GENETICS AND ANTIDEPRESSANT: WHERE WE ARE

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Abstract

Nowadays antidepressants are still administrated by a trial and error principle and a substantial proportion of patients does not benefit from treatment or suffers from significant side effects. Clinical features failed to predict the antidepressant response and tolerability, so pharmacogenetic seems to be the most promising way to achieve the target of an individualized therapy. The aim of this paper is to review the current knowledge of findings in pharmacogenetic of antidepressant, and to analyze how they could impact the everyday clinical practice. We mainly focused on pharmacodynamics associated genes where promising results have been found, although still poor replicated to allow clinical applications. On the other hand evidences regarding pharmacokinetics genes, although consistent enough to allow the design of genetic chips, seem to have less relevance to predict antidepressant response. The main results are underlined, new promising polymorphisms are suggested. Finally, the clinical impact of pharmacogenetic studies is debated.

Key Words: pharmacogenetics, antidepressants, gene, SNP, depression

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1 Introduction

Nowadays one of the more promising focus of psychiatric research is pharmacogenetic. The aim of pharmacogenetic is to detect genetic factors that determine variations both in clinical response and in side effects under pharmacotherapy. The hope is to reach a genetic knowledge that allows to chose the best treatment for any single patient a priori, after a genetic analysis. Unfortunately we are still far from this aim and up to this time, medication are still administrated by a trial and error principle, a substantial proportion of patients does not benefit from treatment and most of them may suffer from serious side effects. Furthermore antidepressant response is usually associated with 2 to 4 weeks lag before improvement and this period may be easily associated with risk of clinical worsening, higher risk of premature discontinuation (Masand 2003), and worse hopelessness feelings. In order to identify in advance whether drug is likely to be effective and tolerable several clinical and anamnestic factors have been investigated, unfortunately with discouraging results (Nierenberg, 2003). In contrast pharmacogenetic studies have shown more interesting and promising results (O'Reilly et al. 1994, Perlis 2007, Serretti et al. 1998), and may also be useful to better understand molecular pathways involved in antidepressant mechanism of action and identify possible therapeutic targets (Lorenzi et al. 2004). So far pharmacogenetic studies used two main approaches in order to identify the genetic variants associated with antidepressant response and side effect profile. The first useful approach is the candidate polymorphisms approach, i.e. the association analysis between genetic variants selected a priori on the basis of molecular/biochemistry studies and treatment response/tolerability. Unfortunately the identification of the key variations from millions of polymorphisms detected in the human genome remains difficult to achieve. In the last years, thanks to the technical improvement, another approach was progressively used: the genome-wide association method. This approach consists in a large association analysis between clinical features and variations in the whole genome. Despite the high expectations on this new approach, results were often contradictory and poorly replicated, probably due to the presence of a wide range of stratification factors (Serretti et al. 2008), and to the enormous DNA sequence variability in target sites, metabolizing enzymes and transport proteins of drugs (Roden and George 2002). Moreover the possibility of false positive findings needs to be carefully considered in both approaches (Sullivan 2007) and therefore every result needs to be extensively replicated before becoming useful in clinical practice.

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Despite these limitations pharmacogenetic represent nowadays the most promising way in order to reach in the next years an individualized therapy for psychiatric patients.

At present time, most pharmacogenetic studies investigated genes related to metabolism, genes coding for receptors and transporters and genes related to the second messenger system (Perlis 2007). Concerning pharmacokinetics, the most promising results have been reported for the genetic variations of CYP2D6 and, with less replicated results, for P-glycoprotein. On the other hand, there are several pharmacodynamic genes with interesting and replicated results. Among these the most important are: serotonin transporter (HTT), serotonin 1A receptor (5-HT1A), serotonin 2A receptor (5-HT2A), tryptophan hydroxylase 1 and 2 (TPH1, TPH2), catechol-O-methyltransferase (COMT), monamine oxidase A (MAOA), norepinephrine transporter (NET), Brain-derived neurotrophic factor (BDNF), G-protein β3 subunit, Glycogen synthase kinase-3β (GSKβ), Glucocorticoid receptor-regulating cochaperone (FKBP5), Glucocorticoid receptors, corticotrophin-releasing hormone receptors and angiotensin I and II converting enzyme (ACE). However in the last years several associations have been reported concerning other genes, particularly after the spread of genome-wide association studies. Therefore in this review we aimed to synthesize previous reports in order to underline more replicated and promising results and to suggest some other genetic variants in candidate genes that could be interesting to investigate on the basis of a priori molecular evidence.

1.1 Methods

Data on antidepressant genotype-dependent clinical outcomes published in MEDLINE and EMBASE (March 2010) were searched using word combinations of pharmacokinetics, pharmacodynamics, gene, variation, antidepressant, efficacy, depression, mood disorder, genetic, candidate, cytochrome, Pgp, TPH, COMT, MAOA, HTT, NET, DAT, 5HT1A, 5HT2A, 5HT3A, 5HT3B, 5HT6, ACE, CLOCK, NOSe, IL-1B, BDNF, GSK-3β, Beta1 adrenoceptor, dopamine receptors, Gbeta3, CRHR1, glucorticoid receptor, glutamate receptor (also using extensive gene names). References from retrieved papers were also considered. Candidate gene studies and genome-wide association studies were included if: 1) analyzed the relationship between genetic variants within supported candidate genes and antidepressant clinical outcomes (response/remission/drug-related adverse events), but in principle isolated studies which found positive results for not replicated genes were not included; 2) are written in English. Genome-wide association studies are described in a dedicated paragraph. In the included studies response was defined as Hamilton Rating Scale for Depression rate (HAM-D) 50% reduction, Montgomery-Asberg Depression Rate Scale (MADRS) reduction of 50%, 60% or more, Clinical Global Impression (CGI) 1 or 2 or Quick Inventory of Depressive Symptomatology (Clinician-Rated) (QIDS-C16) 50% reduction, while remission was defined as HARS ≤ 7 or < 11 or QIDS-C16 < 6.

Through the Hapmap database (http://hapmap.ncbi.nlm.nih.gov/) we selected the tag single nucleotide polymorphisms (SNPs) in the Caucasian population for any gene of interest, in order to suggest useful SNPs for further candidate polymorphism studies that aimed to better cover the entire gene in exam.

2. Pharmacokinetics

2.1. Cytochrome P450

The Cytochrome P450 (CYP) superfamily is a class of proteins containing a heme cofactor that localize mainly to the liver. They represent the major enzymes responsible for the oxidation and reduction of numerous organic substrates, both endogenous compound and xenobiotic substances and over 50 isoenzymes are known so far. A comprehensive CYP alleles nomenclature can be found in an internet database at http://www.cypalleles.ki.se. Anyway, the most relevant cytochromes in humans are: CYP1A, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A.

The key role of this class of enzymes in drug metabolism makes the study of DNA polymorphisms within their coding genes a topic of interest in the field of pharmacogenetics. As a matter of fact, genetic variants can influence the metabolic rate of substrates, with increased risk of drug overdose in some subjects (Maier and Zobel 2008).

With regard to pharmacogenetic studies, CYP2D6, CYP2B6 and CYP2C19 are the most investigated as candidate genes. Recently CYP1A2, CYP2C9 (Serretti et al. 2009) and CYP3A4, CYP3A5 (Peters et al. 2008) were not found positively linked to antidepressant treatment, suggesting that these cytochromes genes maybe do not play a major role in antidepressant response. On the other hand Kirchheiner and colleagues reported that combination of polymorphisms pertaining to pharmacokinetic and pharmacodynamic pathways of relevance might contribute to identify response patterns as well as subjects with higher risk of side effects, although pharmacogenetics will be used as a diagnostic tool in clinical practice only if precise and specific treatment options and guidelines based on genetic tests can be provided (Kirchheiner et al. 2004). Therefore, the genotype of an individual subject could inform the choice of a suitable drug or an individually calculated dosage. Thus, the ability to achieve a therapeutic drug level without toxicity could be optimized, purpose that results relevant particularly for tricyclic antidepressant (TCAs).

With regards to CYP2D6 gene, its polymorphisms were associated with the metabolism of most antidepressant drugs (Lin and Lu 1998). So far, more than 100 different alleles were reported at different frequencies in different populations of the word (for information see: http://www.imm.ki.se/cypalleles), with a considerable number of variants which encodes inactive isoforms or with decreased or negligible activity, while other variations consist of gene duplications (Bertilsson et al. 2002). Those gene variants are often associated with different drug metabolism rate. Indeed, individuals can be classified

as poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM) metabolizers, according to their inherited genetic profile (Nebert and Dieter 2002, Thuerauf and Lunkenheimer 2006). Extensive metabolism (EM) of a CYP2D6-substrate drug is characteristic of the most part of population and on a genotype level it is due to the presence of two functional wild type alleles (1 or 2); intermediate metabolism (IM) is characteristic of those with one functional allele; while poor metabolism (PM) typically is an autosomal recessive trait that involves the mutation or deletion of both alleles – 97% of all PM phenotypes can be explained by the presence of four deficient activity CYP2D6 alleles (3, 4, 5, 6) (Sachse et al. 1997) –. UM is thought to be an autosomal dominant trait that arises from functional gene duplication (< 30% of cases) or gene multiplication (Dahl and Sjoqvist 2000), with a direct influence on plasma drug concentration (Sachse et al. 1997). Beside this, it has been demonstrated that the genetic background impacts the rate of enzymatic inhibition in a way that is substance specific (Smith et al. 1998a). With regard to the distribution of different metabolism rate isoforms among ethnic groups, the PM phenotype has been found in the 5–10% of Caucasian population – the low activity 4 allele accounts for >75% of the mutant CYP2D6 alleles in this population (Arneth et al. 2009) –, while it is much rarer in Black Americans and in Orientals. As a matter of fact, PMs prevalence in non white populations has been recently estimated to be as high as 3% (de Leon 2007) and poor metabolizers and ultrarapid metabolizers were assessed at 0.22% and 1.25%, respectively, in a Korean sample (Lee et al. 2006). Nevertheless, the 10 allele causing decreased even if not absent CYP2D6 activity occurs quite frequently in those populations (Fukuda et al. 1999, Kim et al. 2003, Mihara et al. 1999, Someya et al. 1999, Yue et al. 1998). It has been hypothesized that PM phenotype may be associated with an increased risk of depression and anxiety, because 5-methoxy-tryptamine (5-MT), a precursor of serotonin, is considered to be an endogenous substrate of CYP2D6, but it was not confirmed (Bijl et al. 2009).

Pharmacogenetic studies which investigated the influence of CYP2D6 variants on antidepressant outcome actually does not reach univocal results; this may at least partly due to the heterogeneity of studied populations and antidepressants. As a matter of fact, some authors reported positive association with therapeutic effects during SSRI or SNRI treatment (Kawanishi et al. 2004, Rau et al. 2004, Tsai et al. 2010) but the larger part of studies did not found any relationship (Gerstenberg et al. 2003, Gex-Fabry et al. 2008, Murphy et al. 2003, Peters et al. 2008, Serretti et al. 2009, Whyte et al. 2006).

We found analogous results for side effects: some positive results for SSRIs (Suzuki et al. 2006), SNRIs (Rau et al. 2004, Shams et al. 2006) or amitriptyline (Steimer et al. 2005) and association with suicidal risk (Zackrisson et al. 2009), contrasting with the lack of association found by the most part of authors (Gerstenberg et al. 2003, Grasmader et al. 2004, Murata et al. 2010, Peters et al. 2008, Roberts et al. 2004, Stedman et al. 2002, Sugai et al. 2006). Several authors found an association between CYP2D6 variants and antidepressant serum levels (Charlier et al. 2003, Grasmader et al. 2004, Suzuki et al. 2010, Tsai et al. 2010), but without univocal results (Murphy et al. 2003, Ohara et al. 2003).

We have summarized the available results in **table 1**. It is manifest that the best correlation results between PM phenotype and the risk of side effects.

Table 1.

Phenotype	Terapeutic effects	Side effects
PM	---	+++----
UR	+--	+--
IM	+-	--
EM	--	---

+ = one report that finds an association
- = one report that does not find any association

As stated above, the CYP2C19 gene is on another cytochrome gene largely investigated concerning antidepressant response. It is a candidate gene because it is active in the metabolism of several antidepressants, such as escitalopram (Rudberg et al. 2008b), citalopram (Yin et al. 2006), sertraline (Rudberg et al. 2008a), fluoxetine (Liu et al. 2002b) and imipramine (Schenk et al. 2010). The detection of different isoforms of the gene allowed a classification in phenotypes which is reminding to the CYP2D6 one, with a group of subjects labeled as extensive metabolizers (EM) and another one with impaired catalytic capacity, called poor metabolizers (PM) (Smith et al. 1998a, Smith et al. 1998b). With a not clear mechanism, PMs seem to have a lower risk to develop depressive symptoms than homozygous EMs (Sim et al. 2010). CYP2C19*17 (rs12248560), an ultrarapid metabolizer isoform, has recently been added: it has been demonstrated that its presence is associated with a reduced concentration of escitalopram to about its half, while its deletion produces a 5.7 fold increase of escitalopram concentration (Rudberg et al. 2008b). The effect of CYP2C19 genotype on escitalopram plasma level was confirmed in further studies, even if without identical results, probably due to the different allele distribution in the examined populations (Jin et al. 2010, Tsai et al. 2010). Indeed there is a large interethnic variation in the frequency of the different CYP2C19 phenotypes: e.g. the frequency of the CYP2C19 PM phenotype observed in Orientals is about 20%, while in Caucasians it reaches only 2–5% (Smith et al. 1998a, Smith et al. 1998b). It has recently reported that citalopram treatment efficacy and side effects are influenced by CYP2C19 in a Chinese sample (Yin et al. 2006); besides, the side effect profile associated with amitriptyline treatment was partially dependent on the combination of the number of alleles coding for the CYP2D6 and the CYP2C19 (Steimer et al. 2005). On the other side, more recent studies analyzing both therapeutic and side effects during treatment with different ADs did not found any significant correlation (Peters et al. 2008, Serretti et al. 2009).

Finally, concerning the CYP2B6 gene, variation in functional activity has been reported for some polymorphisms: the aminoacidic substituition from Leu

to Phe in position 264 seems to determine lower expression and activity of CYP2B6 (Hofmann et al. 2008) and the common allele 516G>T is associated with lower expression due to aberrant splicing events (David et al. 2007a). In literature data concerning this gene are mainly focused on buproprion metabolism and its clinical effects. Kirchheiner et al. found an influence of CYP2B6 genotype on buproprion total clearance (Kirchheiner et al. 2003), but for clinical effects the available data only pertain to smoke abstinence during bupropion treatment (David et al. 2007b, Kirchheiner et al. 2003, Lee et al. 2007)

2.2 P glycoprotein

P-glycoprotein, a member of the superfamily of ATP-binding cassette (ABC) transporter proteins, is a product of the ABCB1 gene. It is a member of MDR/TAP subfamily, which is an ATP-dependent drug efflux pump for xenobiotic compounds, so it decreased drug accumulation in multi-drug resistant cells and limit uptake of some lipophilic drugs into key organs such as the brain. As a matter of fact, P-glycoprotein is widely expressed in human tissues, including the main organs involved in the catabolism and the elimination of drugs (the biliary canalicular membranes in the liver, the luminal membranes of proximal tubular epithelial cells in the kidney and the apical membranes of the gastrointestinal tract), the testes, the placenta and the luminal membranes of endothelial cells of the blood–brain barrier (Cordon-Cardo et al. 1989). Because of this last localization, which limits the drug intake in the brain, variations in its function may significantly influence the drug treatment response and the side effect profile. Animal studies showed that a wide variety of

Table 2. *P glycoprotein*

More investigated SNP		
SNP	Terapeutic effects	Side effects
G2677 (rs2032582)	++----	--
3435C (rs1045642)	+---	+-
Promising SNPs		
1236T (rs1128503)	(Dong et al., 2009; Kato et al., 2008a)	
rs2032583 and rs2235015	(Uhr et al., 2008)	
rs3842, rs17064, rs10276036, rs2235020, rs2214103	(Dong et al., 2009)	
61A>G	(Gex-Fabry et al., 2008)	
TAG SNPs		
TAG SNPs	DNA position	
rs868755	chr7 87027866 (intron) Band: 7q21.12	
rs1202185	chr7 87051320 (intron) Band: 7q21.12	
rs2235035	chr7 87017022 (Intron boundary) Band: 7q21.12	

+ = one report that finds an association
- = one report that does not find any association

structurally unrelated drugs are efficaciously carried out from the brain thanks to P-glycoprotein activity and among them, a long list of antidepressants (amitriptyline, nortryptyline, citalopram, venlafaxine, sertraline and trimipramine) (Ejsing et al. 2006, Uhr et al. 2003, Uhr et al. 2000, Uhr et al. 2008, Wang et al. 2008), even if there are some exceptions (fluoxetine, bupropion) (Uhr et al. 2003, Wang et al. 2008). Moreover, some antidepressants could influence on P-glycoprotein activity, i.e. nefazodone has been reported to inhibit the P-glycoprotein function (Stormer et al. 2001), while the St John's wort has been found to enhance it (Weber et al. 2006).

So far, several SNPs have been studied for their possible effect on antidepressant treatment outcome. The most studied ones are at positions 2677 (rs2032582) and 3435 (rs1045642), because they have been associated with alteration of Pgp expression and/or function (Eichelbaum et al. 2004). Several authors found positive associations between rs2032582 (Kato et al. 2008a, Nikisch et al. 2008) or rs1045642 (as well as haplotype with rs2032582 and rs1128503) (Kato et al. 2008a) and SSRI response. Sarginson et al. recently replicated result by Uhr and colleagues (Uhr et al. 2008) finding two associations with rs2032583 and rs2235040 in patients treated with paroxetine, whilst not significant results were reached in the sub-sample treated with mirtazapine (which is though not to be a substrate of P-glycoprotein) (Sarginson et al. 2010b).

Nevertheless, other authors failed to find any association between paroxetine response and rs2032582 (G2677) and rs1045642 (3435C) (Gex-Fabry et al. 2008, Mihaljevic Peles et al. 2008); negative findings have been reported also for rs10280101, rs7787082, rs2032583, rs2235040 and duloxetine response (Perlis et al. 2010b). Some authors analyzed both therapeutic and adverse effects finding negative results for rs2032582, rs1045642 and rs1128503 (C1236T) in patients treated with citalopram (Peters et al. 2008) or amitriptyline (rs2032582) (Laika et al. 2006), while Roberts et al. demonstrated a relationship between rs1045642 and nortriptyline-induced postural hypotension (Roberts et al. 2002).

In **table 2** we reported the available results. With regard to the proposed tag SNPs, they have not been studied in the psychiatric field so far.

3. Pharmacodynamics

3.1.Monoamine metabolic enzymes

3.1.1 Tryptophan hydroxylase (TPH)

Tryptophan hydroxylase (TPH) gene has been considered one of the most promising genes concerning the genetic modulation of antidepressant response in the last years. It has been proposed and studied as candidate gene for several reasons: firstly TPH catalyzes the rate-limiting step in serotonin biosynthesis and secondarily animal studies give some evidences of an effect of SSRIs treatment on the mRNA transcription, and consequently on protein levels, of TPH (Kim et al. 2002); moreover a change of TPH1 level during antidepressant treatment was confirmed also in humans (Belzeaux et al. 2010). TPH has two isoforms: TPH1 and TPH2.

TPH1 is ubiquitarious but predominantly expressed in peripheral organs such as the gut, pineal gland, spleen and thymus compare to the brain. In this gene the most investigated variant is the rs1800532, a biallelic SNP on position 218 (TPH1 A218C) located in a potential GATA transcription factor binding site. It has been reported that the rarer A allele was associated with a decreased serotonin synthesis (Jonsson et al. 1997), therefore intuitively it should be associated with worst response to SSRIs. Accordingly to this hypothesis the first studies found an association between this allele and suicidal behavior and worse response to SSRIs (Ham et al. 2007, Serretti et al. 2001b, Serretti et al. 2001c), indirectly confirming monaminergic theory of depression. Unfortunately following studies found controversial results, both for suicidal behavior (Bellivier et al. 2004, Rujescu et al. 2003) and SSRI (Ham et al. 2005, Yoshida et al. 2002b) or various AD (Hong et al. 2006) response, particularly in non Caucasian samples. Moreover also others independent studies failed to find any association between rs1800532 and both response to SSRIs treatment (Illi et al. 2009, Kato et al. 2007, Peters et al. 2004, Serretti et al. 2004c) and side effect profile (Kato et al. 2007). Furthermore negative findings have been reported also concerning SNRIs response and side effects (Higuchi et al. 2009). Nevertheless recently studies found an association between rs1800532 and antidepressant response, concerning both clinical response (Viikki 2010) and side effect profile (Secher et al. 2009) suggesting that the role of this polymorphisms has not been deeply understand and need further investigation, particularly considering also other polymorphisms in the same gene and/or in other correlated genes. The possibility that other TPH polymorphisms – or maybe variant within related genes (Anttila et al. 2007) –, with larger effect size, undercover the effect of rs1800532 need to be considered, therefore further studies should investigate other genetic variants, ideally covering the entire TPH gene. In this view three other TPH1 polymorphisms (-7180T/G, -7065T/C and -5806T/G) seem to be interesting because they have been associated with fluoxetine response (Peters et al. 2004). To data no others TPH polymorphisms have been investigated concerning antidepressant response, nonetheless some positive associations have been reported concerning schizophrenia (Saetre et al. 2010) and suicidal behavior (Liu et al. 2006) suggesting a possible role in antidepressant response as well. Finally with the aim of better covering the entire gene it could be appropriate investigate also known tag SNPs (**table 3**). Among these rs211105 has yet been studied in relation to genetic predisposition to bipolar disorder, with negative result (Lai et al. 2005), whilst rs10488683 has been associated to the diathesis for suicide attempts (Brezo et al. 2009). On the contrary rs685657 has not been studied until now.

On the other side, TPH2 gene (position 12q21.1) seems to be a more promising candidate gene because it was more selectively expressed in brain areas with respect to TPH1 (Sakowski et al. 2006, Zill et al. 2005). Consistently, animal studies showed that mice with mutation in the TPH2 gene showed reduced serotonin

Table 3. *Tryptophan hydroxylase 1 (TPH1)*

More investigated SNP		
SNP	Terapeutic effects	Side effects
rs1800532 (A218C)	+++++----------	+--
Promising SNPs		
-7180T/G	(Peters et al., 2004)	
-7065T/C		
-5806T/G		
rs1799913 (A779C)	(Liu et al., 2006; Saetre et al., 2010)	
Promising TAG SNPs		
TAG SNPs	DNA position	
rs685657	chr 11 18017245 (intron) Band: 11p15.1	
rs211105	chr 11 18011880 (intron) Band: 11p15.1	

+ = one report that finds an association
- = one report that does not find any association

tone in the Central Nervous System (CNS), whilst TPH1 KO mice did not show altered serotonin tone in the brain (Calcagno et al. 2007, Walther et al. 2003, Zhang et al. 2004). Furthermore animal studies on antidepressant (SSRI) response showed an up-regulation of the TPH2 expression (Di Lieto et al. 2007), simultaneously with the antidepressant effect (Shishkina et al. 2007). Nevertheless also conflicting results has been reported, particularly two studies reported that citalopram decreased the TPH2 mRNA expression in the dorsal raphe nucleus of stressed and not stressed animal models (Abumaria et al. 2007, Dygalo et al. 2006). Evidences supporting the role for TPH2 in the antidepressant response derive also from association studies. As a matter of fact TPH2 gene variations have been associated with major depression (Zill et al. 2004), suicidal behavior (Zhou et al. 2005, Zill et al. 2004), attention-deficit hyperactivity and obsessive-compulsive disorders (Mossner et al. 2006b, Sheehan et al. 2005, Walitza et al. 2005). In particular two interestingly functional polymorphisms have been identified for the TPH2 gene: arginine441/proline447 (Zhang et al. 2004) and 1463G/A (Zhang et al. 2005), which resulted in a reduction of serotonin synthesis (about of 55% and 80%, respectively); the last one has been associated with unipolar depression by the same author. Nevertheless, this result was not replicated by further studies (Bicalho et al. 2006, Delorme et al. 2006, Garriock et al. 2005). Moreover De Luca and colleagues did not find any association with both suicide and depressive disorder (De Luca et al. 2006, De Luca et al. 2004). Finally the same polymorphism has been associated with response to fluoxetine treatment by Peters and colleagues (Peters et al. 2004).

Recently others TPH2 polymorphisms have been associated with antidepressant response: rs1843809, rs1386494 and rs1487276 in patients treated with fluoxetine (Peters et al. 2004), rs10897346 and rs1487278 in a sample treated with various ADs (Tzvetkov et al. 2008) and rs2171363 for fluoxetine and citalopram (Tsai et al. 2009b); interestingly Anttila and colleagues reported also an association between rs1386494 and the severity of treatment resistant depression (Anttila et al. 2009). Although these results need to be clearly replicated, overall these data suggested a role for TPH2 gene in antidepressant pharmacogenetics.

In the last years other promising polymorphisms, with a functional effect, have been identify within the TPH2 gene: rs11178997 (Scheuch et al. 2007), rs7305115 and rs4290270 (Lim et al. 2007), rs4448731 and rs4641527 (de Lara et al. 2007), rs4570625 (Gutknecht et al. 2007). Among these, the most relevant seems to be the rs7305115, whose A-allele increases

Table 4. *Tryptophan hydroxylase 2 (TPH2)*

More investigated SNP		
SNP	Terapeutic effects	Side effects
(1463G/A)	++---	
rs1386494	++-	
Promising SNPs		
rs1843809	(Peters et al., 2004)	
rs1487276	(Peters et al., 2004)	
rs10897346	(Tzvetkov et al., 2008)	
rs1487278		
rs2171363	(Tsai et al., 2009b)	
TAG SNPs		
TAG SNPs	DNA position	
rs7955501	chr12 70636293 (intron) Band: 12q21.1	
rs17110477	chr12 70630130 (intron) Band: 12q21.1	
rs10879358	chr12 70702137 (intron) Band: 12q21.1	

and the G-allele decreases the levels of TPH2 mRNA. Furthermore also the rs4570625 appears to be interesting because it is located in the promoter zone of the gene and it has been associated with amygdala reaction to fearful stimuli (higher in T allele carriers) (Brown et al. 2005, Canli et al. 2005, Herrmann et al. 2007). However, a recent report did not found any association between rs4570625 and citalopram treatment in depression secondary to brain injury (Lanctot et al. 2010); nonetheless the LD with rs7305115 could have masked a stronger association with this variant (Lim et al. 2007). Consistently with results from imaging studies, rs4570625 has been associated with cluster B and cluster C personality disorder as well as with emotional instability personality traits (Gutknecht et al. 2007). Considering these data together these last variants seem to be the most promising for further pharmacogenetic studies focused on TPH2 gene.

We have synthesized results in **table 4**, with a section dedicated to tag SNPs. rs7955501 has been studied yet to determine a possible influence on bipolar disorder or suicidal behaviour, but with negative findings (Campos et al. 2010), while it has been demonstrated that rs10748185 affects TPH2 mRNA expression, but it did not appear associated to suicide (Perroud et al. 2010a); finally, to our knowledge there are not any report about rs17110477 and rs10879358.

3.1.2. Catechol-O-methyl transferase (COMT)

COMT is an intracellular enzyme located in the post-synaptic neuron; it is involved in the inactivation of catecholamine neurotransmitters such as dopamine, norepinephrine and epinephrine. The COMT gene is located on human chromosome 22 and it was mapped to 22q11.1-q11.2. The size of the gene is about 27 Kpb and 345 polymorphisms have been identified so far.

The most studied genetic polymorphism is Val108/158Met (rs4680), which implies a valine to methionine amino acid substitution at codon 158 in the membrane

Table 5. *Catechol-O-methyl transferase (COMT)*

More investigated SNP		
SNP	Terapeutic effects	Side effects
rs4680 (Val108/158Met)	++++++++++-	+++
Promising SNPs		
rs165737	(Perlis et al., 2009a)	
rs165774		
rs174696		
rs174697		
rs165599		
TAG SNP		
TAG SNP	DNA position	
rs174674	chr22 18314025 (intron) Band: 22q11.21	
rs2239393	chr22 18330428 (intron) Band: 22q11.21	
rs737866	chr22 18310109 (intron) Band: 22q11.21	

+ = one report that finds a positive association
- = one report that does not find any association

bound form of COMT and in position 108 in the soluble one (Lachman et al. 1996). It has been shown that the Val/Val genotype catabolizes dopamine at up four times the rate of Met/Met homozygote (Weinshilboum et al. 1999), resulting in a significant reduction of synaptic dopamine following neurotransmitter release. Moreover, we have significant evidence of interaction between dopaminergic and serotoninergic systems in CNS: the different activity level of the enzyme may modulate the dopamine bioavailability in the frontal cortex and clinical response to SSRIs (Arias et al. 2006, Mossner et al. 2006a). In animal models of depression decreased availability of extracellular dopamine in the nucleus accumbens was found to be reversible by treatment with serotonergic antidepressants accompanied by improvements in depressive-like behaviour (Dremencov et al. 2004, Zangen et al. 2001). Reciprocally, blockade of dopamine D2/D3 receptors has been reported to acutely reverse the antidepressant effect of SSRIs in animal models of depression as well as in patients suffering from major depression (Willner et al. 2005). Also an imaging study on healthy subjects underline the relevance of serotoninergic and dopaminergic systems on SSRIs effects: SERT binding profile resulted lowered whereas the DAT binding profile was higher during treatment with citalopram, paroxetine and also venlafaxine (Shang et al. 2007), but not with bupropion, that actually not have a direct serotoninergic profile.

The Val108/158Met functional single nucleotide polymorphism has been repeatedly associated with antidepressant response, although negative findings have been reported as well. As a matter of fact several studies showed an effect of this polymorphism on antidepressant response (Arias et al. 2006, Baune et al. 2008a, Benedetti et al. 2009, Szegedi et al. 2005, Tsai et al. 2009a, Yoshida et al. 2008), although with controversial results. Particularly Met/Met genotype has been associated both with better (Baune et al. 2008a, Benedetti et al. 2009, Tsai et al. 2009a, Yoshida et al. 2008) and worse response (Arias et al. 2006, Szegedi et al. 2005) to a variety of antidepressants. On the other hand only one study by Illi and colleagues (Illi et al. 2010b) did not find any association between this variant

Table 6. *Monoamine Oxidase A* (*MAOA)*

More investigated polymorphism		
VNTR	Terapeutic effects	Side effects
1.2 kb upstream the gene coding sequence	+++----	+-
Promising SNPs		
rs1799835 (T941G)	(Tadic et al., 2007)	
rs1465108	(Peters et al., 2004)	
rs6323	(Peters et al., 2004) (Leuchter et al., 2009)	
TAG SNP		
TAG SNP	DNA position	
rs3810709	chrX 43472812 (intron) Band: Xp11.3	
rs6520894	chrX 43411492 (intron) Band: Xp11.3	

+ = one report that finds a positive association
- = one report that does not find any association

and antidepressant (SSRIs) response. Moreover stressful life events seem to not interact with rs4680 to predict treatment outcome (Bukh et al. 2010).

With regard to side effects, the Met/Met homozygote seems to have a higher risk to gain weight during treatment with various antidepressants (SSRI, SNRI, noradrenergic and specific serotoninergic antidepressants and their combination) (Secher et al. 2009). Consistently an effect of this variant on weight gain has been reported also during buproprion treatment for smoking cessation, although only in association with the DRD2 (Dopamine receptor type 2) Taq1 locus polymorphism (Hu et al. 2006). Finally Hilli and colleagues suggested a possible effect of rs4680 on the risk of respiratory distress symptoms in infants with prenatal exposure to SSRIs (Hilli et al. 2009).

Recently Perlis and colleagues investigated other SNPs within the COMT founding an association with citalopram response (Perlis et al. 2009a); although so far not replication studies have been performed, this result supporting the role of COMT gene variants on the antidepressant response.

We have synthesized results in **table 5**, with a section dedicated to tag SNPs suggested for future research. Among these rs2239393 and rs737866 have been yet studied only in oncology (Rakvag et al. 2008) and rs2239393 has been related to Attention Deficit Hyperactivity Disorder (ADHD) susceptibility (Biederman et al. 2008).

3.1.3. Monoamine Oxidase A (MAOA)

Monoamines oxidases (MAO) are a family of enzymes that catalyze the oxidation of monoamines. In the CNS they are localized in neurons and astroglia. The first evidence of an influence of MAOA activity on human behavior derived from the realization that indivuals with a punctual non sense mutation in the MAOA gene (that means the production of a truncated protein without its native function) showed a psychiatric – like syndrome characterized by borderline mental retardation and impulsive aggression, attempted rape and exhibitionism (Brunner et al. 1993).

An interesting VNTR (Variable Number of Copy Repeats) is located 1.2 kb upstream the MAOA coding

sequences: it seems to influence the transcription rate of the gene on the basis of experiments in vitro. As a matter of fact, alleles with 3.5 or 4 copies of the repeat sequence are transcribed 2-10 times more efficiently than those with 3 or 5 copies of the repeat, suggesting an optimal length for the regulatory region (Sabol et al. 1998). Furthermore, Jonsson found that healthy female carriers of at least one copy of the alleles associated with more efficient transcription displayed higher concentrations of 5-HIAA (5-Hydroxyindoleacetic acid, the main metabolite of serotonin in the human body) in cerebrospinal fluid (Jonsson et al. 2000). It seems reasonably that a higher amount of MAOA contributes to higher levels of a resulting metabolite, 5-HIAA. Nevertheless, a more recent study reported that MAOA activity as measured by imaging techniques showed no association with the genotype (Fowler et al. 2007). Pharmacogenetic studies on this polymorphism also reached contrasting results. As a matter of fact several reports did not found any correlation with SSRI (Cusin et al. 2002, Peters et al. 2004, Yoshida et al. 2002b) or moclobemide (Muller et al. 2002), response; nevertheless three recent studies showed an association between the longer MAOA alleles and lower antidepressant response, one in a whole sample treated with mirtazapine (Tzeng et al. 2009) and two only in female patients treated with fluoxetine (Yu et al. 2005) and various ADs (SSRIs, SNRIs, mirtazapine, TCAs, IMAO or AD combinations) (Domschke et al. 2008).

With regard to the relationship between this polymorphism and antidepressant side effects, Yoshida and colleagues found an association between the three repeats allele and lower incidence of nausea in an Asiatic sample treated with fluvoxamine (Yoshida et al. 2003), whilst a recent report failed to find any association with side effects during milnacipram treatment (Higuchi et al. 2009).

Other polymorphisms within this gene were more marginally studied, with some positive but not replicated result. Particularly Peters and colleagues reported an association between rs1465108 and rs6323 and fluoxetine response (Peters et al. 2004) whilst Tadic and colleagues found an association between rs1799835 and mirtazapine response only in the female sample (Tadic et al. 2007). Finally it has been reported an effect of the rs6323 genotype on the placebo response (Leuchter et al. 2009).

We have reported in table 6 an overview of the results. So far there are 61 SNPs validated in human (http://hapmap.ncbi.nlm.nih.gov/). Nonetheless the use of tag SNPs permit to cover easily the most part of the gene, considering e.g. that rs6520894 enables to cover the 34% of the gene variability. To our knowledge the following proposed tag SNPs do not result in any study until now.

3.2. Monoamine transporters

3.2.1. Serotonin transporter (SLC6A4)

The serotonin transporter (SERT or SLC6A4) regulates brain serotonin neurotransmission by transporting the neurotransmitter serotonin from synaptic cleft to presynaptic neurons. Since it was the main site of action of the most part of antidepressant (mainly SSRI, SNRI, TCA), it represents a target of primary interest in the antidepressant pharmacogenetics.

Evidences from animal studies supported a role for SERT also in the genesis of depression symptomatology, particularly it was reported that SERT KO mice showed a behavioral phenotype that is reminding of some of the symptoms of depressive episodes: increased anxiety and inhibited exploratory locomotion, together with a reduction in aggressive behavior and home cage activity (Holmes et al. 2003a, Holmes et al. 2003b).

Without doubt the most investigated variant within the SERT gene is the 5-HTTLPR, located in the promoter zone. In 1996 Helis and colleagues describes for the first time this polymorphism as a 44bp insertion/deletion involving two units in a sequence of sixteen repeated elements. Authors reported that the presence of different allele could affect SERT expression, with the long (L) 5-HTTLPR allele associated with a twice basal SERT expression compared to short (S) allele (Heils et al. 1996). After this interesting finding, 5-HTTLPR polymorphism has been widely studied in the psychiatric field and associated with several psychiatric disorders with affective symptomatology (i.e. bipolar disorder, anxiety disorders, eating disorders, substance abuse) and to pathological behaviors and personality traits related to anxiety, impulsivity and stress (Serretti et al. 2006). In the last years it has been extensively investigated also with regard to antidepressant response. As a matter of fact, several studies in Caucasians showed a positive association between L allele and better response to SSRIs (Arias et al. 2003, Bozina et al. 2008, Durham et al. 2004, Huezo-Diaz et al. 2009, Illi et al. 2010a, Joyce et al. 2003a, Mandelli et al. 2009, Mrazek et al. 2009, Murphy et al. 2004, Pollock et al. 2000, Rausch et al. 2002, Serretti et al. 2004c, Smeraldi et al. 1998, Zanardi et al. 2000, Zanardi et al. 2001) although negative findings have been reported as well in studies using various antidepressants (Baffa et al. 2010, Minov et al. 2001, Wilkie et al. 2009) or SSRIs (Dogan et al. 2008, Hu et al. 2007, Kraft et al. 2007, Maron et al. 2009) or augmentation strategy (Reimherr et al. 2010). More controversial results have been found investigating Asian populations, with studies reporting better outcome associated with both S allele – during SSRI (Kim et al. 2000, Kim et al. 2006, Umene-Nakano et al. 2009, Yoshida et al. 2002a), mirtazapine (Kang et al. 2007a) or milnacipram (Higuchi 2010) treatments –, and L allele – during SSRI (Hong et al. 2006, Kato et al. 2006, Kato et al. 2005, Yu et al. 2002), SSRI or SNRI (Min et al. 2009) or various AD (Lee et al. 2004b) treatments) or no association as well – SSRI (Takahashi et al. 2002, Yoshimura et al. 2009) or milnacipram (Higuchi 2010, Yoshida et al. 2004) treatments –. These conflicting findings between Caucasian and not Caucasian samples may be due to various factors. Firstly, carriage of the L allele is much less frequent for Asian populations compared to Western populations, so further studies with larger samples are needed to clear this possible bias. Secondly, further stratification factors may be of strict genetic nature. Indeed, Hu and colleagues identified a second polymorphism in the L

allele (rs25531A/G): the G variant (L_G) would result in a reduced expression of the gene, equivalent to that conferred by the S allele (Hu et al. 2005). This relevant finding implies a re-examination of all the investigations published before the role of this mutation was detected. Moreover recent findings gave rise to further complications: firstly Lotrich and colleagues finding a significant association between antidepressant response and paroxetine blood concentration only in patients with S allele (Lotrich et al. 2008). Secondarily when the augmentation strategies have been investigated (in particular with pindolol and lithium), the S allele has been associated with a better response (Benedetti et al. 2008, Stamm et al. 2008). Further, recently Dong and colleagues reported an association between three haplotypes and remission during antidepressant response suggesting the relevance of cover the entire gene in order to better underpinning the role of the SERT on the antidepressant response (Dong et al. 2009). Finally, Walderhaug and colleagues showed that females are more sensitive to mood imbalance after tryptophan depletion if they are homozygotes at HTTLPR (Walderhaug et al. 2007). These data underlined that some uncertainties need to be clarified so far, nonetheless a growing body of evidences supporting a role for the HTTLPR polymorphism in the antidepressant response. Consistently in a recent meta-analysis Serretti and Kato showed an association between s/s genotype and worse response of depressive "core" and somatic anxiety symptoms (Serretti et al. 2007b). On the other hand, a more recent large meta-analysis did not replicate this result (Taylor et al. 2010a), although some methodological bias could explain these contradictory results (i.e. Taylor and colleagues did not consider separately Asian and Caucasians).

Nonetheless overall it is clear that the effect of this polymorphism on mood disorders and antidepressant response as well needs to be better elucidated. Some suggestion came from different studies: Ruhe and colleagues showed in a recent imaging study that l_A/l_A carriers may have a more dynamic serotonergic system that seems to confer higher probability to response to SSRIs (Ruhe et al. 2009). Other studies focused on the possible interaction between genetic and environment finding that stressful life events could interact with 5-HTTLPR genotype to determinate antidepressant response (Bukh et al. 2009, Keers et al. 2010, Mandelli et al. 2009), although this topic is still controversial (Coventry et al. 2010). Interestingly a positive association between 5-HTTLPR and post-partum depression has been found as well (Binder et al. 2010a) underlining the relevance of the interaction between genetic and environment on mood disorders.

On the other side HTTLPR has been investigated in relationship with side effects as well. First reports in this field were promising: Smits and colleagues found that the l/l genotype was associated with a lower risk of adverse effects during SSRI treatment (dermatologic reactions, weight change and fatigue above all) (Smits et al. 2007a), consistently with the result achieved by Hu and colleagues, who reported that the low expression allele (S or L_G) was the strongest risk factor associated with adverse effect profile (Hu et al. 2007). This result has been recently replicated by two independent studies (Dombrovski et al. 2010, Reimherr et al. 2010). On the other side one study reported an opposite result (Lanctot et al. 2010). Interestingly Murphy and colleagues showed an interaction between the HTLPR genotype and the antidepressant used on the side effect profile suggesting that the effect of this polymorphism on outcome may depend on the mechanism of antidepressant action (Murphy et al. 2004). Concerning sexual side effects, only one study reported an association between L/L genotype and sexual dysfunction in females taking oral contraceptives during SSRI treatment (Bishop et al. 2009). Nevertheless also negative studies concerning side effect profile are present in literature, both in Caucasians during therapy with various ADs (Secher et al. 2009) and Oriental samples treated with milnacipram (Higuchi et al. 2009), also regarding paroxetine-discontinuation syndrome (Murata et al. 2010). Finally, Oberlander and colleagues investigated the field in one other light, focused on the side effects that may affect children who have been exposed to antidepressants in uterus. They found that the adverse events occurring to new born infants of SSRIs treated mothers shown a mixed association with genotype, being L/L genotype more at risk for respiratory distress, and S/S genotype more at risk for neuromotor symptoms (Oberlander et al. 2008). In a following study they found that maternal SSRIs exposure during pregnancy and maternal anxiety may interact with 5-HTTLPR child genotype to promote the onset of anxiety and depression (s/s) or increased aggression and externalizing behaviors (l/l) during early childhood (Oberlander et al. 2010).

Another polymorphism influencing SERT expression, described as a 17bp VNTR, was identified by Ogilvie and colleagues within intron 2 (STin2). We have some evidences suggesting a possible role of this polymorphism as a risk factor in depressive disorder (Gutierrez et al. 1998, MacKenzie and Quinn 1999, Ogilvie et al. 1996) and suicide behavior (Gaysina et al. 2006, Lopez de Lara et al. 2006), creating a synergistic effect with 5HTTLPR (Hranilovic et al. 2004). Moreover, different authors reported an effect of STin2 on SSRI (Bozina et al. 2008, Kim et al. 2000, Kim et al. 2006, Min et al. 2009, Mrazek et al. 2009, Peters et al. 2004), SNRI (Min et al. 2009), nortriptyline (Kim et al. 2006) or various AD (Wilkie et al. 2009) response, but without unanimous agreement – escitalopram or nortriptyline (Huezo-Diaz et al. 2009); sertraline (Dogan et al. 2008) –. It was suggested that the 10/12 genotype may be associated with a poorer antidepressant effect, especially in Asiatic samples (Smits et al. 2004), but this finding was not replicated by others authors (Hong et al. 2006, Ito et al. 2002). Stin2 10 allele has also been found as associated with the risk of side effects of several AD classes (SSRIs, SNRIs, TCAs, mirtazapine, IMAO) (Popp et al. 2006) but lack of association with side effects was reported as well during SSRI (Smits et al. 2007a) or milnacipram (Higuchi et al. 2009) treatment.

More recently rs25531, a single nucleotide polymorphism located just upstream of the 5HTTLPR, was found to affect the antidepressant response and, consistently, it was shown to modulate the effect of the other 5HTTLPR alleles (Kraft et al. 2005, Smeraldi et al. 2006). It has been recently hypothesized (although still debated) that rs25531 is the same SNP Hu described

Table 7. *Serotonin transporter* (*HTTLPR)*

More investigated polymorphism		
Polymorphism	Terapeutic effects	Side effects
5-HTTLPR	++	+++++++++---
STin2	++++++++----	+--
Promising SNPs		
rs2020933	(Huezo-Diaz et al., 2009)	
7-83-TC: some evidence of association with remission, but probably due to LD with STin2	(Mrazek et al., 2009)	
TAG SNPs		
TAG SNPs	DNA position	
rs140701	chr17 25562658 (Intron boundary) Band: 17q11.2	

in 2005, in the I/D variation of HTTLPR, and that it might play a role in anxiety clusters of symptoms in OCD patients (Wendland et al. 2007, Wendland et al. 2006). More recent studies on 5HTTLPR polymorphism usually take into account also this variant; nevertheless the results are still controversial with both negative (Baffa et al. 2010, Kraft et al. 2007, Maron et al. 2009) and positive findings (Bonvicini et al. 2010, Kraft et al. 2005, Mrazek et al. 2009).

In conclusion, bearing in mind that a number of still unknown alleles within this genetic region may impact the expression of the serotonin transporter, every previous finding will be of poor relevance if this influence will be reported to be as high as for the rs25531, since they have been blinded to significant genetic stratification factors (Rasmussen and Werge 2007). Indeed, the pharmacogenetic field of research is rather young and, as every new born experimental field, it probably requires a relatively long preliminary period of research before well-established results can be find out and transposed into clinical recommendations. Nonetheless encouraging results supporting the research in this field, e.g. Smits and colleagues reported that a genetic oriented pretreatment test, based on HTTLPR, has been associated with a better clinic outcome (Smits et al. 2007b) and Oestergaard and colleagues partially replicated this result finding an association between the clinical outcome and an interaction of some genetic variants, among which the HTTLPR (Oestergaard and Moldrup 2010).

Table 7 provides a synthesis of the results. Rs140701 has been included yet in an antidepressant pharmacogenetic study, but it did not result part of the haplotypes associated with antidepressant response (Dong et al. 2009). This polymorphism has also been associated to panic disorder and social anxiety disorder (Strug et al. 2010).

3.2.2. Norepinephrine transporter (SLC6A2)

The norepinephrine transporter or NET (or noradrenaline transporter, NAT) is a monoamine transporter responsible of the reuptake of the neurotransmitter norepinephrine from the synapse back to the cytosol, from which other transporters (vescicular monoamine transporter, VMAT) sequester NE into vesicles for storage and later release. NET is 617 amino acids in length, contains 12 transmembrane domains and is encoded by the SLC6A2 gene (solute carrier family 6 member 2). It shows a notably share with Dopamine Transporter (DAT) in the amino acid sequence and the reuptake of norepinephrine occurs via a specific Na^+ and Cl^- dependent transport system, which is the target for tricyclic antidepressants such as desipramine and imipramine. Some genetic variants deeply influence the transporter function: A369P (rs5566) variant was reported to be associated with lack of transport activity, while N292T (rs5563) was found to impede surface expression of the transporter. On the other hand, the F528C (rs5558) variation is associated with increased functionality of NET.

Regard to polymorphisms studied in connection to antidepressant response, T allele in rs2242446 (T-182C) was associated to better response to milnacipram, while NET rs5569 (G1287A) A/A genotype showed

Table 8. *Norepinephrine transporter* (*NAT)*

More investigated SNPs		
SNP	Terapeutic effects	Side effects
rs2242446 (T-182C)	++--	-
rs5569 (G1287A)	++--	-
Promising SNPs		
rs36029	(Uher et al., 2009)	
rs1532701		
rs5564	(Dong et al., 2009)	
rs1362621		
TAG SNP		
TAG SNP	DNA position	
rs36016	chr16 54277535 (intron) Band: 16q12.2	
rs187714	chr16 54264000 (intron) Band: 16q12.2	

+ = one report that finds a positive association
- = one report that does not find any association

slower onset of response (Yoshida et al. 2004); the association between T allele in rs2242446 and better response to milnacipram was confirmed in a recent study (Higuchi 2010). Further Kim and colleagues partially replicated the results concerning rs5569 founding a positive association between G/G genotype and better response to nortryptiline, although no effect on SSRIs response has been detected (Kim et al. 2006). Consistently one other study did not find any association between these polyorphisms and SSRIs (fluoxetine, paroxetine or citalopram) or venlafaxine response in an Asiatic sample of depressed patients (Min et al. 2009). Finally, these polymorphisms did not result associated to milnacipram side effects (Higuchi et al. 2009).

Recently other NET polymorphisms have been investigated founding promising results: analyzing the GENDEP sample Uher and colleagues found an association between two SNPs (rs36029 and rs1532701) and nortriptyline response (Uher et al. 2009) while Dong and colleagues reported an association between rs5564 and rs1362621 and remission respectively with desipramine and fluoxetine treatment (Dong et al. 2009). Despite these positive results a recent report did not found any association with seven polymorphisms in the promoter, intronic and exonic region of NET (rs35915, rs28386840, rs168924, rs2242446, rs36017, rs47958, rs171798), although an impact of the rs58532686 genotype on treatment response in a subset of patients with melancholic depression has been found (Baffa et al. 2010), suggesting that these gene may be relevant at least for a particular subgroup of depressed patients.

We have summarized the found results in **table 8**. SLC6A2 gene has 268 SNPs validated in human (http://hapmap.ncbi.nlm.nih.gov/). To our knowledge the proposed tag SNPs have not been studied so far.

3.2.3 Dopamine transporter (DAT)

The dopamine transporter is a membrane-spanning protein that provides the primary mechanism through which dopamine is cleared from the synapses, except in NA-rich areas such as the prefrontal cortex, where

Table 9. *Dopamine transporter* (*DAT)*

Promising polymorphism to data	
VNTR in exon 15	(Kirchheiner et al., 2006; Lavretsky et al., 2008)
TAG SNP	
TAG SNP	DNA position
rs2042449	chr5 1469646 (intron) Band: 5p15.33
rs250681	chr5 1481011 (intron) Band: 5p15.33

+ = one report that finds a positive association
- = one report that does not find any association

norepinephrine transporter seems to play this key role (Carboni et al. 1990, Moron et al. 2002). DAT is thought to be implicated in several dopamine-related disorders, including ADHD (Barr et al. 2001), schizophrenia (Prata et al. 2009) and alcoholism (Heinz et al. 2004).

A 40bp VNTR (Variable Number of Tandem Repeats) polymorphism in exon 15 was reported to affect the DAT expression (Fuke et al. 2001). The 9/10 and 9/9 genotypes seem to be associated with a higher risk of poorer and slower response than the 10/10 genotype in patients treated with different antidepressants (SSRIs, venlafaxine, mirtazapine or TCAs) (Kirchheiner et al. 2006). On the other hand, the 10/10 genotype seems to be associated with an endophenotype of late-life depression that responds preferentially to methylphenidate added to a SSRI (Lavretsky et al. 2008). The results are summarized in **table 9**. In this gene 72 SNPs have been validated in human (http://hapmap.ncbi.nlm.nih.gov/). To our knowledge rs2042449 and rs250681 have not been studied in psychiatry until now.

3.3. Monoamine receptors

3.3.1.5HT1A receptor

The 5-HT1A receptor is encoded by an intronless gene located on human chromosome 5q11.2–q13 and it spans about 1200 bp (http://www.ncbi.nlm.nih.gov/). The expression of the serotonin 1A receptor (5HT1A) is different among the different brain areas and it could be express both pre and post synaptically. In the midbrain dorsal raphe nucleus, at the level of serotonin cell bodies (i.e. as an autoreceptor), 5HT1A receptor stimulation determinate an inhibition of the firing of serotonin neurons and diminishes the release of 5HT in the prefrontal cortex (negative feedback). On the other side, post-synaptic 5HT1A seems to play different roles, so far not completely understand: postmortem brains from depressed suicide victims displayed elevated 5HT1A density in the raphe nuclei (as autoreceptor) but not at postsynaptic sites, which may lead to decreased serotonergic activity (Stockmeier et al. 1998), compared with non depressed individuals.

A role for this gene in the AD response has been postulated because several AD desensitize raphe 5-HT1A autoreceptors, leading to an enhancement of the 5HT neurotransmission that could be associated with the antidepressant effect of these drugs. Moreover there are some evidences that the block of the 5HT1A autoreceptors may accelerate the AD action (Perez et al. 1997).

The most investigated polymorphism within this gene is rs6295 (1019C/G), a single nucleotide polymorphism in the upstream regulatory region. The rs6295 G allele has been associated with an up regulation of the expression of the receptor (Albert and Lemonde 2004, Lemonde et al. 2003). Interestingly Lemonde and colleagues showed an association between this allele and depression and suicide, suggesting a role for this functional effect in mood disorder and in suicidal behavior (Lemonde et al. 2003). Furthermore it was hypothesized that this allele may contrast the therapeutic effect of antidepressant drugs through a higher number of inhibitory 5HT1A autoreceptors. Several studies supported this hypothesis founding an association between this SNP and antidepressant response in patients treated with SSRI (Arias et al. 2005, Villafuerte 2009, Hong et al. 2006, Serretti et al. 2004a), SSRI/SNRI (Kato et al. 2009), fluoxetine or nefazodone with augmentation (Lemonde et al. 2004) or various antidepressant classes (Parsey et al. 2006), some evidences of association exist also for SSRIs in panic disorder (Yevtushenko et al. 2010). Nonetheless contradictory results have been reported

Table 10. *Serotonin receptor 1A (5-HT1A)*

More investigated SNP		
SNP	Terapeutic effects	Side effects
rs6295 (-1019C/G)	+++++++++------	+-
rs1800042 (Gly272Asp)	+----	-
Promising SNPs		
rs1364043	(Kato et al., 2009; Villafuerte et al., 2009)	
rs10042486	(Kato et al., 2009)	

+ = one report that finds a positive association
- = one report that does not find any association

as well for SSRIs (Illi et al. 2009, Levin et al. 2007, Lin et al. 2009, Peters et al. 2004) SNRIs (Lin et al. 2009) and others (Noro et al. 2010). Interestingly Yu and colleagues showed a positive association between rs6295 and fluoxetine response only in females, suggesting an interaction with gender (Yu et al. 2006), whilst Baune and colleagues showed a positive association only in patients with melancholic depression which were treated with a variety of antidepressants, suggesting a role of this SNP only in a subgroup of depressed patients (Baune et al. 2008b). In reverse no interaction has been found between this SNP and stressful life events with the antidepressant response (Bukh et al. 2010).

Suzuki and colleagues showed an association between antidepressant response and another SNP, Gly272Asp (rs1800042). Particularly Asp allele has been reported associated with a better outcome during fluovoxamine treatment (Suzuki et al. 2004). Unfortunately subsequent studies failed to replicate this association with SSRI response (Levin et al. 2007, Yu et al. 2006). With regard to drug related adverse events, neither rs1800042 nor rs6295 seem to be significantly associated to paroxetine discontinuation syndrome (Murata et al. 2010).

Despite these controversial findings, a recent paper by Kato and colleagues showed an association between better response to SSRIs and milnacipram and several others polymorphisms, in particular strong associations have been reported for rs10042486 C/C and rs1364043 T/T (Kato et al. 2009), suggesting that other variants within 5-HT1A gene need to be considered in order to better elucidate the role of this gene on antidepressant response. Finally a recent study by Villafuerte and colleagues underlined the relevance of considering at the same time variants within related genes, reporting an interaction between rs1364043 in 5-HT1A and rs6298 in 5-HT1B on the citalopram response (Villafuerte et al. 2009).

Regarding this point of view, we recently performed a review focused on 5HT1A gene suggesting a number of new SNP for further studies in psychiatry (Drago et al. 2008). In **table 10** we reported a selected set of the most promising SNP concerning antidepressant response based on the literature data.

3.3.2. 5HT2A receptor

An increasing number of studies suggested a role of 5HT2A receptor in Major Depressive Disorder (MDD) (Bhagwagar et al. 2006, Meyer et al. 2001, Yamauchi et al. 2005, Yatham et al. 1999). Consistently, Newton and colleagues showed euphoriant effects for drugs with agonist proprieties on this receptor (Newton et al. 1996). Furthermore it has been hypothesized that the antidepressant effect of both paroxetine and nefazedone is due to a regulation of 5HT2A receptors, at least partially (Hemrick-Luecke et al. 1994, Maj et al. 1996, Meyer et al. 2001), although controversial findings have been reported as well (Akin et al. 2005, Hrdina and Vu 1993). A role for 5HT2A receptor in depression was finally supported by studies on animal models of the disease (Skrebuhhova et al. 1999).

Consistently, Minov and colleagues showed an association between the 5HT2A rs6313 SNP (102T/C) and AD response, even with very non-homogeneous treatments (also ECT, repetitive transcranial magnetic stimulation and AD associations) (Minov et al. 2001). Two following studies found an association between the rs6311 (1438G/A) SNP and SSRI response (Choi et al. 2005, Kato et al. 2006). These two variants are in Linkage Disequilibrium (LD) and they can be considered together (Spurlock et al. 1998), therefore studies by Choi et al. and Kato et al may be considered replications of results from Minov and colleagues. On

Table 11. *Serotonin receptor 2A (5-HT2A)*

More investigated SNP		
SNP	Terapeutic effects	Side effects
rs6311 (-1438A/G)	+++---	+++-
rs6313 (102T/C)	++---	+--
rs6314 (452His/Tyr)	++-	-
rs7997012	++++++---	
rs1928040	+--	
Promising SNPs		
rs17288723, rs2770297	(Horstmann et al., 2010)	
rs9316233, rs2224721	(Uher et al., 2009)	
rs9534505, rs1923884, rs2760351	(Perlis et al., 2009a)	
TAG SNPs		
TAG SNPs	DNA position	
rs643627	chr 13 46326612 (intron) Band: 13q14.2	
rs1928040	chr 13 46345237 (intron) Band: 13q14.2	
rs985934	chr 13 46353726 (intron) Band: 13q14.2	
rs6561333	chr 13 46318313 Band: 13q14.2	
rs2770296	chr 13 46338561 (intron) Band: 13q14.2	

the other side several studies failed to replicate positive results for SSRIs (Cusin et al. 2002, Hong et al. 2006, Illi et al. 2009, Peters et al. 2004, Sato et al. 2002). Recently one study of gene-gene interactions identified a significant 3-locus model among 5-HT2A (rs6311) and two other serotonin-related genes, GNB3 (rs5443) and SLC6A4 (rs25533), which appeared to affect short-term antidepressant response (Lin et al. 2009). This result suggest that the effect of 5-HT2A polymorphisms may be balanced by other variants in related genes, which need to be considered together in order to detect any possible associations. Finally no interaction between this polymorphism and stressful life events in the determination of treatment outcome was found (Bukh et al. 2010). Concerning the side effect profile, associations were reported between rs6311 and the risk of SSRI-induced sexual dysfunction (Bishop et al. 2006) and fluvoxamine-induced gastrointestinal side effects (Suzuki et al. 2006). Nevertheless, other independent studies failed to find any association with nausea and

Table 12. *Serotonin receptor 3A, 3B (5-HT3A, 5-HT3B)*

More investigated SNP		
SNP	Terapeutic effects	Side effects
rs1062613 (178C/T) in HTR3A	+	+---
rs1176744 (129Tyr/Ser) in 5HT3B		+---
Promising polymorphisms to data		
-100 -102 AAG deletion variant in 5HT3B	(Tanaka et al., 2008)	
TAG SNPs		
TAG SNPs	DNA position	
rs11214769 (5HT3B)	chr11 113295878 (intron) Band: 11q23.2	
rs2276308 (5HT3B)	chr11 113309186 (intron) Band: 11q23.2	

sweating induced by milnacipram (Higuchi et al. 2009) and paroxetine-discontinuation syndrome (Murata et al. 2010).

In any case overall data supporting the role of the 5HT2A gene in the AD response, indeed several other variants have been reported to influence the response to SSRIs (Cusin et al. 2002, Kishi et al. 2009b, McMahon et al. 2006, Peters et al. 2009, Peters et al. 2004, Uher et al. 2009), duloxetine (Perlis et al. 2009a), nortriptyline (Uher et al. 2009) or to a variety of antidepressants (Horstmann et al. 2010, Horstmann et al. 2008, Lucae et al. 2010, Wilkie et al. 2009). Among these the most promising were reported in **table 11**. With regard to the proposed tag SNPs, rs643627 and rs6561333 have been associated with suicidal behavior and suicide risk respectively (Brezo et al. 2009, Giegling et al. 2006), supporting a possible role for 5HT2A gene also on suicidal behavior, although another tag SNP (rs2770296) did not show any association with suicide in a sample of schizophrenic patients (Fanous et al. 2009). Moreover rs2770296 was included in a haplotype that seems to influence genetic liability to bipolar disorder (McAuley et al. 2009). Furthermore among these tag SNPs, rs643627 and rs2770296 have been investigated also concerning personality traits, founding respectively negative (Serretti et al. 2007a) and positive (Heck et al. 2009) results. Finally rs6561333 has been studied also in ADHD patients, founding a nominal significant association with cognitive impulsivity (Oades et al. 2008). To our knowledge, rs1928040 and rs985934 have not been studied so far.

3.3.3 5-HT3A, 3B receptors

Among the serotonin receptors, 5-HT3 has been studied in association with AD response as well. To date five subtypes of 5-HT3 genes (HTR3) have been cloned, among these the most studied are 5-HT3A, 5-HT3B and 5-HT3C.

Polymorphisms within these genes have been mainly associated with side effects profile rather than with clinical response. Particularly 5-HT3A rs1062613 (178C/T) and the -100 -102 AAG deletion variant of the 5-HT3B have been associated with vomiting and nausea, both in the course of chemotherapy and paroxetine treatment (Kato et al. 2006, Tanaka et al. 2008, Tremblay et al. 2003). Consistently, 5-HT3B 129Tyr/Ser (rs1176744) polymorphism was found to be associated with nausea induced by paroxetine (Sugai et al. 2006). Nonetheless negative finding concerning gastrointestinal side effects during SSRIs treatment have been found as well both for 5-HT3B rs1176744 (Suzuki et al. 2006, Tanaka et al. 2008) and 5-HT3A rs1062613 and 195C/T (Sugai et al. 2006). Finally no

Table 13. *Serotonin receptor 6 (5HTR6)*

More studied SNP		
SNP	Therapeutic effects	Side effects
TC 267	+---	-
TAG SNP		
TAG SNP	DNA position	
rs10917509	chr1 19864653 (5' UTR) Band: 1p36.13	

+ = one report that finds a positive association
- = one report that does not find any association

association with paroxetine discontinuation syndrome has been found studying rs1062613 in 5-HTR3A and rs35312182 and rs1176744 in 5-HT3B (Murata et al. 2010).

The available results are resumed in **table 12**. To our knowledge the proposed tag SNPs have not been investigated up till now.

3.3.4. 5HT6 receptor

This subtype of receptor is a G protein coupled receptor that stimulates adenylyl cyclase via Gs coupling, together with receptors 5HT4 and 5HT7. The 5HT6 genetic sequence is 14276 bp long, with three exons and two introns, 120 genetic variations are known so far. Results from animal studies suggested an implication of this gene in some behavior trait, such as novelty seeking and instrumental learning (Ballaz et al. 2007, Mitchell et al. 2007). Moreover it has been reported an involvement of this gene in the AD mechanism (Svenningsson et al. 2007, Wesolowska and Nikiforuk 2007), therefore it is an interesting candidate gene for Pharmacogenetic studies. In this field a variant reported within 5HT6 gene by Purohit and colleagues, which is a substitution of a serine in position 267 instead of a lysine, showed a 10-fold higher affinity for serotonin compared to the native receptor and it demonstrated an agonist-independent activity (Purohit et al. 2003). Indeed, it seems to be an ideal candidate polymorphism. Previously Kohen et al founded one other interesting polymorphism: a silent polymorphism consisting of a thymidine to cytosine substitution at position 267 (TC 267, rs1805054) within the first exon of this gene (Kohen et al. 1996). Rs1805054 has been investigated for association with AD response in several studies. Though preliminary negative results (Wu et al. 2001), in a subsequent study C/T genotype carriers showed greater efficacy of the AD treatment (various drugs) (Lee et al. 2005). Nevertheless, this finding has not been replicated by further studies with a variety of antidepressants (Wilkie et al. 2009[or SSRIs (Illi 2009). Finally, the same SNP and a trinucleotide repeat polymorphism (GCC(2/3)] in the 5' upstream region of the gene were found to be not associated with suicidal behavior (Okamura et al. 2005).

In **table 13** we have summarized the found results about this gene, which has been poorly studied so far. To our knowledge, the tag SNP rs10917509 has not been studied up to this time.

3.3.5. Beta1 adrenoreceptor (B1AR) and Alpha2 adrenoreceptor (ADRA2A)

The beta1 adrenergic receptor, also known as ADRB1, is a G-protein associated receptor that through the Gs heterotrimeric G protein stimulates adenylate cyclase, while the alpha 2 adrenoreceptor counts three highly homologous subtypes, alpha 2a, 2b and 2c and it is associated to a Gi protein that causes the inactivation of adenylate cyclase.

B1AR represents an important regulator of the central nervous system mediated behavior and of several neural functions, including mood, memory, neuroendocrine control, stimulation of autonomic function and it is involved in the mediation of AD effects (Crissman et al. 2001). As a matter of fact repeated administration of a number of antidepressant drugs of different classes resulted in the down-regulation of the beta1 adrenergic receptor in CNS (Gould et al. 2003, Ordway et al. 1991) and beta adrenergic antagonists can block the behavioural effects of antidepressant medications, as demonstrated in rat (Mancinelli et al. 1991). Anyway, also the clinical experience suggests that beta adrenoreceptors antagonists can be associated with side effects such as depression and lethargy, although these effects seem to be rare and mild with various beta-blockers (Dimsdale and Newton 1992, Gengo et al. 1987, Greenblatt et al.

1993). B1AR gene is highly polymorphic and the recently identified functional polymorphism G(1165)C (rs1801253), leading to the amino acid variation Gly389Arg, was associated with an enhanced coupling to the stimulatory G(s)protein and increased adenylyl cyclase activation. Zill and colleagues found a relation between rs1801253 CC homozygosity and a better and even faster response to various antidepressant medications (Zill et al. 2003); nevertheless this finding was not confirmed in a following study on the STAR*D sample (treatment with citalopram) (Crowley et al. 2008).

Concerning the alpha 2a adrenoreceptor gene, it seems related to the pretreatment HPA axis hyperactivity and increased adrenocorticotropin in male depressed patients (Haefner et al. 2008). Finally the rs11195419 SNP within this gene was recently associated to suicidality ideation among nortriptyline treated patients (Perroud et al. 2009).

3.3.6. Dopamine receptors

Dopamine system is highly involved in the genesis of depressive symptomatology (Geracitano et al. 2006). Particularly, it has been hypothesized that pathophysiologic process in melancholic depression involves a decreased dopaminergic neurotransmission due to hypersensitive inhibitory 5HT2 hetero receptors located on dopaminergic neurons. Treatment with most antidepressant drugs down regulates these receptors and this event coincides with the emergence of the antidepressant effect; consistently it may explain the time needed for therapeutic effect (Landen and Thase 2006).

Dopamine receptors are divided into D1-like family (D1 and D5), which are coupled to a Gs protein and so activates adenylate cyclase, and D2-like family (D2, D3 and D4), which are coupled to a Gi protein that inhibits adenylate cyclase. Among dopamine receptors subtypes, only the D2-like family was associated to depressive disorder and D2 was the most investigated. Furthermore polymorphisms within this gene have been associated with various field in psychiatry: risk of schizophrenia (Betcheva et al. 2009, Cordeiro et al. 2009, Fan et al. 2010, Golimbet et al. 2009), impulsive self-damaging behaviours and borderline personality traits (Nemoda et al. 2010), working memory deficits (Bertolino et al. 2010, Markett et al. 2010), worse sustained attention (Golimbet et al. 2009), Parkinson's disease (Tinsley et al. 2009) and Post-traumatic stress disorder (Voisey et al. 2009). Nonetheless the main field involving D2 receptor is the antipsychotic action, especially concerning positive symptoms, with a clear key role for this receptor.

Focusing on AD response, we have some line of evidence suggesting a role for D2 receptor as well. As a matter of fact, in vitro experiments showed that antidepressants exposure causes a dose-dependent increase in D2 receptor gene promoter activity (Dziedzicka-Wasylewska and Solich 2004) and animal studies have demonstrated sensitisation of the D2-like dopamine receptors in the mesolimbic system during chronic antidepressant treatment (Maj et al. 1989). Consistently the clinical antidepressant effects of SSRIs are reversed by acute administration of a D2 receptor selective antagonist; so it has been suggested that dopaminergic mesolimbic pathway may represent a final common pathway in antidepressant action (Willner et al. 2005). Concerning pharmacogenetic studies, a functional polymorphism (S311C, rs1801028) within D2 receptor gene has been repeatedly investigated, unfortunately without any positive findings for SSRI response (Serretti et al. 2001a), total sleep deprivation response in bipolar subjects (Benedetti et al. 2003b) and risk of switch in bipolar patients during antidepressant treatment (Serretti et al. 2004b). Nonetheless recently Perlis and colleagues founded an association between one other D2 SNP, rs4245147, and lamotrigine response in a sample of bipolar depressed patients (Perlis et al. 2010a), suggesting a role of this gene also in antidepressant response. Concerning D3 receptor, studies on animal model of depression showed long-lasting changes in rat brain during D3 agonists administration, similar to the effect of antidepressant treatments (Breuer et al. 2009). One of the most studied polymorphism within this gene is a residue change from serine to glycine at position 9 of the N-terminal domain of the receptor. It has been associated with personality trait of persistence (Czermak et al. 2004), with obsessive-compulsive personality traits (Joyce et al. 2003b) and with depression in patients with coexistant obsessive-compulsive personality disorder (Light et al. 2006). Furthermore a recent study by Perlis and colleagues reported an association between three other D3 receptor SNPs (rs167770, rs6280 and rs2134655) and olanzapine/fluoxetine combination response in a sample of Bipolar I depressed patients. The same Authors reported also a marginal association between a SNP in D4 receptor gene (rs936461) and lamotrigine response (Perlis et al. 2010a). Among the D2-like family receptors, overall the D4 receptor gene is the less investigated concerning psychiatric field. Nonetheless it seems to be a promising candidate gene, particularly considering that it has high homology to both DRD2 and DRD3 genes. Moreover DRD4 is expressed in limbic areas involved in cognition and emotion and mutations in this gene have been associated with various behavioral phenotypes, including autonomic nervous system dysfunction, attention deficit/hyperactivity disorder, and the personality trait of novelty seeking. The most investigated polymorphism within this gene is a VNTR polymorphism in exon 3: it was associated to novelty seeking trait (Benjamin et al. 1996; Ebstein et al. 1996), even if there are some conflicting findings (Gelernter et al. 1997, Malhotra and Goldman 2000). Furthermore some reports investigated this variant in relationship with SSRI (Serretti et al. 2001a) and sleep deprivation (Serretti et al. 1999) response but with negative results. Nonetheless one study by Garriock and colleagues showed a significant modulation effect on various antidepressant medications (Garriock et al. 2006), suggesting a possible role also for this gene on the antidepressant response. Clearly further studies are required in order to elucidate this possible role.

Table 14 gives an overview of the results, including some tag SNPs for future research. DRD2 and DRD3 genes have respectively 80 and 152 validated SNPs in human (http://hapmap.ncbi.nlm.nih.gov/). To our knowledge the proposed tag SNPs do not resulted studied up till now.

Table 14. *Dopamine receptors 2, 3, 4 (DRD2, DRD3, DRD4)*

More investigated polymorphisms		
Polymorphism	Terapeutic effects	Side effects
rs1801028 (S311C) in DRD2 gene	---	
VNTR in exon 3 of DRD4 gene	+--	
Promising SNPs		
rs4245147 in DRD2	Association with olanzapine/fluoxetine or lamotrigine response in bipolar I depressed patients (Perlis et al., 2010a)	
rs6280 in DRD3		
rs2134655 in DRD3		
rs167770 in DRD3		
rs936461 in DRD4		
TAG SNP		
TAG SNP	DNA position	
rs2734838 (DRD2)	chr11 112791711 (intron) Band: 11q23.1	
rs2245805 (DRD2)	chr11 112795909 (intron) Band: 11q23.1	
rs4245147 (DRD2)	chr11 112823217 (intron) Band: 11q23.2	
rs324026 (DRD3)	chr3 115373732 (intron) Band: 3q13.31	
rs226082 (DRD3)	chr3 115363703 (intron) Band: 3q13.31	

+ = one report that gives a positive association
- = one report that does not find any association

3.4. Intracellular signal transduction pathways

3.4.1. G protein Beta 3 Subunit (GNB3)

Heterotrimeric guanine nucleotide-binding proteins (G proteins) are composed of an alpha, a beta and a gamma subunit, which are encoded by families of related genes. They have a fundamental function in the transduction of signals between receptors and effectors (Wess 1998). Because of the great complexity generated by G proteins in the signal transduction cascade and their large diffusion as transduction proteins, it has been suggested they may contribute to mechanism by which neurons acquire the flexibility for generating the wide range of responses observed in the nervous system (Chen et al. 1999). Furthermore a

Table 15. *G protein Beta 3 Subunit (GNB3)*

More investigated SNP		
SNP	Terapeutic effects	Side effects
rs5443 (C825T)	++++++----	
TAG SNP		
TAG SNP	DNA position	
rs5446	chr12 6826723 (3'UTR) Band: 12p13.31	

+ = one report that gives a positive association
- = one report that does not find any association

possible involvement in the pharmacogenetic of antidepressant response has been suggested as well.

In this field the most investigated polymorphism within GNB3 gene is rs5443 (C825T) that is associated with the occurrence of a splice variant which appears to have an altered activity. The T allele mutation is responsible of the production of a splice variant called G beta 3s that seems to be less active than the wild form in terms of modulation of ion channels and formation of heterodymers with other proteins (Ruiz-Velasco and Ikeda 2003). Several independent studies founded that the T variant predict better response to different antidepressants (Joyce et al. 2003a, Lee et al. 2004a, Serretti et al. 2003b, Wilkie et al. 2007, Zill et al. 2000), although both opposite (Lin et al. 2009) and negative results (Hong et al. 2006, Kang et al. 2007b, Kato et al. 2008b) have been reported as well.

In **table 15** we have summarized the found results about this gene. We found 55 validated SNP in human by searching in Hapmap (http://hapmap.ncbi.nlm.nih.gov/). To our knowledge, rs5446 has not been studied yet in psychiatry.

3.5. HPA axis and stress hormone system

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction is one of the major neuroendocrine abnormalities found in major depression, since it regards up to 70% of depressed patients (Holsboer, 2000). The HPA axis hyperactivity is thought to be tightly linked to the pathogenesis, treatment and course of this disorder (Nemeroff 1996, Nemeroff and Owens, 2002). The principal neuro-endocrine regulator of the HPA axis is the corticotropin releasing hormone (CRH), a 41-amino acid peptide derived from a 191-amino acid preprohormone that is secreted by the paraventricular nucleus (PVN) of the hypothalamus in response to stress. It plays an important role in coordinating the endocrine, autonomic, immune and behavioral responses to stress. Several studies reported that the concentrations of CRH in the cerebrospinal fluid (CSF) are elevated in depressed patients (Liu et al. 2002a, Nemeroff et al. 1984). Furthermore both imaging studies, animal models and human studies confirmed the key role of CHR in depression (Brady et al. 1992, Gold and Chrousos 2002, Michelson et al. 1997, Nemeroff et al. 1988, Raadsheer et al. 1994). Consistently most antidepressant treatment seems to attenuate or normalize HPA axis activity (De Bellis et al. 1993, Ising et al. 2007, Ising et al. 2005, Schule et al. 2009).

3.5.1 CRH receptors (CRHR1 and CRHR2)

In the CNS we found two fundamental subtypes of CRH receptors: CRHR1 (corticotrophin releasing hormone receptor 1) and CRHR2 (corticotrophin releasing hormone receptor 2). Some findings suggest that the CRHR1 gene may play an important role as an intermediary of CRH effects on the anterior pituitary gland (Van Pett et al. 2000) and CRHR1 antagonists have repeatedly demonstrated antidepressant effect in experimental animals and humans (Kehne 2007, Overstreet and Griebel 2004, Seymour et al. 2003), even if this finding was not constantly replicated (Binneman et al. 2008). Furthermore this gene has been associated also to the depression susceptibility (Liu et al. 2006).

Concerning our main focus, we have some line of evidence of its involvement in the antidepressant response. As matter of fact, several polymorphisms within CRHR1 gene were found related to treatment response, particularly the rs242941 G/G genotype and one haplotype including two other SNPs beyond rs242941 (rs1876828 and rs242939) were found related to fluoxetine response (Licinio et al. 2004, Liu et al. 2007). Interestingly in both these two studies the association was more pronounced in patients with

Table 16. *Corticotropin releasing hormone (CRH) receptors*

More investigated SNPs		
SNP	Terapeutic effects	Side effects
rs242941	++-	
Promising SNPs		
rs2270007	(Papiol et al., 2007)	
rs10473984, rs10055255, rs10474485 in CRHBP gene	(Binder et al., 2010b)	
rs12942300 in CRHR1 gene		
rs2267716 in CRHR2 gene		
rs6472258 in CRH gene		
rs7307997 in AVPR1A gene		
TAG SNP		
TAG SNP	DNA position	
rs17689882 (CRHR1)	chr17 41262609 (intron) Band: 17q21.31	
rs242924 (CRHR1)	chr17 41241147 (intron) Band: 17q21.31	
rs2267710 (CRHR2)	chr7 30662715 (intron) Band: 7p15.1	

+ = one report that gives a positive association
- = one report that does not find any association

anxious depression. On the other hand Papiol and colleagues failed to find any association between CRHR1 variants and citalopram response, although the Authors showed a relation between rs110402 and the risk to develop a seasonality pattern of depression and an early onset of the disease. Moreover an association between CRHR2 gene rs2270007 and citalopram response has been reported in the same study (Papiol et al. 2007). Finally, a recent paper by Binder and colleagues investigated genetic variants within genes regulating the CRH system in order to better dissect the role of this system in antidepressant response. Interestingly, beyond confirming previously results on CHRH1 and CHRH2 genes variants, Authors found an association between rs10473984 variant within CRH-binding protein gene (that encode for a plasma protein involved in the inactivation of CRH) and citalopram response, finding also a correlation with serum levels of corticotrophin concentration independently from the mood status (Binder et al. 2010b). Overall these data support the role of CRH system on the antidepressant response, although further studies are required in order to better dissect the different influence of the various genes involved in this complex system.

Table 17. *Glucocorticoid receptor* (*GR)*

More investigated SNPs		
SNP	Terapeutic effects	Side effects
rs1360780 (FKBP5)	++++++----	+ (suicide)
rs3800373 (FKBP5)	++	+ (suicide)
Promising polymorphism to data		
rs4713916 (FKBP5)	(Binder et al., 2004); (Lekman et al., 2008)	
ER22/23EK (NR3C1)	(van Rossum et al., 2006)	
BclI (NR3C1)	(Brouwer et al., 2006)	
rs852977 (NR3C1)	(Uher et al., 2009)	
rs10482633 (NR3C1)		
rs10052957(NR3C1)		
TAG SNPs		
TAG SNP	DNA position	
rs2395634 (FKBP5)	chr6 35675738 (intron) Band: 6p21.31	
rs258750 (NR3C1)	chr5 142642082 (intron) Band: 5q31.3	
rs11745958 (NR3C1)	chr5 142696550 (intron) Band: 5q31.3	

+ = one report that gives a positive association
- = one report that does not find any association

In **table 16** we give an overview of the results. With regard to the following tag SNPs, the study of rs17689882 in CRHR1 allows the covering of 23% of the variability of the gene. Rs242924 has been associated by some authors to the risk to develop adult depression following childhood maltreatment (Bradley et al. 2008, Polanczyk et al. 2009) and to the cortisol response to the DEX/CRH test in maltreated child (Tyrka et al. 2009).

3.5.2 Glucocorticoid receptor (GR)

The glucocorticoid receptor, also known as NR3C1 (nuclear receptor subfamily 3, group C, member 1) is expressed in almost every cell in the body and regulates the transcription rate of genes controlling the development, metabolism and immune response through the binding with specific chromatin sequences. In the absence of hormone, the glucocorticoid receptor resides in the cytosol where it is complexed with a variety of proteins including the heat shock protein 90 (hsp90), the heat shock protein 70 (hsp70) and the protein FKBP5 (FK506-binding protein 52) (Pratt et al. 2006). FKBP5 is a co-chaperone of hsp90 which regulates glucocorticoid receptor (GR) sensitivity. When it is bound to the receptor complex, cortisol binds with lower affinity and nuclear translocation of the receptor is less efficient. Consistently, it has been

suggested that polymorphisms in the FKBP5 gene may result in a deregulation of stress response duration, so this gene may be involved in the pathogenesis of psychiatric diseases (Binder 2009). Furthermore, both NR3C1 and FKBP5 genes have been associated to antidepressant response. Particularly Binder and colleagues showed several associations between variants within the FKBP5 gene (rs1360780, rs3800373 and rs4713916) and antidepressant response (SSRIs, TCAs and mirtazapine), although only the result concerning rs1360780 was confirmed in both the two independent sample in exam (Binder et al. 2004). The association between these polymorphisms and antidepressant response was replicated for citalopram in the STAR*D (Lekman et al. 2008) and for various ADs (particularly venlafaxine and combinations) (Kirchheiner et al. 2008). A recent work showed an interaction between FKBP5 rs1360780 and GRIK4 rs12800734 in a SNP predictive model for depression remission (Horstmann et al. 2010). On the other side, these results were not confirmed by other studies using SSRIs (Papiol et al. 2007, Perlis et al. 2009a, Sarginson et al. 2010b, Tsai et al. 2007, Uher et al. 2009). Moreover Zobel and colleagues failed to find any association between several polymorphisms (rs3800373, rs4713916, rs1334894, rs1360780 and rs755658) and citalopram response, but interestingly they showed an association between the same SNPs and unipolar depression (Zobel et al. 2010) suggesting a role of this gene in the pathogenesis of the disorder. Finally Brent and colleagues reported that FKBP5 rs1360780TT and rs3800373GG genotypes were associated with suicidal events in a sample of adolescent subjects treated with SSRIs or venlafaxine (Brent et al. 2010); although interesting, this result clearly need replication studies in order to be confirmed.

Concerning NR3C1 gene, we have a fewer number of studies in pharmacogenetic field. Particularly, the functional polymorphism ER22/23EK was related to faster clinical response to SSRIs, TCAs and mirtazapine, without any significant finding in functional HPA axis measures (van Rossum et al. 2006), while another report found that carriers of the BcII polymorphism had higher baseline ATCH values and showed a trend towards lower decrease of Hamilton Rating Scale for Depression rates than non-carriers during treatment with paroxetine (Brouwer et al. 2006). Finally, Uher and colleagues identified three markers (rs852977, rs10482633, rs10052957) associated with response in the GENDEP sample (drugs: escitalopram or nortriptyline), although none survived after correction for hypothesis-wide effective number of comparisons (Uher et al. 2009).

We have summarized the results in **table 17**. We detected 298 validated SNPs in FKBP5 gene and 39 in NR3C1 one (http://hapmap.ncbi.nlm.nih.gov/) and selected the beneath tag SNPs. The study of rs258750 and rs11745958 variants in the NR3C1 gene covers respectively the 28% and the 23% of the variability of the gene.

3.5.3 c-AMP response-element binding (CREB)

C-AMP response-element binding (CREB) is a protein that acts as a transcriptional factor. It binds to specific DNA sequences called c-AMP response elements (CRE) and regulates gene expression. CREB was first described in 1987 as a regulator of the transcription of somatostatin gene (Montminy and Bilezikjian 1987, Vallejo et al. 1992). Other genes whose transcription is regulated by CREB include BDNF and many neuropeptides, such as vascular endothelial growth factor (VEGF) and corticotropin releasing hormone. Recent findings have shown that CREB is essential even if not sufficient for the activation of CHR transcription (Liu et al. 2008), suggesting the requirement of a co-activator, that may be represent by TORC, the transducer of regulated CREB activity (Liu et al. 2010).

Several studies on animal models suggest an involvement of CREB in antidepressant action (Boer et al. 2010, Kuipers et al. 2006, Tardito et al. 2006, Thome et al. 2000), even if we have not univocal results about antidepressant effect on CREB activity. A possible explanation of these controversial results is that the effect on CREB activity may be both drug and brain area dependent, with a complexity not well understand until now. In spite of the suggest involvement of this gene in antidepressant action, CREB polymorphisms were still poorly investigated in the field of pharmacogenetic of antidepressant response. Particularly Dong and colleagues failed to find any association between several CREB SNPs and fluoxetine or desipramine response [confirming previous result by Wilkie et al. (Wilkie et al. 2007)], although they showed a significant association between one SNP (rs3730276) and MDD (Dong et al. 2009). Finally, Perlis and colleagues suggested a role of genetic variants within CREB gene on treatment-emergent suicidal ideation during citalopram treatment. Interestingly they found significant associations only in men, suggesting a significant gene x sex interaction (Perlis et al. 2007).

3.6 ACE substance P-system

3.6.1. Angiotensin converting enzyme (ACE)

The angiotensin converting enzyme is an exopeptidase produced especially by pulmonary endothelial cells and involved the renin-angiotensin system (RAS) cascade. ACE is also expressed in the CNS, where it have a relevant role in the degradation of some neuropeptides such as opioid peptides and substance P (SP) (Igic and Behnia 2003). SP antagonists seem to have antidepressant effect and SP level is diminished after monoamine uptake inhibitors administration, so SP may play a role in depressive biological mechanisms and treatment (Kramer et al. 1998, Nutt 1998, Shirayama et al. 1996). A deletion variant in the ACE I gene was found associated with higher ACE plasma levels (Rigat et al. 1990), higher substance P levels (Arinami et al. 1996) and a faster response to different antidepressant treatments (Baghai et al. 2001), including total sleep deprivation (Baghai et al. 2003), particularly among female patients (Baghai et al. 2004). This association was confirmed in another report (Bondy et al. 2005), although another study using selectively venlafaxine or fluoxetine did not replicate it (Hong et al. 2002). Further another study by

Table 18. *Angiotensin converting enzyme (ACE)*

More investigated polymorphisms		
polymorphism	Terapeutic effects	Side effects
Insertion/Deletion 287bp DNA fragment in ACE I gene	+++++--	
Promising SNPs		
rs4295	(Mendlewicz et al., 2005)	
rs4309		
A1166C in AT1	(Bondy et al., 2005)	
TAG SNP		
TAG SNP	DNA position	
rs4343 (ACE I) complete LD with I/D pol.	chr17 58919763 (exon) Band: 17q23.3	

+ = one report that gives a positive association
- = one report that does not find any association

Mendlewicz and colleagues, investigating six variant within the gene (including I/D polymorphism), supporting the role of ACE I variants on antidepressant response (Mendlewicz et al. 2005). Recently another polymorphism within the gene (rs4291 A/T) was studied to detect the possible influence of stressful-life events on the genetic factor modulation of treatment outcome in a natural setting, but with negative results (Bukh et al. 2010). Finally A1166C variant in the angiotensin II receptor gene (AT1), another component of RAS, was associated with antidepressant treatment, with an evidence of better outcome in C/C carriers (Bondy et al. 2005). Also in this study a variety of different antidepressants were used.

Table 18 gives a summary of the results. The ACE I gene has 83 validated SNPs in human (http://hapmap.ncbi.nlm.nih.gov/). rs4343 is cited in several works: it seems to influence significantly the enzyme activity and so the response to ACE-inhibitors (Chung et al. 2010), it has also been associated to Alzheimer Disease (Helbecque et al. 2009, Kehoe et al. 2004, Meng et al. 2006, Thornton-Wells et al. 2008).

3.7. Endogenous CLOCK system

3.7.1 Circadian Locomotor Output Cycles Kaput (CLOCK)

A wide range of physiological functions shows a circadian rhythm. This rhythm is regulated by a tiny brain region of the hypothalamic suprachiasmatic nucleus (SCN) that expresses several CLOCK genes in a rhythmic fashion. SCN are regulated by positive and negative feedback loops, through transcriptional and posttranslational mechanisms (Reppert and Weaver 2002). In particular, two clock-gene products, CLOCK (circadian locomoter output cycles kaput protein) and ARNTL (aryl hydrocarbon receptor nuclear translocatorlike), seem acting as transcription factors for other clock genes, including period (Per) genes, by binding to Ebox enhancers in their promoter regions; in turn, (Per) genes can regulate the expression of other clock gene transcription factors. Moreover, they can act as transcription factors also for not circadian genes (clock-controlled genes or CCGs) and among the candidate CCGs we find the noradrenaline and dopamine transporters, the tyrosine hydroxylase and some dopamine receptors (Manev and Uz 2006). This model is probably more complex, indeed psychoactive drugs can influence a number of promoter regions near the Ebox in the promoter sequence, e.g. CREB (cAMP response element) and AP1 (activating protein 1).

Evidences from animal studies suggest that CLOCK gene may play a relevant role in the antidepressant action: as a matter of fact repeated doses of fluoxetine or cocaine influenced CLOCK gene expression in mice, together with enhanced serotonin N-acetyltransferase (Uz et al. 2005). Concerning human, it has been suggested that the “eveningness” or

"morningness" is genetically defined and this trait may influence the course of depression and the prognosis. Particularly, in healthy subjects the C allele of the CLOCK 3' flanking region polymorphism 3111T/C was coupled with significantly higher "eveningness", i.e. the preference of evening for activity (Katzenberg et al. 1998). In mood disorders the same C variant was associated with higher recurrence rates in bipolar patients (Benedetti et al. 2003a), increased lifetime sleep disturbances (Serretti et al. 2003a) and persistence of insomnia during fluvoxamine or paroxetine treatment (Serretti et al. 2005), whilst no effect of this polymorphism on sleep disturbances was demonstrated in untreated depressed patients (Serretti et al. 2010). More recently a significant association between rs3736544 (T allele) and fluvoxamine response and between rs3749474 (C allele) and remission has been reported (Kishi et al. 2009a).

To our knowledge the tag SNPs proposed in **table 19** have not been studied until now.

3.8. Other relevant genes

3.8.1. Nitric Oxide Synthase (NOS)

Nitric Oxide Synthase (NOS) is the enzyme responsible for the synthesis of nitric oxide from arginine in the presence of NADPH and dioxygen (O_2). Three different isoforms of the NO Synthase (NOS) enzyme are known so far: neuronal (NOS1), endothelial, and inducible NOS.

The NOS1 gene was mapped to chromosome 12q24.2q24.31 (Kishimoto et al. 1992, Xu et al. 1993) and 748 genetic variations of its coding sequence are known so far. Recently, some line of evidence suggested that the NOS gene might be involved in the mechanism that underlies the therapeutic efficacy of antidepressants (Paul 2001, Suzuki et al. 2003, Wegener et al. 2003). Consistently animal studies suggested a modulation of serotonergic system through NOS with relevant effects on behavior: more in details, NOS knockout mice exhibits an excessive aggressiveness and impulsiveness that seems to be caused by selective decrements in serotonin turnover and deficient 5HT1A and 5HT1B receptor function in brain regions regulating emotion (Chiavegatto et al. 2001). Although these findings make NOS an interesting candidate gene, it has been poorly investigated in the field of Pharmacogenetics up to this time and preliminary evidence did not support a relevant role of this gene. Indeed, Yu et al. failed to find any association between NOS1 rs2682826 SNP and fluoxetine response or risk of developing a depressive episode (Yu et al. 2003); more recently, analogous results were found in a Japanese sample treated with fluvoxamine (Okumura et al. 2010).

3.8.2. Interleukin 1 Beta (IL1 beta)

Growing evidence suggests that pro-inflammatory cytokines play a major role in the complex pathophysiology of major depressive disorder (Capuron and Dantzer 2003, Irwin and Miller 2007, Raison et al. 2006) and administration of proinflammatory cytokines can induce sickness behaviour in animals (Kent et al. 1992) and humans (Capuron and Ravaud 1999, McDonald et al. 1987, Rosenstein et al. 1999). In depressed individuals reductions in measures of cellular immune competence as well as elevated levels of systemic inflammation markers has been demonstrated (Dentino et al. 1999, Herbert and Cohen 1993, Kiecolt-Glaser and Glaser 2002, Zorrilla et al. 2001). Moreover a number of authors suggested an association between IL1 levels and mood disorders (Anisman et al. 2002, Anisman et al. 1999, Licinio and Wong 1999, Maes et al. 1993), although some negative reports was reported as well (Yang et al. 2007).

Inflammatory cytokines have been shown to access the brain, so they can virtually interact with every pathophysiologic domain known to be involved in depression, including neurotransmitter metabolism, neuroendocrine function and neural plasticity (Miller et al. 2009). As a matter of fact, several lines of evidence suggest strong influences in both the directions: from cytokines to neurotransmitters and from neurotransmitters to cytokines. For example, it has been found that IL1 activates brain serotonergic (Gemma et al. 1997, Linthorst et al. 1994, Shintani et al. 1993) and noradrenergic (Dunn 1988, Kabiersch et al. 1988) systems, reduces acetylcholine release in the hippocampus (Rada et al. 1991) and enhance GABA effects (Li et al. 1993, Miller et al. 1991, Zeise et al. 1992). On the other side, it has been reported that serotonin increases IL1β mRNA in the hypothalamus (Gemma et al. 2003), while noradrenaline enhances and ACh inhibits the release of IL1β from neurons in hypothalamic explants (Tringali et al. 1996).

Concerning pharmacogenetics , we have the first evidences of an influence of IL1 beta gene on antidepressant response. Indeed, homozygosity for the T allele at rs16944 (511C/T in the promoter of the gene) was found to be associated with a trend of less severity of depressive symptoms and more favorable fluoxetine response (Yu et al. 2003). This result was partially replicated by Baune and colleagues (Baune et al. 2010). Moreover they showed also an association between one other SNP (rs1143643) and response to antidepressant treatment (different antidepressants, also combinations), whilst no association has been founded concerning rs1143634. Interestingly in the same paper Authors investigated also a subgroup of patients with fMRI founding an association between the number of G-alleles in both rs16944 and rs1143643 and reduced responsiveness of the amygdala and anterior cingulated cortex to emotional stimulation. The significant role of rs16944 was confirmed also by Tadic and colleagues concerning paroxetine response; they also examined a variable number of tandem repeats (VNTR) in interleukin-1 receptor antagonist (IL-1Ra), but with negative result (Tadic et al. 2008). Finally, a recent genome-wide association study on GENDEP sample found another SNP in the interleukin 1 Beta gene (rs1126757) as the best predictor of escitalopram response (Uher et al. 2010).

Available results are summarized in **table 20**, together with promising tag SNPs.

Interestingly, cytokines (IL1β included) seem to influence the regulation of the μ-opiod receptor (OPRM1) gene expression in humans. Particularly, it has been reported that IL1, IL4, IL6 and tumor necrosis

Table 19. *Circadian Locomotor Output Cycles Kaput* (*CLOCK)*

Promising SNPs	
3111T/C	(Serretti et al., 2005; Serretti et al., 2004d)
rs3736544	(Kishi et al., 2009a)
rs3749474	
TAG SNP	
TAG SNP	DNA position
rs13132420	chr4 56087570 (intron) Band: 4q12
rs6811520	chr4 56009935 (intron) Band: 4q12

factor induce the up-regulation of μ-opioid receptor gene expression in neuronal and immune effector cells, whilst its down-regulation is stimulated by interferon-gamma and granulocyte/macrophage colony-stimulating factor (Kraus 2009). Furthermore evidences from animal models suggested that μ-opioid receptor gene is involved in the antidepressant mechanism of action (Chen and Lawrence 2004, Giaroni et al. 2008), finding then confirmed in humans. Indeed, women with major depressive disorder who did not respond to fluoxetine showed lower binding potential for the μ-opioid receptor when compared with depressed women who responded to medication (Kennedy et al. 2006). Recently, the role of μ-opioid receptor gene as a candidate gene for pharmacogenetic studies was supported by the finding of an association between the rs540825 variant and citalopram response in the STAR*D sample (Garriock et al. 2010). Overall these results suggest a complex interaction between cytokines and opioid receptors, maybe involved in the mechanism of action of antidepressant drugs. Although fascinating these data need further studies in order to better dissect this complex modulation and then, ideally, to lead to the development of new antidepressant drugs acting specifically on these systems.

3.8.3. Brain-derived neurotrophic factor (BDNF)

Brain-derived neurotrophic factor is a member of neurotrophin family of growth factors, which are related to the nerve-growth factor. BDNF acts on both central and peripheral neurons supporting their survival and promoting the growth and differentiation of new neurons and synapses (Acheson et al. 1995, Huang and Reichardt 2001). BDNF functions are finely regulated: as a matter of fact 9 different transcription sites were identified, each of whose correspond to a transcriptional variant with different expression in various brain regions (Liu et al. 2005, Pruunsild et al. 2007). Several line of evidence suggested that numerous antidepressant drugs (among these imipramine, tianeptine, duloxetine, fluoxetine, mirtazapine), the vagus stimulation, ECT and sleep deprivation are associated with modified BDNF expression in different areas of the brain (Calabrese et al. 2007, Conti et al. 2007, Follesa et al. 2007, Jacobsen and Mork 2004, Reagan et al. 2007, Rogoz and Legutko 2005, Rogoz et al. 2005, Rogoz et al. 2007). Consistently, it has been reported that different antidepressant treatments trigger the enhancement of specific BDNF alternative splicing products (Dwivedi et al. 2006, Khundakar and Zetterstrom 2006). Particularly it was found that chronic SSRIs or electroconvulsive seizure treatments provoked an increased BDNF expression in the hippocampus of adult rats (Nibuya et al. 1995). After several confirms of this finding, the hypothesis of a contribution of BDNF reduction to hippocampal atrophy observed in depressed patients was proposed.

Concerning the pharmacogenetic field, the most investigated genetic variant within this gene is a 196G/A (rs6265) substitution which results in a valine to methionine (V66M) substitution (Egan et al. 2003). A growing body of evidences supports a role of rs6265 in the antidepressant response, although negative findings have been reported as well for several antidepressants (Kang et al. 2009, Rajewska-Rager et al. 2008, Wilkie et al. 2007). Nonetheless there is still controversial whether allele or genotype has to be considered the risk factor. Indeed, some studies showed a better outcome for the heterozygote genotype during treatment with milnacipram or fluvoxamine (Yoshida et al. 2007) or a trend in this direction during fluoxetine treatment (Tsai et al. 2003, Zou et al. 2010b), whilst other Authors reported that the Val/Val genotype was associated with better outcome (Mandelli et al. 2010, Zou et al. 2010a), also in a sample of drug-resistant patients treated with repetitive transcranial magnetic stimulation (Bocchio-Chiavetto et al. 2008). On the other hand other studies reported an association between the Met allele and better response to SSRIs or desipramine (Choi et al.

Table 20. *Interleukin 1 Beta* (*IL1 beta)*

More investigated SNPs		
SNP	Terapeutic effects	Side effects
rs16944 (511C/T)	+++	
Promising SNPs		
rs1143643	(Baune et al., 2010)	
rs1126757	(Uher et al., 2010)	

+ = one report that gives a positive association
- = one report that does not find any association

2006, Licinio et al. 2009), also in elderly patients treated with escitalopram (Alexopoulos et al. 2010, Taylor et al. 2010b) [although in elderly patients results are more controversial (Benjamin et al. 2010)]. This finding mismatch may be partially linked to different ethnicity in the examined samples (Mandelli et al. 2010); indeed it has been found considerable BDNF allele and haplotype diversity among global populations (Petryshen et al. 2010). With regard to side effects, an association between the Met allele and lower side effects during fluoxetine treatment has been reported (Zou et al. 2010b). Finally a recent paper suggested an association between rs6265 and the presence of stressful life events prior to the depression onset (Bukh et al. 2009), although this result was not confirmed in a further study by the same Authors (Bukh et al. 2010).

Despite of rs6265 is the most extensively studied polymorphism within the gene, some other ones have been associated with antidepressant response, such as rs90887 (Gratacos et al. 2008), rs61888800 (Licinio et al. 2009), rs7124442 (Domschke et al. 2010, Licinio et al. 2009) and rs11030104 (Licinio et al. 2009, Mandelli et al. 2010). Interestingly the last one was found to be part of a haplotype together with rs6265 that was associated with the treatment outcome; further, a interaction with temperamental trait harm avoidance has been reported as well (Mandelli et al. 2010). Furthermore rs6265 and rs988748 were associated also with prophylactic lithium response in a sample of bipolar patients (Dmitrzak-Weglarz et al. 2008). Interestingly, a recent genome wide association study (GWAS) in the GENDEP project showed an association between several polymorphisms within the BDNF gene and an increase in suicidal ideation during escitalopram or nortriptyiline treatment, among these the stronger association was found for rs962369. A significant interaction between BDNF gene and NTRK2 gene variants (that encode the BDNF receptor) has been reported as well (Perroud et al. 2009). Consistently another recent study revealed a correlation between several SNPs in NTRK2 gene and suicide attempts in depressed patients (Kohli et al. 2010), while an association between BDNF and suicidal behaviour was suggested both in bipolar (Kim et al. 2008) and unipolar depressed patients (Sarchiapone et al. 2008). Moreover, two coding SNPs (rs2289657 and rs56142442) in NTRK2 gene and the haplotype CAG at rs2289658 (splice site), rs2289657 and rs2289656 were recently found associated to antidepressant response in Mexican-Americans (Dong et al. 2009). Finally, the BDNF gene polymorphisms rs908867 and rs1491850 seem to affect the antidepressant treatment outcome in patients with obsessive-compulsive disorder (Real et al. 2009), after a series of reports that have suggested the role of this gene in the pathogenesis of the disorder (Alonso et al. 2008, Hall et al. 2003, Hemmings et al. 2008, Katerberg et al. 2009).

Table 21 gives an overview of the results concerning the gene polymorphisms. The BDNF gene shows 37 validated SNPs in human (http://hapmap.ncbi.nlm.nih.gov/), so the study of rs1013402 allows to cover the 16% of the gene variability. To our knowledge the proposed tag SNPs have not been studied up till now.

3.8.4 Glutamatergic receptors

The vast majority of excitatory neurotransmission in the central nervous system is mediated by the amino acid glutamate, which acts on ionotropic and metabotropic receptors. Ionotropic glutamate receptors are present both presynaptically and postsynaptically, where they modulate neurotransmitter release or excitatory neurotransmission. They play a key role in the plasticity of synapses and are involved in long-term potentiation, an activity-dependent increase in the efficiency of synaptic transmission which is thought to underlie certain kinds of memory and learning.

Table 21. *Brain-derived neurotrophic factor* (*BDNF)*

More investigated SNPs		
SNP	Terapeutic effects	Side effects
rs6265 (196G/A)	++++++++++++---	+
Promising SNPs		
rs7124442	(Domschke et al., 2010; Licinio et al., 2009)	
rs11030104	(Licinio et al., 2009; Mandelli et al., 2010)	
rs90887	(Gratacos et al., 2008; Real et al., 2009)	
rs61888800	(Licinio et al., 2009)	
rs962369	(Perroud et al., 2009)	
rs1491850	(Real et al., 2009)	
TAG SNP		
TAG SNP	DNA position	
rs7127507	chr11 27671460 (intron) Band: 11p14.1	
rs1013402	chr11 27668957 (intron) Band: 11p14.1	
rs16917237	chr11 27658959 (intron) Band: 11p14.1	
rs11030119	chr11 27684678 (promoter) Band: 11p14.1	

+ = one report that gives a positive association
- = one report that does not find any association

Several line of evidences suggested that the glutamate system has a relevant role in the pathogenesis of depression. Indeed, proton magnetic resonance spectroscopy allowed to ascertain that glutamate levels are increased in patients with major depressive disorder (Sanacora et al. 1999), suggesting enhanced glutamatergic transmission. Furthermore, some studies in rodents suggested a role of ionotropic glutamate receptors in antidepressant action (Nowak et al. 1996, Skolnick et al. 1996) and chronic SSRI treatment has been reported to attenuate glutamatergic transmission in the rat cerebral cortex (Boyer et al. 1998), therefore a significant role in both acute antidepressant response and maintenance of response has been hypothesized for glutamate system (Machado-Vieira et al. 2008). Consistently, a number of studies were performed in humans to test this hypothesis and recently Paddock et al found in the STAR*D sample an association between the rs1954787 polymorphism in the GRIK4 gene and citalopram response (Paddock et al. 2007). This

Table 22. *Glutamatergic receptors*

More investigated SNPs		
SNP	Terapeutic effects	Side effects
rs1954787 (GRIK4)	+++--	
Promising SNPs		
rs12800734, rs2276319, rs1621211, rs513548, rs2282586, rs2156633, rs1944522 (GRIK4)	(Horstmann et al., 2010)	
rs2518224 (GRIK2)	(Laje et al., 2007)	
rs9404130, rs2518302, rs513216 (GRIK2)	(Perlis et al., 2009b)	
rs1994862, rs10515697, rs1864205 (GRIA1)	(Perlis et al., 2009b)	
rs2285127, rs2269551, rs550640 (GRIA3)	(Perlis et al., 2009b)	
rs1323427, rs1323423, rs2050641 (GRIN3A)	(Perlis et al., 2009b)	
TAG SNP		
TAG SNP	DNA position	
rs12225735 (GRIK4)	chr11 120305249 (intron) Band: 11q23.3	
rs11218066 (GRIK4)	chr11 120314138 (intron) Band: 11q23.3	
rs2852615 (GRIK2)	chr6 102607059 (intron) Band: 6q16.3	
rs1461233 (GRIA1)	chr5 153143846 (intron) Band: 5q33.2	
rs5958217 (GRIA3)	chrX 122257803 (intron) Band: Xq25	
rs2417289 (GRIN3A)	chr9 103468151 (intron) Band: 9q31.1	

+ = one report that gives a positive association
- = one report that does not find any association

preliminary finding was confirmed in a following report (Horstmann et al. 2008) although more recently studies did not replicate these results (Horstmann et al. 2010, Perlis et al. 2010b). In following studies, GRIK2 and GRIA3 receptors were associated to treatment-emergent suicidal ideation in the STAR*D (Laje et al. 2007) and in the Munich Antidepressant Response Signature (MARS) project (Menke et al. 2008), while GRIK2, GRIA1, GRIA3 and GRIN3A to sexual dysfunction induced by citalopram in the STAR*D (Perlis et al. 2009b). Nevertheless, a following genome-wide association study again in the STAR*D did not found any marker associated with suicide within this genes (Laje et al. 2009). For metabotropic receptors genes GRM2 e GRM3 preliminary results are negative with regard to fluvoxamine response (Tsunoka et al. 2009). Overall these data confirm the genetic variants in the glutamate system as promising topic for future studies in the field of antidepressant pharmacogenetic.

We have summarized the available results in **table 22**. To our knowledge the proposed tag SNPs have not been studied as far as now.

3.8.5 Channel-protein coding genes

Potassium channel subfamily K member 2 gene (KCNK2 or TREK1) codes for a two-pore-domain potassium channel involved in the regulation of excitability and resting potentials of neurons. In the last years it has been hypothesized to be involved in antidepressant mechanism of action because animal studies demonstrated a strong antidepressant phenotype in TREK1 knockout mice (Heurteaux et al. 2006). Particularly SSRIs action may partly depend on TREK1 inhibition (Gordon and Hen 2006, Tsai 2008). Consistently, Perlis and colleagues reported an association between several polymorphisms within this gene (rs2841616, rs2841608, rs12136349, rs10494996, rs7549184, rs10779646) and citalopram response in the STAR*D sample (Perlis et al. 2008). Further, another report found an association between the rs6686529 variant and both susceptibility to depression and response to citalopram and fluoxetine (Liou et al. 2009). Interestingly, also neuroimaging studies supported the involvement of this gene in the pathogenesis of depression and antidepressant action. Indeed, in humans and rodents TREK1 reached high concentrations in the basal ganglia structures (Medhurst et al. 2001, Talley et al. 2001), which have great importance to reward processing. Therefore, it is thought that TREK1 may be associated with reduced motivation and anhedonia (Heurteaux et al. 2006) and this hypothesis found support in fMRI studies: genotypes previously associated with antidepressant response by Perlis et al. (rs10494996, rs2841608 and rs2841616) resulted more frequent in subjects with potentiated basal ganglia activity to gain (Dillon et al. 2010).

Among Channel-protein coding genes another promising candidate gene is calcium channel voltage-dependent L type alpha 1C subunit (CACNA1C) gene. Strong evidence supported an association at the polymorphism rs1006737 with the risk of bipolar disorder and recently it has been found that the risk allele confers susceptibility also for schizophrenia and major depressive disorder (Green et al. 2009). Further a preliminary study in the STAR*D sample shows that rs10848635 and rs1006737 variants within the gene influence symptomatology severity at baseline and treatment-emergent suicidality during citalopram treatment (Casamassima et al. 2010). Considering these data together we could hypothesize that this gene may be related more with symptomatology severity than with a particular psychiatric diagnosis, although further studies are clearly required in order to better dissect its role in psychiatric disorder and treatments.

3.9 Genome Wide Association Studies (GWAS)

Recently, a new approach in genetic studies has acquired importance, the so-called genome wide association studies, a multiplex technology that can accomplish thousands genetic tests in parallel, in large samples of cases and controls. This innovative method seems particularly useful to study complex diseases, such as psychiatric disorders, since the contribution of multiple loci with small effect size is expected. Anyway, it has been applied in several fields of medicine besides psychiatry, e.g. to study genetic variants predisposing to coronary artery disease, type 1 and 2 diabetes and rheumatoid arthritis (Wellcome Trust Case Control Consortium 2007). Nevertheless, an important problem of this methodology is a high risk of false positive results. With regard to antidepressant pharmacogenetics, the number of GWAS performed so far is still limited and results need replication, thus further studies on larger samples are needed. Three recent GWAS were performed within the GENDEP project; one of them detected a number of markers not previously associated neither to depression susceptibility nor to antidepressant response. Indeed, polymorphisms in two regions on chromosomes 1 [nearest known gene: zinc finger protein 326 (ZNF326) and 10 (nearest gene: plexin domain containing 2 (PLXDC2)], were found associated to the therapeutic outcome, regardless of the antidepressant used. Copy number variants that may influence the expression of genes at longer distances through changes of the chromatin structure have been identified in both regions. Moreover, a strong genome-wide significant association was detected between the rs2500535 variant in the uronyl 2-sulphotransferase gene and response to nortriptyline and between the rs1126757 variant in the interleukin-11 gene and response to escitalopram (Uher et al. 2010). The other GWAS on the GENDEP sample were focused on suicidal risk during antidepressant treatment. In the first of them the strongest association was found with rs962369 in the BDNF gene; additionally, an interaction between variants in the BDNF and NTRK2 (the gene encoding BDNF receptor) genes resulted to affect suicidal ideation, as well as rs11195419 in the ADRA2A gene was associated to suicidal risk only in nortriptyline treated men (Perroud et al. 2009). In the other one the most significantly associated marker was rs11143230, located 30kb downstream of a gene encoding guanine deaminase (GDA) on chromosome 9q21.13, whilst KCNIP4 (Kv channel-interacting protein 4) and near ELP3 (elongation protein 3 homolog) were selectively

associated to escitalopram response. Moreover, the significance of NTRK2 gene was replicated (Perroud et al. 2010b).

On the other side, other two GWAS were realized within the STAR*D, once again with regard to antidepressant response and emergent suicidal ideation during citalopram treatment. The polymorphism more strongly associated to treatment response was rs6966038, located 51 kb from the ubiquitin protein ligase E3C gene (UBE3C) and 77 kb from the motor neuron and pancreas homeobox 1 gene (that controls gene expression at the caudal end of the developing notochord of an embryo), while the second one (rs6127921) is closest to the bone morphogenic protein 7 (BMP7) gene (Garriock et al. 2009). Two markers within the genes PAPLN and IL28RA were associated to suicidal ideation during citalopram treatment (Laje et al. 2009). Although several genetic variants have been associated to suicidal risk, suicide remains a multifactorial phenomenon, with specific biological, psychological and environmental risk factors (Crisafulli et al. 2010).

A hurdle to clear for GWAS is the incapacity to detect rare genetic variants (<1% of the population). Indeed, current GWAS technologies are able to detect only association for genetic variants present in 5% or more of the population (Craddock and Sklar 2009). Thus, resequencing studies on large samples with carefully selected designs can be useful until 'fourth generation' methods will likely make large-scale high throughput sequencing feasible for most investigators. Ising et al. (Ising et al. 2009) gave an example of such type of approach, since they studied a sample from the 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 detected genes could be grouped in 3 interrelated clusters. The first one includes genes related to metabolic pathways and brain development, with the strongest effect observed with a combined phenotype of treatment outcome in the MARS sample for rs1502174, located downstream of EPHB, from the ephrin family. The second one pertains to genes related to metabolic and cardiovascular diseases, which frequently co-affected depressed patients, and the third one includes neuregulin 1 (NRG1) and genes related to GABA-ergic (gamma-aminobutyric acid neurotransmitter transporter, SLC6A11) and glutamatergic neurotransmission (homer homologue 1, HOMER1; glial high affinity glutamate transporter, SLC1A2).

Even if combining different samples can result helpful, poor and difficult comparability of data across centres may represent a problem; nevertheless, it seems so far necessary, since the effect sizes of common risk variants found by GWAS have been much lower than anticipated, so large meta-analysis to reach genome-wide significance are often needed (McCarthy et al. 2008).

4. Conclusions

Until now all observed gene mutations do not reach the putative 50% of variance explained by genetic factors in the complex trait of antidepressant response. On the other hand, only explained variance of 40-60% have substantial clinical impact (Serretti 2004). Therefore the current aim of pharmacogenetic studies is to find out more candidate genes. In this view genome-wide association studies will suggest new candidates to investigated, although findings so far have been discouraging, maybe also because the inconsistent use of sever methodological strategies (Teo 2008). One more problematic issue for pharmacogenetic studies is the risk of false positive findings. A recent paper by Sullivan elegantly demonstrated in a simulation of a classic case control investigation that the possibility of false results is about 96%. Considering that the simulation was conducted with a set of 10 SNPs in the COMT gene with a sample composed by 500 cases and 500 controls, the possibility of false findings in classical association studies (frequently with smaller sample than one simulated by Sullivan) is notably high. Therefore the need for several replication studies before the risk of a false positive finding is ruled out, and replication of a disease association in one or more samples has become a requirement for publication in many high-impact biomedical journals (Sullivan 2007).

Concerning the pharmacokinetics variations, the results reached so far allowed the design and production of chip set able to predict the reaction, in terms of kinetics, to the exposure to a certain drug. Nonetheless the impact for drugs with a relatively large therapeutic range may be minimal, as we recently confirmed (Serretti et al. 2009). Furthermore one main problem in pharmacokinetic studies is the presence of several confounding factors: e.g. 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. E.g. the enzyme activity of a genetic PM can not be increased or decreased by substances which are inducers or inhibitors of the enzyme. In contrast, EMs or UMs can convert to the PM phenotype by strong enzyme inhibitors. Finally, drugs can be metabolized by a set of cytocromes: they should all be investigated in a single test in order to infer sufficient predictive information about the drug blood levels. In order to overcome this problematic issue in the pharmacokinetic field, further studies considering these confounding factors are clearly required to provide useful and definitely results. Future studies on this topic should also solve some methodological deficits of past studies. Indeed, the larger part of available studies have included too few subjects to establish if CYP genetic variants have a significant role in antidepressant response, since to obtain a reasonable number of CYP2D6 PMs (30) it is necessary to recruit > 400 Caucasians (de Leon et al. 2006). Moreover, many studies are based on evaluations made after a single or a limited number of doses, with no data about the steady state and clearly, saturation pharmacokinetics, irreversible enzyme blockade or enzyme up- or down-regulation might change the outcome when repeated doses are administered (Sindrup et al. 1992). Another problem is the lack of homogeneity in antidepressant treatment, population studied and CYP polymorphisms

examined among different studies.

On the other side evidences from pharmacodynamic studies seems to be more promising in order to identify different response and side effect patterns. Nonetheless until now results concerning the pharmacodynamics is still partial and sparse as well, therefore so far the design of the useful genetic chips able to detect the ideal therapy for each patient is not possible. On the other hand the number of replication findings is increasing every day, among these the most replicated findings are found regarding the promoter of the serotonin transporter. However also concerning this polymorphism the results are more consistent in Caucasian populations with the L allele of the promoter being associated with a better response to treatment. In other populations the replication rates are very low and often in another way, e.g. in Asian samples the s allele has been associated with a better antidepressant response. The reason for this opposite results is still under investigation. A confounding factor may be the different allele and genotype frequency among different ethnic groups, since e.g. the s allele frequency was estimated to be 72.0% in Chinese, 38.0% in Croatian and 40.4% in German population (Noskova et al. 2008). Indeed, stratification is the most important limitation in pharmacogenetic studies and it is frequently due to different ethnic origin. To overcome this bias, pharmacogenetic studies should include only subjects belonging to a specific ethnic group for at least two generations. Recently it has been suggested that a possible explanation of these contradictory results may be also the so-called flip-flop phenomenon, which is a multilocus effect. Indeed, multiple loci and environmental effects play a role in determining susceptibility to complex diseases and chance of treatment response; if the interrelated effects of these factors are not take into account, ambiguous results may be produced. Flip-flop associations are seen particularly when the risk allele at the target locus is a relatively common allele. Additionally, for loci with a minor-allele frequency <5%, it may be more likely that flip-flop phenomena indicate spurious results than confirmatory results confounded by the multilocus effect. Flip-flop associations can also be due to investigation of a noncausal variant in LD with a genuine causal variant, indeed notable difference in LD across populations were found (e.g. for COMT gene) and, less obviously, sampling variation can leads to variation in observed LD patterns. For this reason, markers in weak LD with each other (e.g., r^2<0.3) may need to be considered carefully (Lin et al. 2007). Obviously, also for pharmacodynamic studies the lack of homogeneity in population studied, outcome measures and antidepressant treatment is a limitation, and often in the same study different classes of antidepressants are used. To give some examples, some studies included both bipolar and unipolar patients or patients with multiple and a single episode of major depression, who seem to have a lower genetic load (Tsuang 1990). As far as now, in order to avoid this stratification, growing importance is given to the identification of peculiar and homogeneous subgroup of patients, the so-called endophenotypes (e.g. early onset, psychotic symptoms). Under this point of view, the use of the HAMD as a whole to measure the outcome does not allow to value if a patient reach remission of some symptoms with persistence of others. Another limitation is that some pharmacogenetic studies have ignored some very important confounding variables, such as age, concurrent medical conditions, baseline depression levels and drug plasma levels.

This given, the possible clinical impact of the genetic variations that are found in genes involved in the pharmacodynamics of the antidepressant response are discussed below.

5. Clinical implications of genetic studies

We have already underlined how the clinical impact of genetic variations is still of poor extent for antidepressant treatments (Garriock and Moreno 2011). Nevertheless results obtained by genetic studies in other field of medicine allow to be moderately optimistic for further application also in the psychiatric field. Indeed, despite the suppose distance between research results and clinical practice, findings obtained by genetic researches have been already turned into clinical implications in several fields of medicine, with relevant effects. Particularly, in oncology some genetic tests have been already introduced in the clinical practice: they are based on the analysis of a number of polymorphic genetic loci in order to evaluate prognosis and predict the individual response to a certain treatment and individualize treatment. For example it has been already commercialized a microarray-based multigene assay for breast cancer patients (the MammaPrint assay) that allows to predict the risk of recurrence of the disease, with a significant contribute in the definition of the best management for the single patient (Slodkowska and Ross 2009). Moreover a multi-analyte reverse transcription–PCR genomic test, which allows to classify patients with breast cancer in relation to their risk of recurrence, has been clinically validated in multiple studies (Habel et al. 2006, Paik et al. 2004, Paik et al. 2006). Considering the lack of clinical data that could predict treatment outcomes in this disease, molecular genomic methods seem to be the most promising way to improve clinical oncology diagnostics (Cronin et al. 2007). With regard to the psychiatric field, the AmpliChip™ test was approved by the Food and Drug Administration (FDA) in early 2005 and was the first pharmacogenetic test to be commercialized. It is based on one of the major technological advance genetic testing, the so-called DNA chip (DNA microarray or GeneChip), able to test simultaneously one sample for many alleles. It allows to classify individuals on their CYP2D6 phenotype (UMs, EMs, IMs, and PMs), since CYP2D6 is the major responsible of psychotropic medications metabolism, while for CYP2C19 it allows to distinguish two phenotypes, EMs and PMs (de Leon et al. 2006). The AmpliChip™CYP450 Test represents an important impulse towards personalized therapy and several other test are in phase of development e.g. General Electric Health Care (CodeLink™ P450 SNP Bioarray), Tm Bioscience (Tag-It™ Mutation Detection Kit), Third Wave Technologies Inc. (Invader? Technology) and Jurilab Ltd (DrugMet™ Genotyping Test). Anyway, guidelines not recommend the use of CYP genotyping tests yet, because lack of evidences

linking this test to clinical outcomes was found and cost-effectiveness studies have not been published yet (EGAPP 2007). So far, it is not known if one of the described genotype tests and which of them will spread in the clinical practice. Anyway, this should happen if the clinical significance of genotyping will be demonstrated and these technologies will become more readily available. The detection of useful pharmacogenetic tests to estimate pharmacokinetic profile may result particularly relevant in patients who need drugs with narrow therapeutic index and important adverse reactions, like TCAs.

Furthermore the usefulness of genome sequencing has been proposed also to predict the individual risk to develop specific diseases in subjects with positive familiarity for certain diseases. In this point of view also the risk to develop psychiatric disease in patients with positive familiarity may be predicted. Recently a study by Ashley and colleagues (Ashley et al. 2010) reported promising results in this way: they sequenced the entire genome of a patient with a family history of vascular disease and sudden death in order to better predict the risk of this single patient to develop several diseases on the basis of the current genetic knowledge. The post-test probabilities to develop a certain disease resulted significantly different from pre-test probabilities (i.e. the general risk of a patient with the same familiarity) for a number of diseases like obesity (56% vs 25%), type 2 diabetes (55% vs 28%), coronary artery disease (58% vs 50%) and Alzheimer disease (2% vs 10%). Concerning the psychiatric field also the risk to develop depression was significant modified after the analyses of genetic variants (25% vs 12%). Although preliminary data, this promising result suggested that in a near future physicians may integrate clinical and genetic data in order to identify patients with high risk of diseases, including psychiatric ones, and consequently to prevent the diseases itself, or at least to begin to care it at an early phase. In the same way, it will be possible to predict individual response and side effect risk for different drugs, a target of particular interest in the psychiatric field where drugs are now prescribed only on the basis of clinical experience and of the side effect profile. Further, a set of information coming from clinical evaluation such as concomitant personality diseases, social support and psychological features must complement the genetic information.

In conclusion the possibility to achieve an individualized therapy on the basis of genetic profile is getting closer, with clear advantages for the daily clinical practice.

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