances after tryptophan depletion if they are homozygous for the short or long allele, with heterozygotes having the most protective genotype.<sup>195</sup> Finally, the adverse events occurring in newborns of mothers treated with SSRIs had a

mixed association with genotype, with those with the heterozygous long genotype being at higher risk of respiratory distress and those with the homozygous short genotype being at higher risk for neuromotor symptoms.<sup>196</sup> Regarding the inconsistent findings between white and nonwhite populations, it must be remembered that, compared with Western populations, carrying the long allele is much less frequent in Asian populations: inconsistent results found in Asian populations could be influenced by this event, and further studies with larger samples are needed. Moreover, relevant stratification factors may be strictly genetic: in 2005 Hu and colleagues<sup>197</sup> reported that only carriers of the A allele at the A>G SNP within the long allele of the 5-HTTLPR insertion polymorphism yielded high mRNA levels, whereas carriers of the G allele were similar to carriers of the low-expressing short allele. This finding could partially explain the inconsistent evidence throughout the studies, and it mandates a reconsideration of all the investigations published before the identification of this mutation. A study by Hu and colleagues<sup>197</sup> reported that the low-expression alleles (short allele and G variant within the long allele) were one of the strongest risk factors associated with adverse effects from antidepressants. Another polymorphism influencing 5-HTT expression was identified by Ogilvie and colleagues<sup>198</sup> within intron 2 (STin2) and described as a 17bp VNTR polymorphism. It was reported that the STin2 polymorphism can play a role as a risk factor in MDD<sup>198-200</sup> and suicidal behaviour,<sup>201,202</sup> creating a synergistic effect with 5-HTTLPR.<sup>203</sup> The STin2 polymorphism seems to also affect antidepressant response, as reported by different authors,<sup>85,175,182,191</sup> and it was proposed that a STin2 10/12 genotype (where 10/12 indicates the number of repeats in the 2 alleles) may be associated with a poorer antidepressant effect, especially in Asian populations.<sup>204</sup> Some studies were not able to replicate these findings.<sup>83,205</sup> The STin2 10/12 allele has also been found to be associated with greater side effects,<sup>206</sup> but lack of association with side effects has also been reported.<sup>163</sup> More recently, an SNP (rs25531) located just upstream of 5-HTTLPR was reported to affect antidepressant response, and it was shown to modulate the effect of other 5-HTTLPR alleles.<sup>207,208</sup> It has been recently reported that rs25531 is the same SNP described by Hu and

**Table 5: Relevant pharmacogenetic association studies that focused on MAOA**

Study	Gene	Drug	Results	Quality (0-31)	Sample size
Tzeng et al. <sup>150</sup>	MAOA	Mirtazapine	Long-form polymorphism ↓ response	15	58
Leuchter et al. <sup>133</sup>	MAOA	Placebo, various antidepressants	rs6323 G allele ↓ placebo response	15	132
Domschke et al. <sup>151</sup>	MAOA	Various antidepressants	In female alleles 3a, 4, 5 ↓ response	18	340
Tadic et al. <sup>154</sup>	MAOA	Mirtazapine, paroxetine	In female alleles 3a, 4, 5 ↓ response	15	102
Yu et al. <sup>148</sup>	MAOA	Fluoxetine	In female allele 3a ↑ response	14	230
Serretti et al. <sup>119</sup>	MAOA	Various	No association	22	185
Peters et al. <sup>85</sup>	MAOA	Fluoxetine	rs1465108G/A and rs6323A/C ↑ response	19	96
Yoshida et al. <sup>155</sup>	MAOA	Fluvoxamine	MAOA VNTR ↑ iatrogenic nausea	16	54
Cusin et al. <sup>153</sup>	MAOA	Fluvoxamine, paroxetine	No association	22	217
Yoshida et al. <sup>81</sup>	MAOA	Fluvoxamine	No association	15	66
Müller et al. <sup>152</sup>	MAOA	Moclobemide	No association	12	62

↑ = positive association; ↓ = negative association; VNTR = variable number tandem repeat.

colleagues in 2005<sup>197</sup> (the insertion/deletion variation in 5-HTTLPR), and that it might play a role in anxiety clusters of symptoms in patients with obsessive-compulsive disorder.<sup>209,210</sup> It is still possible that a number of other unknown alleles within this genetic region may affect the expression of 5-HTT: if this influence is found to be as great as for the rs25531, previous findings will become much less relevant, having being blind to important genetic stratification factors.<sup>211</sup> Nevertheless, this should not be discouraging, and a genetic oriented pretreatment test based on 5-HTTLPR has been found to be associated with a better clinical outcome.<sup>212</sup> Table 6 lists association studies that dealt with the relation between the 5-HTTLPR variations and the antidepressant response.

**Norepinephrine transporter**

The *NET* gene (*SLC6A2*) encodes a NET that is responsible for reuptake of NE into presynaptic nerve terminals and is a regulator of NE homeostasis.<sup>226</sup> The reuptake of NE occurs via

a specific Na<sup>+</sup>- and Cl<sup>-</sup>-dependent transport system, which is the target for tricyclic antidepressants such as desipramine and imipramine. Genetic variations have been proven to influence function: the alanine-to-proline substitution at position 369 (rs5566) has been associated with lack of transport activity, whereas the asparagine-to-threonine substitution at position 292 (rs5563) has been found to impede surface expression of *NET*.<sup>229</sup> Moreover, the phenylalanine to cysteine (rs5558) variation at position 528 was reported to be associated with increased functionality of *NET*.<sup>229</sup> It has recently been found that the norepinephrine reuptake inhibitors (NRIs) response is associated with the *G1287A* polymorphism (rs5569): GG genotype was associated with better response.<sup>184</sup> Consistently, one study investigated whether *NET* gene variants could affect response to milnacipram,<sup>185</sup> and significant associations were reported with the T-182C (with the T allele predicting a better response).

Nevertheless, associations between *NET* polymorphisms

**Table 6: Relevant pharmacogenetic association studies that focused on 5-HTTLPR (part 1 of 2)**

Study	Gene	Drug	Results	Quality (0–31)	Sample size
Mrazek et al. <sup>175</sup>	5-HTTLPR	Citalopram	White non-Hispanic: Int2 VNTRs 12/12 and LL genotype ↑ remission	25	1914
Yoshimura et al. <sup>186</sup>	5-HTTLPR	Paroxetine	No association	21	60
Gressier et al. <sup>213</sup>	5-HTTLPR	Various antidepressants	In females L allele ↑ response	19	103
Min et al. <sup>191</sup>	5-HTTLPR	SSRI, SNRI	5-HTTLPR L/L or STin2 12/12 genotype ↑ response to SSRI	25	657
Huezo-Diaz et al. <sup>174</sup>	5-HTTLPR	Escitalopram, nortriptyline	L allele ↑ response to escitalopram, > effect in males	20	795
Capozzo et al. <sup>214</sup>	5-HTTLPR	Citalopram	l/l carriers ↑ response	8	21
Maron et al. <sup>180</sup>	5-HTTLPR	Escitalopram	No associations in response S allele ↑ severe headache	20	135
Wilkie et al. <sup>179</sup>	5-HTTLPR	Paroxetine	SLC6A4 intron 2 repeat homozygosis ↓ remission and response	11	163
Benedetti et al. <sup>194</sup>	5-HTTLPR	Lithium augmentation	s/s genotype ↑ response	21	161
Bozina et al. <sup>173</sup>	5-HTTLPR	Paroxetine	L allele and STin2 10/10 ↑ response	21	130
Dogan et al. <sup>178</sup>	5-HTTLPR	Sertraline	No association	NA	64
Ferreira et al. <sup>215</sup>	5-HTTLPR	Various	L allele ↓ switch into a manic episode	9	112
Oberlander et al. <sup>196</sup>	5-HTTLPR	SSRIs exposed neonates	l/l genotype ↑ respiratory symptoms (respiratory distress and rapid breathing) s/s genotype ↑ neuromotor symptoms	13	37
Lotrich et al. <sup>192</sup>	5-HTTLPR	Paroxetine	In s carriers paroxetine concentrations ↑ response (elderly population)	16	110
Schillani et al. <sup>216</sup>	5-HTTLPR	Sertraline	L carriers ↑ response	10	11
Smits et al. <sup>163</sup>	5-HTTLPR	Various SSRIs	In female s-allele ↓ response	13	214
Stamm et al. <sup>193</sup>	5-HTTLPR	Lithium augmentation	s/s genotype ↑ response	14	55
Tanaka et al. <sup>217</sup>	5-HTTLPR	Paroxetine	No association with iatrogenic nausea	15	72
Kang et al. <sup>181</sup>	5-HTTLPR	Mirtazapine	s/s genotype ↑ response	18	101
Kirchheiner et al. <sup>218</sup>	5-HTTLPR	Various	No association	19	77
Kronenberg et al. <sup>219</sup>	5-HTTLPR	Citalopram	In children l/l genotype ↑ response	24	312
Hu et al. <sup>177</sup>	5-HTTLPR	Citalopram	L(A) allele ↑ side effects	19	1655
Kim et al. <sup>184</sup>	5-HTTLPR	Fluoxetine sertraline nortriptyline	STin2 12/12 ↑ response to SSRIs S allele ↑ response to SSRIs and to nortriptyline	19	208
Masoliver et al. <sup>220</sup>	5-HTTLPR	Various antidepressants	s alleles ↑ manic switch	8	188
Ng et al. <sup>221</sup>	5-HTTLPR	Sertraline	No association with response and side effects	16	35
Smeraldi et al. <sup>208</sup>	5-HTTLPR	Fluvoxamine	l allele ↑ response 16F *l ↑ partial response 16D *l ↑ response	21	228
Popp et al. <sup>206</sup>	5-HTTLPR	Various	STin2 10/10 ↑ side effects s/s genotype ↑ side effects	9	109



and antidepressant response have not been recently replicated.<sup>191</sup> In a genome-wide association study, rs36029 and rs1532701 showed nominally significant associations with response to nortriptyline, but neither of them survived after gene-wide or hypothesis-wide correction.<sup>230</sup>

### Dopamine transporter

The gene for DAT (*DAT1*) is located at position 5p15,3,<sup>231</sup> and it spans 52 635bp. There are at least 502 known variants of this gene. A 40bp VNTR polymorphism in exon 15 has been reported to affect DAT expression,<sup>232</sup> and it was associated with a faster onset of antidepressant response when the allelic variant associated with enhanced expression (10 repeat variant) was present.<sup>218</sup> This association was proven to be present in a diverse class of antidepressants.<sup>218</sup> Mutations in this gene have been associated with anxiety traits related to BDNF variations<sup>233</sup> and with the relapse rate after smoking cessation.<sup>234</sup>

### Monoamine receptors

#### Serotonin 1A

The 5-HT<sub>1A</sub> receptors are present pre- and postsynaptically in different brain regions. At the level of 5-HT cell bodies in the midbrain dorsal raphe nucleus, the 5-HT<sub>1A</sub> receptor acts as an autoreceptor in a short negative feedback loop, and its activation inhibits the firing of 5-HT neurons and diminishes the release of this neurotransmitter in the prefrontal cortex. Several antidepressant compounds desensitize raphe 5-HT<sub>1A</sub> autoreceptors, an event that results in an enhanced 5-HT neurotransmission, and this is thought to be associated with the antidepressant effect of those drugs. Agents that block 5-HT<sub>1A</sub> autoreceptors (e.g., pindolol) may accelerate the onset of antidepressant action.<sup>235</sup> Postsynaptic 5-HT<sub>1A</sub> receptors probably mediate different actions: postmortem brains from depressed suicide completers versus nondepressed individuals displayed elevated 5-HT<sub>1A</sub> density in the raphe nuclei

**Table 6: Relevant pharmacogenetic association studies that focused on 5-HTTLPR (part 2 of 2)**

Study	Gene	Drug	Results	Quality (0–31)	Sample size
Hong et al. <sup>83</sup>	5-HTTLPR	Fluoxetine	V/I genotype ↑ response	15	224
Kato et al. <sup>190</sup>	5-HTTLPR	Fluoxetine paroxetine	V/I genotype ↑ response	17	100
Kraft et al. <sup>207</sup>	5-HTTLPR	Fluoxetine	rs25531 ↑ response	16	96
Kato et al. <sup>189</sup>	5-HTTLPR	Fluvoxamine paroxetine	I allele ↑ response to fluvoxamine	18	81
Arias et al. <sup>222</sup>	5-HTTLPR	Citalopram	S/S-G/G haplotype ↓ remission	18	130
Serretti et al. <sup>119</sup>	5-HTTLPR	Various	No association	22	185
Yoshida et al. <sup>185</sup>	5-HTTLPR	Milnacipram	No association	17	96
Serretti et al. <sup>120</sup>	5-HTTLPR	Fluvoxamine, paroxetine	s/s genotype ↓ response	22	221
Serretti et al. <sup>223</sup>	5-HTTLPR	Various antidepressants	No association with manic switch	17	416
Lee et al. <sup>188</sup>	5-HTTLPR	Long-term antidepressants	s/s genotype ↓ response	12	128
Peters et al. <sup>85</sup>	5-HTTLPR	Fluoxetine	rs25533 in STin2 ↑ response	19	96
Murphy et al. <sup>171</sup>	5-HTTLPR	Paroxetine, mirtazapine	I allele ↑ response and ↓ side effects to paroxetine but ↑ side effects to mirtazapine	18	246
Durham et al. <sup>172</sup>	5-HTTLPR	Sertraline	S allele ↓ response	18	206
Arias et al. <sup>169</sup>	5-HTTLPR	Citalopram	s/s genotype ↓ remission	18	131
Joyce et al. <sup>170</sup>	5-HTTLPR	Fluoxetine, nortriptyline	< 25 yr: no association > 25 yr: s/s genotype ↓ response	15	139
Perlis et al. <sup>224</sup>	5-HTTLPR	Fluoxetine	s/s genotype ↑ response s allele ↑ insomnia or agitation	19	36
Rousseva et al. <sup>225</sup>	5-HTTLPR	Antidepressants	No association with manic switch	12	305
Takahashi et al. <sup>121</sup>	5-HTTLPR	Fluvoxamine	No association with fluvoxamine induced nausea	21	54
Yu et al. <sup>187</sup>	5-HTTLPR	Fluoxetine	V/I genotype ↑ response	15	121
Rausch et al. <sup>188</sup>	5-HTTLPR	Fluoxetine	V/I subjects ↑ rapid response	19	51
Ito et al. <sup>205</sup>	5-HTTLPR	Fluvoxamine	No association (STin2)	15	54
Yoshida et al. <sup>183</sup>	5-HTTLPR	Fluvoxamine	s allele ↑ response	14	54
Zanardi et al. <sup>166</sup>	5-HTTLPR	Fluvoxamine	I allele ↑ response	21	64
Arias et al. <sup>225</sup>	5-HTTLPR	Citalopram	s/s genotype ↓ response	18	269
Mundo et al. <sup>227</sup>	5-HTTLPR	SSRI, TCA	s allele ↑ manic or hypomanic switch	15	27
Minov et al. <sup>176</sup>	5-HTTLPR	Various antidepressants	No association	9	104
Serretti et al. <sup>77</sup>	5-HTTLPR	Fluvoxamine	I allele ↑ response	22	217
Zanardi et al. <sup>165</sup>	5-HTTLPR	Paroxetine	s allele ↓ response	18	58
Pollock et al. <sup>157</sup>	5-HTTLPR	Paroxetine	s allele ↑ slower response	16	57
Kim et al. <sup>182</sup>	5-HTTLPR	Fluoxetine, paroxetine	s/s genotype and L/L in intron ↑ response	14	120
Smeraldi et al. <sup>164</sup>	5-HTTLPR	Fluvoxamine	I allele ↑ response	16	53

↑ = positive association; ↓ = negative association; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; VNTR = variable number tandem repeat.

(autoreceptors) but not at postsynaptic sites, which may lead to decreased serotonergic activity.<sup>236</sup> Transcription of *5-HT<sub>1A</sub>* is modulated by a common 1019C>G (rs6295) SNP in its upstream regulatory region. The 1019G allele in the *5-HT<sub>1A</sub>* upstream regulatory region fails to bind the repressors Deaf1 and Hes5, thus abolishing Deaf1 action and impairing Hes5 action. This leads to the upregulation of the receptor's expression.<sup>237,238</sup> This mechanism may mediate the association of the 1019G allele with depression and suicide.<sup>237</sup> This allele may also counteract the therapeutic effects of antidepressant drugs by increasing the number of inhibitory 5-HT<sub>1A</sub> auto-receptors on the cell surfaces. This hypothesis has been partially confirmed by a series of studies that reported either a better response to SSRIs in patients homozygous for the C allele of *5-HT<sub>1A</sub>*<sup>83,222,239–242</sup> despite evidence that this variant is not associated with antidepressant response<sup>85,116,243</sup> or restricted solely to the female sex.<sup>244</sup> Baune and colleagues<sup>245</sup> found a better outcome in carriers of the G allele with melancholic depression. A glycine-to-asparatate substitution at amino acid 272 (rs1800042) and its association with antidepressant response has also been explored. Carriers of the asparatate allele seemed to have a greater reduction in depressive symptomatology compared with glycine homozygotes,<sup>246</sup> although this finding was not confirmed in subsequent studies.<sup>243,244</sup> Recently, Kato and colleagues<sup>239</sup> reported several other polymorphisms within this gene associated with better response (e.g., rs10042486 C/C and rs1364043 T/T). Table 7 lists relevant studies on this topic.

### Serotonin 2A

A considerable amount of data support a role of *5-HT<sub>2A</sub>* in MDD.<sup>247–250</sup> It has consistently been reported that drugs with 5-HT<sub>2A</sub> agonist properties may have acute euphoriant effects.<sup>251</sup> Moreover, paroxetine and nefazodone may exert their antidepressant effects through regulation of 5-HT<sub>2A</sub> receptors,<sup>249,252–254</sup> although controversial findings can also be

found.<sup>255</sup> Finally, 5-HT<sub>2A</sub> receptors have been reported to mediate some of the antidepressant effects seen in experimental animal models of depression.<sup>256</sup> Three variations within the coding region of *5-HT<sub>2A</sub>* have been implicated in antidepressant response: 102T>C (rs 6313)<sup>176</sup> and 1438G>A (rs6311)<sup>190,257</sup> and 1420C>T,<sup>153</sup> although results were not unequivocal and some findings not replicated.<sup>52,83,85,116,153,185,258</sup> The variants 102T>C and 1438G>A are 2 of the most investigated polymorphisms of this gene: they are in linkage disequilibrium, and they can be considered together.<sup>259</sup> Several other variants have been reported to predict antidepressant response.<sup>85,117,134,179,229,260,261</sup> Table 8 lists relevant genetic association studies that investigated the impact of these variations on the antidepressant response.

### Serotonin 3A and 3B

To date, 5 different genes coding for *5-HT<sub>3</sub>* receptor subunits have been cloned, and among these, the most studied are *HTR3A*, *HTR3B* and *HTR3C*. Intriguingly, a transcriptional control that gives rise to different isoforms of the *HTR3B* has been reported, characterizing the 5' coding ending in a specific way for the CNS.<sup>264</sup> An association with vomiting and nausea, both caused by chemotherapy and paroxetine, was reported with the -100 -102 AAG deletion variant of *HTR3B*.<sup>265</sup> Conflicting findings were reported for the *HTR3A* 195C>T (rs62625041) and 178C>T SNPs with respect to the gastrointestinal side effects induced by SSRIs,<sup>52,190,266</sup> whereas the *HTR3B* polymorphism at position 129 leading to a tyrosine-to-serine substitution (rs1176744) was found to be associated with nausea induced by paroxetine,<sup>266</sup> but conflicting findings have been reported.<sup>52,217</sup>

### Serotonin 6

This 5-HTT subtype is coded by a gene located on chromosome 1p36.13.<sup>267</sup> It is a G protein-coupled receptor that stimulates adenylyl cyclase via G coupling, together with receptors

**Table 7: Relevant pharmacogenetic association studies that focused on *5-HT<sub>1A</sub>***

Study	Gene	Drug	Results	Quality (0–31)	Sample size
Illi et al. <sup>116</sup>	<i>5-HT<sub>1A</sub></i>	Fluoxetine, paroxetine, citalopram	No association	13	86
Kato et al. <sup>239</sup>	<i>5-HT<sub>1A</sub></i>	SSRIs/SNRIs	rs10042486 C/C, rs6295 G/G, rs1364043 T/T genotypes ↑ response	20	137
Baune et al. <sup>245</sup>	<i>5-HT<sub>1A</sub></i>	Various	In melancholic subtype rs6295 CC genotype ↓ response	20	340
Levin et al. <sup>243</sup>	<i>5-HT<sub>1A</sub></i>	SSRIs	No association	6	130
Yu et al. <sup>244</sup>	<i>5-HT<sub>1A</sub></i>	Fluoxetine	In female rs6295 C/C genotype ↑ response	13	222
Hong et al. <sup>83</sup>	<i>5-HT<sub>1A</sub></i>	Fluoxetine	rs6295 C/C genotype ↑ response	15	224
Suzuki et al. <sup>52</sup>	<i>5-HT<sub>1A</sub></i>	Fluvoxamine	No association	18	96
Parsey et al. <sup>242</sup>	<i>5-HT<sub>1A</sub></i>	Various antidepressants, ECT	rs6295 C/G and GG genotype ↓ response	12	22
Arias et al. <sup>222</sup>	<i>5-HT<sub>1A</sub></i>	Citalopram	rs6295 GG genotype + <i>HTTLPR</i> ss ↓ response	18	130
Serretti et al. <sup>240</sup>	<i>5-HT<sub>1A</sub></i>	Fluvoxamine	rs6295 C/C genotype ↑ response	24	262
Suzuki et al. <sup>246</sup>	<i>5-HT<sub>1A</sub></i>	Fluvoxamine	rs1800042 Gly/Gly genotype ↓ response	17	52
Peters et al. <sup>85</sup>	<i>5-HT<sub>1A</sub></i>	Fluoxetine	No association	19	96
Lemondet et al. <sup>241</sup>	<i>5-HT<sub>1A</sub></i>	Fluoxetine + pindolol Nefazodone+pindolol Flibanserin	rs6295 G allele ↓ response to flibanserin	14	107

↑ = positive association; ↓ = negative association; ECT = electroconvulsive therapy; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

5-HT<sub>4</sub> and 5-HT<sub>7</sub>. Animal studies reported a role of this receptor in some behavioural variables, such as novelty-seeking and instrumental learning.<sup>268,269</sup> Recently, a discrete involvement of this receptor in the antidepressant mechanism has been reported.<sup>270,271</sup> The 5-HT<sub>6</sub> genetic sequence is 14276bp long, with 3 exons and 2 introns; 120 genetic variations are known so far. A serine-to-lysine substitution at position 267 resulted in a 10-fold higher affinity for 5-HT than the native receptor, and it demonstrated an agonist-independent activity.<sup>272</sup>

Kohen and colleagues<sup>267</sup> reported a silent polymorphism at position 267 within the first exon of the 5-HT<sub>6</sub> receptor gene, leading to a thymidine-to-cytosine substitution (267T>C, rs1805054); this SNP was investigated for association with antidepressant response in several studies. Although the first study yielded negative results,<sup>273</sup> in a subsequent study, participants homozygous for the CT genotype experienced greater efficacy of the antidepressant treatment.<sup>274</sup> One recent study was not able to replicate this finding,<sup>179</sup> whereas another did not find association between other SNPs (rs1805054) and antidepressant response.<sup>116</sup> The 267C>T polymorphism in exon 1 and a trinucleotide repeat polymorphism (2 or 3 GCC-repeats) in the 5' upstream region of the gene were found not to be associated with suicidal behaviour.<sup>275</sup>

### β1 adrenoceptor

A number of pharmacologically well characterized subtypes of adrenergic receptors are known, including α<sub>1</sub>, α<sub>2</sub>, β<sub>1</sub> and

β<sub>2</sub>. Of these, both the β<sub>1</sub> adrenoceptor (β<sub>1</sub>AR) and the β<sub>2</sub> adrenoceptor (β<sub>2</sub>AR) stimulate adenylate cyclase, although they are implicated in different physiologic functions. The β<sub>1</sub>AR adrenoceptor serves as an important regulator of the CNS-mediated behaviour and of several neural functions, including mood, memory, neuroendocrine control and stimulation of autonomic function, and it is involved in the mediation of antidepressant effects.<sup>276</sup> An influence of genetic variations in the β<sub>1</sub>AR coding sequence is suggested by a recent animal study,<sup>277</sup> although evidence is lacking in this field. The role of the β<sub>1</sub> adrenergic receptor in antidepressant treatment efficacy is consistent with the clinical findings that drugs that antagonize the β adrenoceptors can be associated with side effects, such as depression and lethargy.<sup>278</sup> Indeed, its molecular action is quite complex. Xu and colleagues<sup>279</sup> in 2003 presented evidence that β<sub>2</sub>AR and β<sub>1</sub>AR form heterodimers when coexpressed in cultured cells; moreover, β<sub>2</sub>AR expression affects the internalization and ligand-binding characteristics of β<sub>1</sub>AR. The β<sub>1</sub> adrenergic receptor gene (*ADRB1*) is located at 10q24–26,<sup>280</sup> spans 1714bp and is composed of a single exon. Eighty polymorphisms have been identified, and a recently identified functional polymorphism in the β<sub>1</sub> adrenergic receptor 1165G>C (rs1801253), leading to glycine-to-arginine substitution at amino acid position 389, has been associated with an enhanced coupling to the stimulatory G(s) protein and increased adenylyl cyclase activation. Those molecular events

**Table 8: Relevant pharmacogenetic association studies that focused on 5-HT<sub>2A</sub>**

Study	Gene	Drug	Results	Quality (0–31)	Sample size
Uher et al. <sup>229</sup>	5-HT <sub>2A</sub>	Escitalopram, nortriptyline	G allele rs9316233 and A allele rs2224721 ↑ response to escitalopram	19	760
Illi et al. <sup>116</sup>	5-HT <sub>2A</sub>	Fluoxetine, paroxetine, citalopram	No association	13	86
Perlis et al. <sup>134</sup>	5-HT <sub>2A</sub>	Duloxetine	rs9534505, rs1923884, rs2760351 ↑ association	13	102
Peters et al. <sup>117</sup>	5-HT <sub>2A</sub>	Fluoxetine, citalopram	rs1923884 ↑ remission rs7997012 ↑ remission and response	17	2049
Wilkie et al. <sup>179</sup>	5-HT <sub>2A</sub>	Paroxetine	rs6314 ↑ remission and response	11	166
Horstmann et al. <sup>261</sup>	5-HT <sub>2A</sub>	Various	rs7997012 G allele ↑ response	3	300
Tanaka et al. <sup>217</sup>	5-HT <sub>2A</sub>	Paroxetine	No association	15	72
Kang et al. <sup>262</sup>	5-HT <sub>2A</sub>	Mirtazapine	No association	17	101
Bishop et al. <sup>263</sup>	5-HT <sub>2A</sub>	Various SSRIs	rs6311 G/G genotype ↑ iatrogenic sexual dysfunction	14	81
McMahon et al. <sup>260</sup>	5-HT <sub>2A</sub>	Citalopram	rs799701 ↑ response	19	1297
Hong et al. <sup>83</sup>	5-HT <sub>2A</sub>	Fluoxetine	No association	15	224
Suzuki et al. <sup>52</sup>	5-HT <sub>2A</sub>	Fluvoxamine	In <i>CYP2D6</i> PM, rs6311 A/G and G/G genotypes ↑ gastrointestinal side effects	18	96
Kato et al. <sup>190</sup>	5-HT <sub>2A</sub>	Fluoxetine, paroxetine	rs6311 G/G genotype ↑ response and nausea in paroxetine treatment	17	100
Choi et al. <sup>257</sup>	5-HT <sub>2A</sub>	Citalopram	rs6311 A/G and GG genotypes ↑ response	17	71
Yoshida et al. <sup>185</sup>	5-HT <sub>2A</sub>	Milnacipran	No association	17	80
Peters et al. <sup>85</sup>	5-HT <sub>2A</sub>	Fluoxetine	rs1923882, rs6314, rs3125 ↑ response	19	96
Murphy et al. <sup>57</sup>	5-HT <sub>2A</sub>	Paroxetine, mirtazapine	rs6313 C/C genotype ↑ paroxetine-induced side effects	18	122
Yoshida et al. <sup>155</sup>	5-HT <sub>2A</sub>	Fluvoxamine	No association with iatrogenic nausea	16	54
Cusin et al. <sup>153</sup>	5-HT <sub>2A</sub>	Fluvoxamine, paroxetine	rs6313 C allele ↑ response	22	217
Sato et al. <sup>258</sup>	5-HT <sub>2A</sub>	Fluvoxamine	No association	15	54
Minov et al. <sup>176</sup>	5-HT <sub>2A</sub>	Various antidepressants	rs6313 C allele ↑ response	9	104

↑ = positive association; ↓ = negative association; PM = poor metabolizer; SSRI = selective serotonin reuptake inhibitor.

have been observed in patients with affective disorders,<sup>281,282</sup> and this has been partially confirmed in a large study reporting that, although the 1165G>C variant did not influence the depressive phenotype, a tendency for a relation between CC homozygosity and a better and even faster response to antidepressant treatment was detected in those patients.<sup>282</sup>

### Dopamine receptors

The DA system is highly involved in depressive spectrum symptomatology:<sup>283</sup> it has been suggested that the pathophysiological process in patients with melancholic depression involves decreased dopaminergic neurotransmission due to hypersensitive inhibitory 5-HT<sub>2</sub> heteroreceptors located on dopaminergic neurons. Treatment with most antidepressants downregulates these receptors, an action that is thought to be associated with increased dopaminergic firing and an antidepressant effect. Moreover, because the downregulation of 5-HT<sub>2</sub> receptors coincides with the emergence of an antidepressant effect, this would consistently explain the therapeutic time lag.<sup>284</sup> Many DA receptors are known so far, and D2 receptors have been widely investigated. The D2 receptors are a G protein-coupled receptor that inhibits adenylyl cyclase activity. A missense mutation in this gene causes myoclonus dystonia, whereas other mutations have been associated with schizophrenia. Alternative splicing of this gene results in 2 transcript variants encoding different isoforms (mainly the long and short forms). A third variant has been described, but it has not been determined whether this form is normal or caused by aberrant splicing. The D2 receptors are important in terms of pharmacodynamic actions because they (the long isoform primarily) are the first target of antipsychotic treatment,<sup>285</sup> especially for the positive cluster of symptoms; however, there is also some evidence addressing an important role in antidepressant treatment as a result of animal, pharmacological and genetic investigations.<sup>286,287</sup> Some evidence addresses a role of D2 receptors in the pharmacodynamics of smoking cessation.<sup>42,288</sup> A functional polymorphism in the *DRD2* gene, which causes a structural change from serine to cysteine at codon 311 (Ser311Cys; rs1801028),<sup>289</sup> showed no significant influence on antidepressant response in some studies.<sup>223,290,291</sup>

The *DRD4* gene has also been investigated as a possible candidate gene in the pharmacogenetics of the antidepressant response. The D4 subtype is a G protein-coupled receptor that inhibits adenylyl cyclase. It is a target for drugs used to treat schizophrenia and Parkinson disease. The gene coding for this receptor has considerable homology to *DRD2* and *DRD3*. Mutations in *DRD4* have been associated with various behavioural phenotypes, including autonomic nervous system dysfunction, attention-deficit/hyperactivity disorder and the personality trait of novelty-seeking. The *DRD4* gene contains a polymorphic number (210 copies) of tandem 48 nucleotide repeats in exon 3 (*DRD4* exon3 VNTR), which makes it one of the most variable genes.<sup>292</sup> Moreover, *DRD4* is expressed in limbic areas involved in cognition and emotion, and high novelty-seeking was found to be associated with the 7 repeat allele independent of race, sex or age,<sup>293,294</sup> although contradicting results have been reported.<sup>295,296</sup> Regard-

ing antidepressant responses, some studies reported no association with this polymorphism;<sup>290,297</sup> however, in a recent study,<sup>298</sup> *DRD4* exon 3 variants revealed a significant modulation effect on various antidepressant drugs.

### Intracellular signal transduction pathways

#### G protein $\beta 3$ subunit

The G proteins are heterotrimers consisting of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, which dissociate after receptor activation. These proteins convey signals in cells initiated by the activation of many receptors, which are then translated into various intracellular systems through interaction with the diverse effector systems.<sup>299</sup> It has been estimated that about 80% of all known hormones, neurotransmitters and neuromodulators elicit cellular responses through G proteins coupled to a variety of intracellular effectors.<sup>300</sup> The high degree of complexity generated by the interactions of G protein-coupled receptors may be one mechanism by which neurons acquire the flexibility for generating the wide range of responses observed in the CNS,<sup>300</sup> suggesting a possible involvement in the pharmacogenetics of antidepressant response.

A polymorphism (825C>T, rs5443) was identified in exon 10 of the gene encoding the  $\beta 3$  subunit (*GN $\beta$ 3*) of the pertussis toxin-sensitive Gi-type proteins.<sup>301</sup> The T allele of this mutation is associated with the occurrence of a splice variant, called G $\beta$ 3s, resulting from the deletion of nucleotides 498–620 of exon 9. The splice variant that is associated with the T allele remains biologically active,<sup>301</sup> although it appears to be less active than the wild-type form in terms of modulation of ion channels and in forming heterodimers with other proteins. It has been suggested that pathological conditions in patients carrying the homozygous 825C>T allele may result from a functional knockout of *GN $\beta$ 3*.<sup>302</sup> The *GNB3* (825)T variant was found to predict a better antidepressant response in 5 independent studies.<sup>170,303–306</sup> Lack of association has also been found.<sup>83,307,308</sup>

### Hypothalamic–pituitary–adrenal axis and stress hormone system

Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis is one of the most robust findings in many patients with MDD (up to 70%).<sup>309</sup> It has been reported that the alterations of CRH function contribute to the pathogenesis of depression: concentrations of CRH in the cerebrospinal fluid (CSF) are elevated.<sup>310,311</sup> Imaging studies on patients with MDD and suicidal behaviour, together with animal studies on models of depression and human studies, confirmed the primary role of CRH in the psychiatric field.<sup>312–316</sup> There are 2 primary receptor subtypes for the CRH in the CNS: corticotropin-releasing hormone receptors CRHR1 and CRHR2. The CRHR1 subtype is considered to play a key role in mediating the CRH-elicited effects in depression and anxiety.<sup>317</sup>

#### Corticotropin-releasing hormone receptor 1

The CRHR binds to CRH, a potent mediator of endocrine, autonomic, behavioural and immune responses to stress.

Corticotropin-releasing hormone, also called corticotropin-releasing factor (CRF), is a 41 amino acid peptide synthesized in the hypothalamus, and it is capable of stimulating the production of adrenocorticotrophic hormone (ACTH) and other proopiomelanocortin products of the anterior pituitary. It is the principal neuroregulator of the hypothalamic–pituitary–adreno–cortical axis and plays an important role in coordinating the endocrine, autonomic and behavioural responses to stress and immune challenge. Sakai and colleagues<sup>318</sup> determined that the *CRHR1* gene contains at least 14 exons spanning 20 kb of genomic DNA. The *CRHR1* isoforms appear to originate from the same gene by alternative splicing. The isoform with the highest affinity for CRH and the ability to transduce the most cyclic adenosine monophosphate (cAMP) accumulation in response to CRH binding is encoded by 13 exons and excludes exon 6.

Antagonists of *CRHR1* have consistently demonstrated antidepressant properties in experimental animals and humans.<sup>319–321</sup> Some evidence stands for a relevance of *CRHR1* variants and antidepressant response, in particular an association within the rs242941 GG genotype and homozygous GAG haplotype of the 3 SNPs (rs1876828, rs242939 and rs242941) and therapeutic response to fluoxetine.<sup>322,323</sup> Moreover, rs110402 has been found to be associated with increased risk to present a seasonal pattern and early onset of the first depressive episode.<sup>324</sup> Interestingly, in the same study, the authors found an association between *CRHR2* gene variants and response to citalopram; in particular, G carriers of rs2270007 showed a worse overall response to citalopram, suggesting a role of both *CRHRs* in antidepressant response.

### Glucocorticoid receptor

Glucocorticoid hormones, like other classes of steroid hormones, exert their cellular action by complexing with a specific cytoplasmic receptor that, in turn, translocates to the nucleus and binds to specific sites on DNA. The glucocorticoid receptor (GCCR) was the first transcription factor to be isolated and studied in detail.<sup>325</sup> The GCCR is crucial to gene expression. It is a 94 kD polypeptide, and it is thought to have distinct steroid-binding and DNA-binding domains. A research group in Munich collected preliminary evidence that a functional polymorphism of the *GCCR* gene (ER22/23EK) and a series of SNPs within the gene encoding the hsp90 co-chaperone FKBP5 (a part of the mature GCCR heterocomplex that regulates GCCR sensitivity) could modulate the onset of response to various classes of antidepressants.<sup>326</sup> Subsequent studies,<sup>324,327</sup> however, did not replicate this finding. Another study reported that homozygous carriers of the *BclI* polymorphism and ER22/23EK carriers were at increased risk for a major depressive episode, and although no genetic associations with functional HPA axis measures in depressed patients were found, the ER22/23EK carriers showed a significantly faster clinical response to antidepressant therapy and a trend toward better cognitive function during depression.<sup>328</sup> Finally, other SNPs within this gene associated with treatment outcome (rs4713916A, rs3800373C and rs1360780T) were recently reported.<sup>329,330</sup>

### Angiotensin-converting enzyme substance P system

#### Angiotensin-converting enzyme

Angiotensin-converting enzyme (ACE) is associated with a series of actions that influence blood pressure through the rennin-angiotensin cascade, interfering with the secretion of hormones (adrenocorticotrophic hormone; CRH),<sup>331</sup> and it is also expressed in the CNS, where its primary function comprises degradation of neuropeptides including substance P. Substance P antagonists have been proven to have possible antidepressant effects, and the level of substance P is diminished after administration of monoamine uptake inhibitors, so the influence of substance P on depressive biological mechanisms and treatment has been hypothesized.<sup>332–334</sup>

The presence of a deletion variant (D/) in the *ACE* gene was found to be associated with higher ACE plasma levels,<sup>335</sup> and it was also found to be associated with higher substance P levels<sup>336</sup> and a faster response to antidepressant treatments,<sup>337</sup> including total sleep deprivation,<sup>338</sup> particularly among women.<sup>339</sup> This finding was replicated in another study,<sup>340</sup> but a further study<sup>341</sup> was not able to replicate those findings. Further, DD genotype carriers displayed the highest cortisol response in the dexamethasone/CRH test administered at the time of admission to hospital.<sup>342</sup> It has been recently reported that rs8066276 and rs4305 were associated with coping style profile in a sample of 540 healthy controls and 194 patients with depression.<sup>343</sup> Another component of the ACE–substance P system, the angiotensin II receptor gene (*ATI*), was included among outcome predictors in MDD.<sup>340</sup>

### Endogenous circadian locomotor output cycles kaput system

#### Circadian locomotor output cycles kaput

A small region of the hypothalamic suprachiasmatic nucleus (SCN) is able to rule circadian rhythms, from the simplest biological systems to the most complex ones, through the rhythmic expression of several *CLOCK* genes. These rhythms are regulated by positive and negative gene expression feedback loops that consist of transcriptional and posttranslational mechanisms.<sup>344</sup> At least 2 *CLOCK* gene products, *CLOCK* and aryl hydrocarbon receptor nuclear translocatorlike (*ARNTL*), function as transcription factors by binding to E-box enhancers in the promoter regions of other *CLOCK* genes, including period (*PER*) genes. In turn, products of the *PER* genes can regulate the expression of other *CLOCK* gene transcription factors. In addition, *CLOCK* genes can influence other noncircadian genes, so-called *CLOCK*-controlled genes (*CCGs*), acting as transcription factors, and this could be related to pharmacologic actions. In fact, within the candidate *CCGs* there are the DA and norepinephrine transporters (*DAT* and *NET*), some DA receptors and tyrosine hydroxylase genes.<sup>345</sup> This model is thought to be more complex, since psychoactive drugs can influence other promoter zones in the genetic sequence such as cAMP response element (CREB) and activating protein 1 (AP1) near the E-box in the promoter sequence.

Animal experiments reported that the mutant *CLOCK* mice with evening-type behaviour had worse performances at spatial learning tests, together with altered cholinergic tone. Normal

serotonergic and dopaminergic tone were also reported.<sup>346</sup> Moreover, repeated administration of fluoxetine or cocaine increased *CLOCK* gene expression in the hippocampus and in the striatum (caudate–putamen) of mice, together with enhanced 5-HT *N*-acetyltransferase in the hippocampus, striatum and frontal cortex.<sup>347</sup> The *CLOCK* gene is located in position 4q12 and it contains 20 exons.<sup>348</sup> One polymorphism in the 3' flanking region of the *CLOCK* gene, a T-to-C substitution at position 3111, is known to affect mRNA stability and half-life.<sup>349</sup> In healthy participants, the C allele was associated with a significantly greater delay in preferred timing for activity or sleep.<sup>350</sup> In mood disorders, the same C variant was coupled with higher recurrence rates in patients with bipolar disorders,<sup>351</sup> increased lifetime sleep disturbances<sup>352</sup> and persistence of insomnia during antidepressant therapy.<sup>353</sup> Recently, a significant association between rs3736544 (T allele) and response and between rs3749474 (C allele) and remission has been found.<sup>354</sup>

#### Other relevant genes

##### Nitric oxide synthase

Nitric oxide is produced from its precursor larginine by the enzyme NO synthase (NOS), which includes at least 3 distinct isoforms: neuronal (NOS1), endothelial and inducible NOS. The *NOS1* gene was mapped to chromosome 12q24.2q24.31,<sup>355,356</sup> spans 14 8604bp and has 748 known genetic variants. Recent studies have implicated *NOS* in the mechanism that underlies the therapeutic efficacy of antidepressant drugs,<sup>357–359</sup> and animal models reported that the aggressive behaviour associated with *NOS* gene ablation is mediated by the serotonergic system.<sup>360</sup> Specifically, the excessive aggressiveness and impulsiveness of *NOS* knockout mice is caused by selective decrements in 5-HT turnover and deficient 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptor function in brain regions regulating emotion.<sup>360</sup> Although this evidence suggests a possible role of this gene's variations in the pharmacogenetics of antidepressant therapy, there are not many pharmacogenetic investigations involving *NOS* coding sequences to date. Moreover, in 2003 Yu and colleagues<sup>361</sup> reported no association between a *NOS1* 276C>T polymorphism (rs2682826) and antidepressant (fluoxetine) response or risk of depressive episodes.

##### Interleukin-1 $\beta$

One potential pathway by which depression may impact health is through modulation of immune function. Depressed individuals have been shown to display reductions in measures of cellular immune competence as well as elevated markers of systemic inflammation.<sup>362–365</sup> Moreover, there is evidence suggesting strong influences in both the direction from cytokines to neurotransmitters and from neurotransmitters to cytokines. For example, it has been reported that IL-1 activates brain noradrenergic<sup>366,367</sup> and serotonergic systems,<sup>368–370</sup> reduces acetylcholine release in the hippocampus<sup>371</sup> and potentiates  $\gamma$ -aminobutyric acid (GABA) effects.<sup>372–374</sup> Moreover, noradrenaline enhances and acetylcholine inhibits the release of IL-1 $\beta$  from neurons in hypothalamic explants,<sup>375</sup> while 5-HT increases IL-1 $\beta$  mRNA in the hypothalamus.<sup>376</sup>

Interleukin-1, produced mainly by blood monocytes, medi-

ates the host reactions of acute phase response. There is some evidence suggesting an association between IL-1 levels and mood disorders,<sup>377–380</sup> although some recent negative reports detract from this theory.<sup>381</sup>

Auron and colleagues<sup>382</sup> assigned the *IL-1* gene to chromosome 2q13–21. The *IL-1 $\beta$*  gene was assigned to the end of 18q.<sup>383</sup> Four SNPs have been reported in the *IL-1 $\beta$*  gene: 31C>T (rs1143627, promoter), 511C>T (rs16944, promoter), 3954C>T (rs1143634, exon 5) and 5810A>G (rs1143633, intron 4).<sup>384–386</sup> The SNP at position 31 is in strong linkage disequilibrium with the SNP at position 511.<sup>387</sup> Homozygosity for the 511T allele of the *IL-1 $\beta$*  gene was found to be associated with a trend of less severity of depressive symptoms and more favourable fluoxetine response.<sup>361</sup> On the other hand, Baune and colleagues<sup>388</sup> recently found an association between rs16944 GG genotype and rs1143643 G allele and nonremission rate. Finally a recent genome-wide study by Uher and colleagues<sup>389</sup> suggested an implication of other IL genes on the antidepressant response; specifically, *IL-11* rs1126757 and *IL-6* rs7801617 were found to be associated with escitalopram response.

##### Brain-derived neurotrophic factor

Brain-derived neurotrophic factor is a prosurvival factor induced by cortical neurons. During neuronal development, most parts of the neuron die; this is thought to ensure correct innervation densities with effector organs or other groups of neurons. In most cases, targets of innervation play a crucial role in determining the fate of their neuronal afferences by producing a limited supply of neurotrophic factors, 1 of which is BDNF. At least 9 different BDNF transcripts are known to be expressed in different parts of the brain, with a variable degree of similarity in terms of length and sequence,<sup>390,391</sup> suggesting a fine control of this prosurvival factor in discrete brain regions. Pruunsild and colleagues<sup>391</sup> determined that the *BDNF* gene contains 11 exons and spans about 70 kb. They identified transcription start sites in 9 exons, each of which was associated with a functional promoter. One of the most investigated genetic variations within the *BDNF* gene is a 196G>A (rs6265) substitution, which results in a valine-to-methionine substitution at amino acid 66 change in the 5' proregion of the protein.<sup>392</sup> It has been reported that this variation is associated with poorer episodic memory and abnormal hippocampal activation (associated with the M substitution),<sup>392</sup> MDD (despite conflicting findings mainly in nonwhite samples),<sup>393–400</sup> obsessive–compulsive disorder (M substitution represents a protective factor),<sup>401</sup> anxiety,<sup>233</sup> restricting anorexia nervosa, low minimum body mass index, binge-eating/purging anorexia nervosa, bulimia nervosa (M substitution preferentially transmitted in cases),<sup>402,403</sup> bipolar disorder (despite conflicting results)<sup>404–406</sup> and psychosis.<sup>407,408</sup> Regarding antidepressant therapy, it has been reported that the vagus stimulation, electroconvulsive therapy, sleep deprivation and diverse antidepressant therapy (e.g., imipramine, tianeptine, duloxetine, fluoxetine, mirtazapine) are associated with modified BDNF expression in different parts of the brain,<sup>409–416</sup> and it has been demonstrated that different antidepressant treatments trigger the enhancement of specific BDNF alternative splicing products,<sup>417,418</sup> suggesting that the

fine modulation of the BDNF-associated cross talking between neurons can be modified by the antidepressant treatment. This may be associated with the antidepressant effect, even though this level of complexity is yet to be understood. It has been reported that BDNF disruption is not sufficient to determine a depressive behaviour by itself, but it has been found to be essential to the antidepressant treatment effect.<sup>419</sup> Regarding the pharmacogenetics of antidepressant treatment, it was reported that the M allele was more represented in patients who experienced a depressive episode and responded to treatment with citalopram.<sup>420</sup> A lack of association has also been reported.<sup>230,307,395,421</sup> Yoshida and colleagues<sup>422</sup> found that the Val/Met genotype was associated with better treatment outcome than Val/Val and Met/Met genotypes. Gratacos and colleagues<sup>393</sup> reported that haplotype TAT (rs12273363, rs908867 and rs1491850) was associated with treatment response. Recent large studies revealed other polymorphisms within this gene: rs61888800 was found to be associated with antidepressant response;<sup>423</sup> rs7124442 TT genotype was significantly related to worse outcome, particularly in patients with anxious depression; and rs7103411 predicted worse response in subtypes of melancholic depression.<sup>424</sup>

### Glutamatergic receptors

The glutamate system appears to have a crucial role in both acute antidepressant response and maintenance of response.<sup>425</sup> Glutamate levels are increased in patients with MDD, as observed by proton magnetic resonance spectroscopy,<sup>426</sup> suggesting enhanced glutamatergic transmission. Ionotropic glutamate receptors are present pre- and postsynaptically, where they modulate neurotransmitter release or excitatory neurotransmission. A role for ionotropic glutamate receptors in antidepressant action has been supported by studies in rats.<sup>427,428</sup> Moreover, continuous treatment of rats with SSRIs has been reported to attenuate glutamatergic transmission in the cerebral cortex.<sup>429</sup> Recently, Paddock and colleagues<sup>430</sup> found an association between the rs1954787 *GRIK4* variant and citalopram response in the large STAR\*D cohort. This first report was replicated in 2 subsequent studies,<sup>261,431</sup> however, a more recent study showed controversial results.<sup>432</sup> Furthermore, genes encoding for *GRIK2*, *GRIA1*, *GRIA3* and *GRIN3A* receptors have been recently investigated in relation with response to sexual side effects from antidepressant treatment.<sup>431,433,434</sup> However, the study of the relation between genetic variants in the glutamate system and antidepressant response is a promising topic in pharmacogenetics.

### Genome-wide association studies

In recent years, the genome-scan approach has become one of the most interesting ways to discover new genetic variants associated with pharmacologic response. This new approach seems to be useful in the investigation of multigenic complex diseases, such as mood disorders, which have a remarkable heterogeneity concerning treatment response. Genome-wide association studies have attempted to solve these issues through the simultaneous analysis of a large number of genetic markers and large samples. However, there are some

negative aspects that need to be considered. First, the effect sizes of common risk variants found by genome-wide association studies have been much lower than anticipated and have often needed large meta-analyses to reach genome-wide significance.<sup>435</sup> Second, combining very large genome-wide association study samples poses additional problems concerning the comparability of data across centres.<sup>436</sup> Third, the possibility of false-positive findings needs to be considered in such studies.<sup>437</sup>

Nevertheless, in recent years some interesting results have been found by genome-wide association studies regarding antidepressant pharmacogenetics. Two studies have been completed involving the STAR\*D cohort. One of them<sup>438</sup> found 2 sets of genes associated with response and remission to citalopram treatment: the top finding (rs6966038) is 51 kb from the ubiquitin protein ligase E3C gene (*UBE3C*) and 77 kb from the motor neuron and pancreas homeobox 1 gene (*MXN1*; that controls gene expression at the caudal end of the developing notochord of an embryo), and the second one (rs6127921) is closest to the bone morphogenic protein 7 (*BMP7*) gene.<sup>438</sup> The second study<sup>439</sup> analyzed the genetic markers associated with emergent suicidal ideation during citalopram treatment. Two markers within the *PAPLN* and *IL28RA* genes were found to be associated with suicidal ideations. The *PAPLN* gene encodes papilin, a protoglycan-like sulfated glycoprotein, whereas *IL28RA* encodes an IL receptor.<sup>439</sup>

Another genome-wide association study<sup>440</sup> involved a sample from the Munich Antidepressant Response Signature (MARS) project and from an independent German replication sample, and finally the SNP set found in association with treatment outcome was genotyped in a third sample from the STAR\*D study. The analysis of alleles associated with treatment response revealed a network of 41 genes that could be grouped into 3 interrelated clusters. The first one includes genes related to metabolic pathways and brain development, such as the transcription factor nuclear receptor subfamily 2, group E, member 1 (*NR2E1*), but the strongest effect with a combined phenotype of treatment outcome in the MARS sample was observed with an SNP (rs1502174) located downstream of *EPHB* from the ephrin family.<sup>440</sup> The second gene cluster includes genes related to metabolic and cardiovascular disorders that frequently co-occur with depression, and the third one includes neuregulin 1 (*NRG1*) and genes related with glutamatergic (homer homologue 1 [*HOMER*]; glial high-affinity glutamate transporter [*SLC1A2*]) and GABA-ergic neurotransmission (GABA neurotransmitter transporter; *SLC6A11*).

A more recent paper<sup>389</sup> on the pharmacogenetics of antidepressant response in the Genome-Based Therapeutic Drugs for Depression (GENDEP) project reported a different set of markers, none of which has previously been reported in genome-wide association studies of depression susceptibility or antidepressant response. The outcome of treatment was associated with polymorphisms in 2 regions on chromosomes 1 and 10, regardless of the antidepressant used. The nearest known gene to the associated locus on chromosome 1 is a gene encoding for zinc finger protein 326 (*ZNF326*), and the nearest gene to the locus on chromosome 10 is plexin domain-containing 2 gene (*PLXDC2*). Common copy number

polymorphisms that may influence the expression of genes at longer distances through structural changes of the chromatin have been reported in both regions. Additionally, a strong genome-wide significant association was found between the rs2500535 variant in the uronyl 2-sulphotransferase gene and response to nortriptyline, and between the rs1126757 variant in the *IL-11* gene and response to escitalopram.<sup>389</sup> Moreover, another genome-wide association study<sup>441</sup> involving the GENDEP sample found an association between some polymorphisms in the *BDNF* gene and an increase in suicidal ideation during treatment. The strongest association was observed for the rs962369 SNP. The authors also found an interaction between variants in the *BDNF* and *NTRK2* (the gene encoding BDNF receptor) genes on suicidal ideation. Finally an association between rs11195419 in the *ADRA2A* gene and suicidal ideation has been reported in men taking nortriptyline.<sup>441</sup>

Genome-wide association studies on antidepressant pharmacogenetics provide preliminary knowledge that needs to be confirmed in future research through new strategies (e.g., using specific pathway scores based on the number of SNPs nominally associated with the outcome and interrelated in an assigned pathway<sup>442</sup>).

## Discussion

All observed gene mutations do not reach the putative 50% of variance explained by genetic factors in antidepressant response.<sup>7</sup> Pharmacogenetics can help discover more candidates: the genomic scans will suggest new candidates to investigate, although results so far have been quite discouraging, probably owing to the inconsistent use of rigorous methodological strategies.<sup>443</sup> Moreover, the risk of false-positive findings is a concern. Sullivan<sup>444</sup> recently demonstrated that the simulation of a classic case-control study investigating a set of 10 SNPs in the *COMT* gene in a sample of 500 patients and 500 controls generated a false-positive rate (the study design was tailored to find spurious associations) as high as 96%. This suggests the need for replication studies before the risk of a false-positive finding is ruled out, and replication of a disease association in 1 or more samples has become a requirement for publication in many high-impact biomedical journals.<sup>444</sup> Overall, as far as the pharmacokinetic variations are concerned, evidence allowed the design and production of genetic chips to predict the reaction, in terms of kinetics, to the exposure to a certain drug. However, pharmacokinetic variations may selectively influence dosing, although, as we recently confirmed, for drugs with a relatively large therapeutic range the impact may be minimal.<sup>49</sup> Moreover, several confounding factors need to be considered in pharmacokinetic studies that may explain previously controversial findings. A single drug is metabolized by specific enzymes, but the result of this product may be an active molecule that can be metabolized by a different enzyme. Moreover, drug interactions may deeply impact the activity of the cytochromes in a way that may be dependent on the genetics, but to an extent that is still difficult to define. Finally, drugs can be metabolized by a set of cytochromes: they should all be investigated in a single test to infer sufficient predictive in-

formation about the drug blood levels. Therefore, further studies considering these confounding factors are required to provide useful and definite results about gene variants involved in pharmacokinetics.

On the other hand, variations in pharmacodynamics may be more relevant in determining different response patterns. However, so far evidence regarding pharmacodynamics is still partial and sparse. The replication rate does not yet allow the design of useful genetic chips able to help clinicians find the correct drug for a specific patient. The most replicated findings are those related to the promoter of *5-HTT*, but this finding was found to be more consistent in white populations, with the L allele of the promoter being associated with a better response to treatment. Interestingly, replication rates in samples other than white populations are very low, and it has been reported that Asian samples are characterized by a significant opposite association between the antidepressant response and the variation within the promoter of *5-HTT* compared with white populations. The reason for this finding is still under investigation, and the clinical impact of the genetic variations found in genes involved in the pharmacodynamics of the antidepressant response is still poor. So far, the knowledge of genetic impact on antidepressant response does not allow the evidence from the literature to be translated into clinical practice. Nevertheless, the increasing evidence of a genetic influence on liability for major depressive disorder and on treatment response (possibly in conjunction with environmental factors that are not well known) suggests that the final target of individualized treatment on the basis of the genetic profile is getting closer.

### Assessment of study designs

As reported in this paper, full replicated findings are still poorly reported in the literature. The development of new experimental designs that combine the methods of linkage analysis, pharmacogenomics and proteomics will help disentangle the path; examples of such sequential approaches have already been published with promising results.<sup>445,446</sup>

Regarding the study designs, there are some points that should be stressed to help define studies with a higher probability of true-positive findings and replication. Case-control studies are better powered to detect small genetic impacts; this format should be used in pharmacogenetic-oriented papers. To design a good case-control study, authors will be required to enrol large samples and check for any stratification factors within the samples. Roughly, these factors could be categorized into sociodemographic data, data relative to the disease characteristics and genetic background.

Basically, patients treated with a certain drug and controls (ideally placebo-treated patients to exclude placebo response, with placebo response in patients with depression estimated to be between 34% and 45%<sup>447</sup>) should be matched for the most relevant sociodemographic variables, including age, sex, marital status, religious beliefs, level of education, employment, stressful life events and number of generations after an immigration event. Moreover, some disease characteristics should be thoroughly investigated, including familiarity, age



at onset, number of events, time spent without symptoms, response to previous treatments, side effect profile, seriousness of symptoms, variation of symptoms during episodes and variation of symptoms in response to environmental events. Consistently, blood drug levels should be obtained from patients, and frequent psychometric assessments should be performed. Finally, the genetic characteristics of participants should be checked in a more extensive way. From the point of the gene, the investigation of a single variation does not seem to be sufficient; a complete tag approach, together with the analysis of relevant variations, should be included in the design. Some free Internet resources may help (Box 1). We reported the quality and sample size across studies included in our review, and we observed that there is a large variation in both, which can be used to evaluate the strength of each gene finding. Moreover, in the future it will likely be mandatory to investigate not a single gene, but the sum of the genes that code for a molecular path. Intuitively, a loss-of-function variation located in a specific gene could be counteracted, in terms of the overall efficacy of the molecular path, by another mutation located in a different gene involved in the same molecular path. For example, 5-HT<sub>2c</sub> is the object of a refined posttranslational control of *HTR2C* mRNA: 5 A-to-G substitutions at positions termed A, B, C, C' and D characterize the editing of the double *HTR2C* mRNA strand and determine a change in the sequence of the second intracellular loop of 5-HT<sub>2c</sub>. Of note, the diverse isoforms have a specific affinity profile and signal transduction efficiency that can be impacted by stress events and antidepressant treatment. The investigation of 5-HT<sub>2c</sub> in an association study would necessitate the investigation of the mRNA editing machinery, otherwise it would be hypothesized that participants with a certain mutation would run higher or lower risks depending on the efficiency of their mRNA editing enzymes. Another interesting point to consider is that GABAergic and glutamatergic interneurons widely mediate the functions of monoaminergic systems: fluctuations in their activity are likely to strongly modulate the impact of a set of variations in a genetic coding for a monoamine receptor or transporter. Consistently, genes that code for enzymes dedicated to neuronal survival or differentiation should be forced in the analysis independently from the molecular path that is under investigation. Finally, to avoid genetic stratification factors that could bias the validity of the results, the study designs

should include some dedicated tools. Some examples include genomic control,<sup>448</sup> structured association,<sup>449</sup> analysis by geographic origin,<sup>450</sup> principal components<sup>451</sup> and family-based association tests (e.g., Family-Based Association Test, transmission disequilibrium test). To our knowledge, there are few investigations that considered all these factors together. As a consequence, most of the published papers appear to be biased toward the items they considered poorly. Moreover, the question of phenotype resurfaces, as genetic variations have been shown to be more strictly associated with clusters of symptoms (e.g., somatic complaints) than with complex phenotypes (e.g., MDD),<sup>187,189,353</sup> which could also be responsible for the inconsistent findings in literature. A more strict control for endophenotypes may then be suggested. A diagnosis of Axis I or Axis II disorders may not be sufficient to detect the influence of a genetic background. The systematic investigation of symptom clusters would probably give more reliable results. In fact, the same genetic variation can be associated with different symptoms. For example, the 5-HTTLPR polymorphism has been associated with different characteristics of mood disorders (i.e., age at onset,<sup>452,453</sup> illness recurrence,<sup>225,454</sup> drug response, reactivity to stressful life events,<sup>455</sup> personality traits)<sup>456</sup> alcoholism,<sup>457</sup> smoking<sup>458</sup> and several psychiatric diagnoses, including psychosomatic disorders,<sup>459</sup> eating disorders,<sup>460,461</sup> suicide,<sup>462</sup> autism<sup>463</sup> and attention-deficit/hyperactivity disorder.<sup>464</sup> Future studies will hopefully clarify whether such phenotypes are all simultaneously present in the same individuals. Genome-wide scans will help discover these mutual influences within the whole genome, although an inductive approach based on evidence and evidence-based theories able to generate lists of genes worth investigating will represent a relevant part of future investigations.

## Conclusion

Further studies should be able to more easily find true-positive associations that, after several replications, could reach a clinical impact of remarkable interest, allowing the design of genetic sets to determine the best treatment for each patient.

**Competing interests:** None declared.

**Contributors:** Drs. Porcelli, Drago, Fabbri, Gibiino, Calati and Serretti designed the review. Drs. Drago, Fabbri, Gibiino and Calati acquired the data. Drs. Porcelli, Drago, Fabbri, Gibiino and Calati wrote the article, which Drs. Porcelli, Drago, Fabbri, Gibiino, Calati and Serretti reviewed. All authors approved publication of the article.

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### Box 1: Free internet resources for investigating complete gene sequence tags

- binCons (<http://zoo.nhgri.nih.gov/binCons/index.cgi>)
- FastSNP ([http://fastsnp.ibms.sinica.edu.tw/pages/input\\_CandidateGeneSearch.jsp](http://fastsnp.ibms.sinica.edu.tw/pages/input_CandidateGeneSearch.jsp))
- F-SNP (<http://compbio.cs.queensu.ca/F-SNP/>)
- LDselect (<http://droog.gs.washington.edu/LdSelect.html>)
- PupasView (<http://pupasuite.bioinfo.cipf.es/>)
- QuickSNP (<http://bioinformoodics.jhmi.edu/quickSNP.pl>)
- SNPselector (<http://snpselector.duhs.duke.edu/hqsnp36.html>)
- Tagger (<http://www.broad.mit.edu/mpg/tagger/>)
- TAMAL (<http://neoref.ils.unc.edu/tamal/>)
- WCLUSTAG (<http://bioinfo.hku.hk/wclustag/>)

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