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Pharmacogenetics of antidepressive treatment

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Abstract The search of the genetic predictors of response to antidepressants is a rapidly expanding field. A large number of clinical studies are reporting partly inconsistent results. Emerging new results focus on new candidate single nucleotide polymorphisms—particularly in the 5HT2a-receptor gene and the gene coding for the co-chaperone FKBP5. The impact of the 5HTTLPR polymorphism on therapeutic outcome and side effects under treatment with SSRIs has to be viewed in a more complex manner than previously proposed. All replicable genetic associations display only a very modest effect. Despite of enormous research efforts, currently pharmacogenetics of therapeutic effects and of side effects of antidepressants are unable to guide decisions on the selection of the most beneficial drug for an individual patient.

Keywords Serotonin transporter gene · FKBP5 gene · TPH1 gene · COMT gene · BDNF gene · 5HT2a-receptor gene · 5HT1a-receptor gene

Introduction

Plenty of pharmacological antidepressant treatments with evidenced efficacy are available since a considerable number of years. Yet, not all depressed patients can profit from a specific efficacious antidepressant. Only one half of patients experience clinically relevant symptomatic improvement (response) in a first treatment course even under optimal quality-controlled conditions, only one-third reveal full remission (no or only minimal residual symptoms) within 12 weeks, up to four treatment trials are needed to achieve full remission for two-thirds of patients [52].

Empirically validated clinical predictors to inform the treatment selection for a single patient are missing [41, 54]. The core question in the treatment of subjects with depression "what is the most beneficial drug for this depressed person?" cannot be answered in a scientifically informed manner despite of substantial research efforts across decades. Thus, clinical practice is still based on a scientifically uninformed "trial and error practice" with the consequence of enormous additional subjective suffering, losses in quality of life and in everyday functioning; it also increases disease associated risks (particularly suicidality) and costs. Apparently, response to antidepressants is less a group phenomenon and more a characteristic of an individual. Genomics offers the first comprehensive scientific approach to define individuality by the use of the DNA-sequence variability. Pharmacogenomics presents, therefore, a promising tool to predict individual response to a specific drug.

Phenotypes

Familiality of response to antidepressants

What are the reasons to assume that the individual response patterns to specific antidepressants are partly driven by

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specific genetic determinants? Appropriate large-scale family and twin studies are missing but:

(a) some previous family and twin studies compared the treatment response to antidepressants in two depressed members of the same family and found more similarities than expected by chance (e.g., [10]),
(b) antidepressants are metabolized (liver) and transported (blood–brain barrier) by enzymes with genetically influenced enzyme activities resulting in interindividually differential availabilities of the active drug components,
(c) antidepressants target various molecular structures and pathways which reveal genetically determined qualitative (amino-acid sequence) and quantitative (magnitude of expressed proteins) differences,
(d) affective disorders themselves are under genetic control, and these causal genetic determinants might affect course and response to antidepressants.

Phenotypes in pharmacogenetics

Three main aspects of the pharmacogenetic phenotype are to be distinguished: plasma levels (given a standard oral dosage), drug effects at the targeted structures determining therapeutic responses, and drug effects at other structures resulting in side effects.

The core genetic determinants of plasma levels of antidepressants are single mutations in Cyp P450 enzymes. Major effects are exerted by these variants with strong impact on plasma levels. Excellent reviews on this pharmacokinetic endpoint with clear-cut recommendations for the individual patient are available [21]; these achievements are already transferred in clinical applications.

Major effects are also produced by specific variants of the transporter gene ABCB1. This gene encodes an active transport protein at the blood–brain barrier influencing on the availability of certain (but not all) antidepressants at the brain action sites [57]. The transfer of these insights into clinical practice has to be accomplished.

The impact of genetic variants on the pharmacodynamic endpoints as response and remission of depressive symptoms and as side effects are substantially less clear. Therefore, we focus in this review on the genetics of pharmacodynamic effects of antidepressants and ignore pharmacokinetic endpoints. We consider only genetic associations with at least one replication.

Phenotypes for pharmacodynamic endpoints: lack of consistency

While the pharmacokinetic phenotypes can be measured in a straightforward manner, the pharmacodynamic phenotypes cannot be defined equivocally: standardization of the measurement of therapeutic effects is required; but it is missing up to now and instead multiple alternative options are used:

(a) *Selection of assessment scales:* Therapeutic treatment outcome is usually defined through global severity scores of depression. Different scales are used for this purpose: HAMD or MADRS as alternative observer rating scales in the vast majority of studies and the self-rating scale QIDS-C16 used in the biggest study in this field (STAR*D).
(b) *Selection of endpoints versus repeated measurements:* Most investigators rely on the endpoints (last measurement) of global scores of depression scales. The repeated measurement approach [46, 54, 55] considering the whole treatment period is to be preferred in a biometric perspective; the advantage is to take the speed of change as well as endpoint behavior into account; this strategy also increases the power and avoids misrepresentations of results [27]; the GENDEP study is the biggest study to apply this approach [17].
(c) *Categorical versus dimensional:* Categorization of outcome by distinction between response and non-response or remission and non-remission is achieved by applying cut-off points to the depression scale in most studies (e.g., [49, 50]); this approach is less powerful than using just the dimensional measurements (as used in repeated measurement procedures).
(d) *Measurement of content:* The concept of response/remission to antidepressant treatment refers to global severity scores and has been called into question: apparently the symptom-based response pattern does not harmonize with a simple severity factor as indicated by the global score; instead a three-factor solution seems to be more appropriate [50, 54].

Meta-analyses are usually just considering the categorical outcomes (response, remission); given this heterogeneity, those combined studies, have (a) to discard a substantial number of studies preferring dimensional approaches, and (b) to ignore the differences in selected scales and in lengths of treatment periods. The measurement of side effects is even less standardized across studies thus increasing the heterogeneity.

Selection of genes

Currently, pharmacogenetics still relies on a candidate-gene approach. The targeted genes are usually related to the presumed mode of action of the investigated drugs.

The straightforward candidates code for transporters, for receptors and for synthesizing or degrading enzymes of

involved neurotransmitters (serotonin, noradrenaline, dopamine) and for downstream substrates of antidepressants (second messengers, growth factors, glucocorticoid receptors). Most reports consider a single gene of interest; yet, in reality a host of other candidate genes is explored without taking the gene–gene interaction and the multiple-testing problem adequately into account. This strategy might cause publication biases, as positive findings are more acceptable to journals [36, 56].

Selection of antidepressant drugs

Pharmacogenetic investigations either treat patients with monotherapy with serotonin reuptake inhibitors (SSRI) or with noradrenaline reuptake inhibitors (NRI) in the more recently sampled cohorts, and naturalistic antidepressant treatment with a broad spectrum of drugs in the more previously sampled cohorts. Limitations of the power in individual studies cause false positive and false negative findings. Thus, most reports cannot be considered in isolation but require a meta-analytic view combining all investigations in the same topic. Yet, the design heterogeneity across studies limits the conclusiveness of meta-analyses.

A core issue in pharmacogenetics of antidepressants is the role of the specificity of an investigated drug. One view is that predictive genetic markers are closely related to the specific antidepressant mechanisms; thus, pharmacogenetics of SSRI might be different from pharmacogenetic markers for another group of antidepressants as NRI. The other view is that predictive markers are based on neurobiologically defined final common pathways, which are common to all antidepressants (e.g., components of the glucocorticoid pathways). In this perspective, genetic markers operate across all antidepressants. These alternative views require to be tested in appropriate clinical comparative trials with randomization across the different antidepressants.

Statistical strategies

Required designs of pharmacogenetic studies depend on the magnitude of the gene effect to be detected. Particularly, the sample size changes with the allelic frequency and the effects to be detected. It is becoming more and more evident that the effect sizes to be detected are very modest (approx. OR $\sim$1.5 or even less when using a categorical outcome measure). Available sample sizes in single studies are usually too limited for the detection of these very modest magnitudes of effect sizes with a sufficient degree of certainty. Only the most powerful prospective pharmacogenetic studies in antidepressants—the STAR*D with monotherapy with citalopram ($n = 1{,}816$) and the GENDEP with randomization between escitalopram and nortriptyline ($n = 811$)—partly fit these statistical requirements. All other studies are substantially smaller ($n = 300$ patients).

Replication of initially positive results is decisive to distinguish "true" and "false" positives. Replication by splitting the sample into a discovery and a replication subsample enables a first validation for "true" positives ("internal validation"). Only the STAR*D study is large enough ($n = 1{,}816$) to allow internal replications by splitting the whole sample into a discovery ($n = 1{,}199$) and a replication subsample ($n = 617$). Replication tests of initially positive studies in independent samples are usually difficult to accomplish and often produce inconsistent results given the very limited sample sizes. A widely accepted compensatory strategy to resolve inconsistencies are meta-analyses: they compensate for the limited power in single studies by combining samples. Published meta-analyses encompass maximally about 1,500 subjects [49]. This report discusses informative meta-analyses on variants of interest as far as they are available.

Design heterogeneity and unresolved issues

Pharmacogenetic publications on antidepressants work with a broad variety of designs and sample sizes. This lack of standardization derives from the fact that only very few studies were specifically designed for pharmacogenetic investigation. Usually, pharmacogenetics is just a "by-product" in clinical studies, which primarily serve other goals. Therefore, many core pharmacogenetic questions cannot be answered in an appropriate manner: e.g., the question "are predictive genetic variants specific for a particular therapeutic substance (or class of substances) or are they unspecific"? Appropriate answers to this question require the delivery of at least two drugs (in monotherapy) in a randomized fashion. Only three studies of this kind were published up to now: the GENDEP study [17], and two smaller studies [20, 39]; these three studies compared SSRIs to drugs with a strong noradrenergic effect or to mirtazapine; placebo-control groups are needed to distinguish substance-specific and spontaneous unspecific response to treatment; this specific kind of studies is not existent at all.

Specific genes

Serotonin transporter gene: the length polymorphism (long/short)

The serotonin transporter (5HTT) is a core drug target for the nowadays antidepressant treatments. This membrane

protein transports serotonin from the synaptic cleft into the presynaptic serotonergic neuron. This mechanism plays a well-documented role in stress adaptation. Antidepressants (particularly SSRIs) act by reducing serotonin binding to the transporter. 5HTT is encoded by the gene SLC6A4—one of the most extensively investigated molecular sites in medicine. This gene hosts several, partly functional polymorphisms, the most well known being located in the promoter site: the 5HTTLPR (serotonin transporter length polymorphism). The underlying insertion/deletion of 44 base pairs (5HTLPR) results in either a long (L), respectively, or a short (S) allele. The three genotypes LL, SL, and SS reveal a frequency of 35–40%, respectively, 40–50%, respectively, 15–20% among Europeans. Their frequencies differ across populations: the frequency of the S-variant is increased among Asians by a factor of 2. The long allele is associated (in vitro) with a higher transcription of the gene, resulting in an increased transporter capacity. The first claim of an increased beneficial response rate to antidepressants for carriers of the 5HTTLPR L-variant in 1996 (reviewed by Serretti et al. [49]) initiated pharmacogenetic research in antidepressants.

Since then, more than a dozen of replication tests were undertaken in various populations with heterogeneous results. 14 of these studies were submitted to the most recent meta-analysis [49]. Given the differences of allele frequencies across populations, samples of European subjects were analyzed separately. 1,435 depressed patients of European decent were included in this meta-analysis with the following results: (a) the L-carriers (genotypes LS and LL) were associated with a significantly more beneficial remission rate (OR = 2.21) and a (non-significantly) better response rate (OR = 1.20); (b) the LL-homozygotic genotypes were associated with a non-significantly better remission rate (OR = 4.2!) and a significantly increased response rates (OR = 2.01). Yet, the population-genetic background matters: (a) ethnic differences were observed confirming the initial hypothesis only among Europeans and with a partly reversed trend among Asians; (b) the effect—although being significant due to the high number of encompassed subjects—was more modest than in the initial reports.

Some further caveats (besides the ethnic background specificities) have to be considered:

(a) The largest study (n = 1,816)—the STAR*D study with 12 weeks monotherapy with citalopram [16]—is not included into the meta-analysis by Serretti et al. [49] as it was published more recently. The STAR*D study did not reveal any influence of the 5HTTLPR on the categorically defined response (measures taken at the last visit) [16] when comparing the L-allele carriers to the SS-genotype; yet, a secondary analysis reported a borderline advantage for LL-genotypes among white none-hispanic subjects in terms of remission [38].

(b) The predictive role of the 5HTTLPR polymorphism may not be valid for all patients with the diagnosis of depression; in the GENDEP study the genetic association to SSRI response was exclusively observed among males with recurrent unipolar depression [17]; this observation is, however, in conflict with a smaller study reporting these associations for females but not for males [3].

(c) The predictive role for a less favorable response of the SS-carriers seems to be strongest for the relationship between 5HTTLPR and SSRI; the relationship to noradrenergic drugs is controversial (e.g., [17, 20]).

(d) There is confirmed evidence that the predictive power is different for the various components of the depressive symptom spectrum; it is strongest for "core" depressive symptoms [50], the response of the vegetative symptoms seems to be less predictable by 5HTTLPR [17].

(e) There is indication for a publication bias although the meta-analyses tested for this possibility without detecting an indication for bias; yet, the tests are underpowered [24], and there is the impression of a biased reporting of results.

(f) The 5HTTLPR genotypes predicting response may differ between initial therapy and second (and later) switch therapies [60].

(g) The L-variant is in itself heterogeneous encompassing multiple repeat variants; each of them might have a specific impact on treatment [40] but only one of them (rs25531, see below) received special attention.

Therapeutic response is difficult to disentangle from the impact of side effects [39], particularly under limitations of sample sizes and insufficient documentations. The meta-analysis by Kato and Serretti [19] concluded a reduced side-effect rate for the L-carriers (L/L and L/S) with an OR of 0.54; it is noteworthy that the same set of studies also argued for beneficial response to antidepressants for L-allele carriers. There is some evidence that a possible predictive role of 5HTTLPR on side effects is limited to SSRIs as a study with mirtazapine came to the reverse conclusion [39]: the L-carriers revealed more side effects under mirtazapine. Yet, the STAR*D study was not included in these meta-analyses: this study did not find an impact of the LPR polymorphism alone on side effects of citalopram [16, 23].

The diversity of results in different ethnicities and their pathophysiological meaning are difficult to understand [31]. It is also difficult to reconcile the purposed hypothesis of an adverse influence of the S-LPR variant on SSRI

response with the knowledge that the brain serotonin turn over (measured by direct jugular venous blood sampling) is increased among S-variant carriers and reduced by SSRIs [2]. Serretti et al. [48] proposed that the SS-variant may reduce the plasticity of the brain serotonergic synapse among Europeans, the magnitude of the effect depends on the serotonergic tone.

Serotonin transporter gene: polymorphisms beyond LPR

Three other polymorphisms are in linkage disequilibrium with 5HTTLPR; they are indirectly or directly related to different levels of 5HTT-gene expression:

- rs25531, a biallelic (A/G) polymorphism in the sixth repeat of 5HTTLPR occurring in the long as well as the short 5HTTLPR variant [15],
- rs2020933, located in the first intron of the 5HTT gene that shares only a small part of variance with 5HTTLPR,
- STin2, representing a repeat polymorphism (VNTR) in intron 2 with the 12 resp. 9 allele.

All three polymorphisms were also explored of their influence on therapeutic response and on side effects – but less intensively as 5HTTLPR:

An incremental role of the rs25531 polymorphism (in addition to the LPR polymorphism) on prediction of drug response was not observed [38] and its impact on gene expression remains to be clarified [15, 17, 34]. Initially it was proposed that the G-variant in the L-variant of the 5HTTLPR induces a reduction of the expression level (to an expression level comparable to the S-variant). Replications were not supportive for this observation [15, 23, 34, 45]. More recent reports (as the GENDEP study [17]) were not able to confirm the modulatory role of rs25531 on response to SSRIs. Additional studies are required for more valid conclusions.

An argument for the relevant functional impact of the rs25531 polymorphism on the LPR polymorphism comes from the STAR*D study on genetics of citalopram-induced side effects: although the LPR polymorphism was not implicated in this phenotype the combination between S-variant of the LRP and rs25531 was strongly related to the emergence of side effects. Particularly, the LA/LA homozygotic genotype is accompanied by reduced side effects—preferentially with regard to gastrointestinal side-effects burden [16, 23], the magnitude of this effect is moderate with OR = 0.7 for L-carriers. These convergences of results on side effects are remarkable given the diversity of assessment methods for side effects.

Only a single report considered rs2020933: the GENDEP study [17] found the major allele in this polymorphism to predict better response—most interestingly not only to escitalopram but also to nortriptyline; Huezo-Diaz et al. [17] argue that the predictive role of rs2020933 is largely independent of the 5HTTLPR effect. This genetic association finding requires replication. The functional role of this specific polymorphism rs2020933 is supported by expression studies: it contributes to 5HTT-gene expression independently of the 5HTTLPR [34].

The impact of the STin2 polymorphism on antidepressive response is controversially discussed and reveals substantial heterogeneity across populations; inconsistent results emerged for the effect of the 12/12 genotype on the antidepressive response [19, 20, 60]. More recent studies among Europeans also provide divergent evidence [17, 38]. Thus, any conclusions would be premature.

Genes for serotonin receptors: 5HT2A, 5HT1A

5HT2A-receptor gene

Another postulated mechanism for serotonergic antidepressants is the blockade of the 5HT2A receptor proposing the 5HT2A-receptor gene as a candidate for pharmacogenetic studies [26]. This gene consists of three exons separated by two introns. It belongs to the most extensively investigated genes.

Most interestingly, the two currently most comprehensive studies in the field, STAR*D and GENDEP, report their strongest associations for 5HT2A-receptor markers when testing a large variety of markers in several dozens of preselected candidate genes. The reported predictive DNA-sequence variants (rs7997012 in STAR*D and rs9316233 in GENDEP) are, however, different between these two studies—yet, they are partly linked and both located in intron 2 [36, 56]: in the STAR*D study the marker rs7997012 was detected in the discovery sample as highly associated with response to citalopram within 12 weeks; this association was internally replicated (in a replication and the total sample). This association was not demonstrated in black subjects [36]. GENDEP tested another set of markers in only European patients and found a maximal association to marker rs9316233; this marker is in linkage disequilibrium to rs7997012. In the GENDEP study, the rs7997012 marker (emerging from the STAR*D study) was also weakly associated with antidepressant response under specific conditions (e.g., categorical outcome definition) [56]. This constellation was interpreted as a partial replication [56]. A functional role of both associated markers is unknown. These multiple genetic associations to two linked, apparently non-functional markers might emerge from a third, not tested functional marker in linkage disequilibrium with both associated markers that directly influences antidepressive response.

Previous studies explored other candidate SNPs in the 5HT2A gene: the 102T/C and/or 1438A/G polymorphisms both being located in the promoter region; those two polymorphisms are not linked to the aforementioned 5HT2A-gene intron2 markers (rs7997012, rs9316233). Both promoter polymorphisms (102T/C, 1438A/G) are extremely closely linked and often end even indistinguishable. Both affect the expression of 5HT2A receptor. At least nine studies explored the antidepressant effect of these hot candidates without providing convincing results. The meta-analysis on seven of these studies clearly excluded any effect on the therapeutic antidepressive outcome [19].

Yet, this global conclusion might not be valid for all ethnicities. Focus on studies in Asian populations with exclusive application of SSRI (altogether four studies) delivered significant beneficial effect for the 1438GG genotype (OR = 1.69) [19]. A reduced gene expression was observed for the GG variant of the 1438A/G polymorphism [43]. 5HT2A antagonism defines an antidepressive treatment mechanism. On this background, the association of the 1438GG variant to beneficial response among Asians gains biological plausibility.

Although there is no consistent relationship to therapeutic response patterns, the 1438 G/G or 102 C/C variants were clearly associated with a significantly increased risk for side effects (OR = 1.9) in European as well as in Asian studies (with altogether 800 patients). Remarkably, not a single of the seven included reports revealed a significant result for a single study what is probably due to reduced sample size (<250 subjects) of each individual study. A most frequent type of side effects, the gastrointestinal complaints, revealed a particularly strong relation to 1438G/G with OR = 2.3 [19]. The impact of 1438A/G polymorphism on side effects did not vary across ethnic groups (in contrast to the antidepressive effect).

5HT1A-receptor gene

The 5HT1A autoreceptor is considered a core element in the machinery of serotonergic antidepressive response [12, 28]. Increase of serotonin transporter inhibition is accompanied by a downregulation of the presynaptic 5HT1A autoreceptor; impaired 5HT1A function was suggested to be a reason for insufficient response to antidepressants.

The coding gene carries a sequence variation 1019C/G in the promoter area; the more frequent C-variant presents a binding site for repressor proteins for the 5HT1A gene; the G-variant abolishes the repressor activity mediating an increased 5HT1A autoreceptor density. Blockade of the presynaptic 5HT1A receptor, e.g., by pindolol, demonstrated an accelerated response to antidepressants in clinical studies [6]. Thus, the C-variant operates like an inbuilt 5HT1A -receptor blocker. It can, therefore, be speculated that the homozygotic genotype 1019C/C predicts a more beneficial response to antidepressants. In addition, indeed, some reports support this hypothesis [14, 30, 48], and other reports were not in favor of this hypothesis (e.g., [4]). A recent meta-analysis [19] was unable to draw clear conclusion on the whole body of investigations.

Motivated by the ethnic differences in allele frequencies in this 5HT1A polymorphism between Caucasians and Asians, ethnicity-specific analysis was performed: Asian samples provided evidence that the G/G genotype carriers had a better response in Asians (OR = 4.3!) [19]. In a first view, this result in Asian populations is counterintuitive to the outlined physiological implications. The meaning and stability of this ethnic-specific association remain elusive.

Genes modulating neuronal serotonergic levels

TPH1 and TPH2

Serotonin is synthesized from noradrenaline through the enzyme tryptophan hydroxylase (TPH) which is occurring in two isoforms TPH1 and TPH2; both isoforms are active in the brain—particularly TPH2. The TPH1 gene carries a DNA-variant 218A/C in a potential transcription-factor binding site with a putative effect on gene expression. This ideal candidate gene received intensive pharmacogenetic attention:

All available nine studies in Caucasian and Asian populations on the impact of the TPH1 gene on the response to antidepressants explored the 218A/C polymorphism: two studies report the CC genotype to predict beneficial response; the remaining investigations did not report significant differences. Among these nine studies, altogether seven fulfilled minimal requirements and were recently submitted to a meta-analysis (about 750 patients): significantly, more responders were found among carriers of the C/C genotype of the 218A/C polymorphism (OR 1.62, [1.15; 2.27]) [19]. Yet, conclusions remain uncertain, as a recent comprehensive study, GENDEP, did not confirm this TPH1 hypothesis [56]. In contrast to TPH1, the TPH2-gene variants received less attention (only two pharmacogenetic studies with antidepressants without consistent results).

Serotonin modulation enzymes: BDNF

Brain-derived neurotrophic factor (BDNF) impacts on the pathogenesis of depression, it is also involved in the mechanism of action of antidepressants [35, 47]. Stress and depression decrease BDNF secretion and BDNF trafficking; furthermore BDNF inhibits the presynaptic uptake of serotonin (like SSRIs) [59]. The BDNF gene carries a coding

DNA-sequence polymorphism (66 val/met): the met allele produces higher BDNF activity [4] and reduces the 5HT uptake; the netto effect is an increased extracellular 5HT level [37]. Antidepressants increase the BDNF secretion; thus, the met variants act like an inbuilt antidepressant.

Several recent studies investigated this hot candidate gene polymorphism [8, 11, 53, 60, 61] and some of them found the met variant to predict response. A recent meta-analysis [19] was able to combine the informative studies applying this polymorphism (about 490 patients) and obtained a moderate effect (OR = 1.63 [1.08–2.46]) on response to antidepressants in favor of the met–variant. Yet, clear advantage of the met/met homozygote was not detected. A more recent study, not included in this meta-analysis—the GENDEP study with $n = 811$ patients—did not confirm the proposed advantage for the met allele carriers [56], like another smaller study [9]. Therefore, the evidence in favor of a beneficial role of the met variant is dubious.

Noradrenaline transporter genes and related genes

The noradrenaline transporter (which is coded by the SLC6A2 gene) presents a crucial element in the response to noradrenaline-reuptake inhibiting antidepressants. Several treatment studies with noradrenergic drugs report associations with different markers in the SLC6A2 gene. These studies, unfortunately, genotyped different not overlapping sets of markers in this specific gene: Uher et al. [56] report association of the functional marker rs185067 with response to nortriptyline; this specific polymorphism induces an amino-acid exchange and influences splicing in an European sample; another marker in weak linkage disequilibrium with the aforementioned variant, rs5569, was also related to the response to nortriptyline in a Korean Sample [20].

A further study with the SNRI milnacipran [20] reports an association to a promoter polymorphism rs1287A in the Asian population. This marker is not linked to the aforementioned other two markers in the SLC6A2 gene.

Thus, there is no convincing replication for the impact of SLC6A2-gene variants on response to noradrenergic or more general antidepressant drugs. Given the very limited number of published reports on SLC6A2 pharmacogenetics, conclusions are not possible.

Dopamine-metabolizing enzymes: COMT

The COMT enzyme degrades dopamine particularly in the forebrain. Brain norepinephrine release is reduced in depressed subjects—particularly in treatment-resistant patients [25]. Brain dopamine release was also recognized to be reduced among treatment-resistant depressed subjects [25]. Dopamine has a well-recognized role in antidepressant treatment. The COMT gene carries an intensively studied polymorphic site 473G/A resulting an amino-acid substitution 158 val/met with the val allele conferring a three- to fourfold increase of enzyme activity (resulting in a decreased dopaminergic tone). Controversial evidence was obtained for the role of the COMT-met/val polymorphism in response to antidepressants: two studies showed a poorer and slower response of the met/met homozygous variant to mirtazapine and SSRI [1, 51]; a more recent study found a negative effect of the val/val variant when using a broad variety of antidepressants for 6 weeks [5]. A recent report on the antidepressant mirtazapine in a Japanese cohort also detected a significant relationship between the met/met variant and a faster therapeutic response [62]. Subsample analyses [51] demonstrated a considerable variation of the effects across various antidepressant substances. Compatible with this interpretation, a recent pharmacogenetic study in 250 duloxetine-treated European depressive patients was unable to detect an association between response and the rs4680 polymorphism [44]. Furthermore, the relationship between the dopaminergic tone and response to serotonergic/noradrenergic antidepressants may be U-shaped resulting in dose-dependent effects of the 158 val/met polymorphism. Thus, there is no evidence for a role of the COMT-met/val polymorphism in the response to antidepressants.

Glucocorticoid and related genes

Extensive evidence suggests that the modification of hypothalamic pituitary adrenocortical (HPA) system activity is a core element of the mechanism of action of antidepressants [13]. The stress reagibility of the HPA system is driven by the glucocorticoid receptor (GR) which is integrated in a heterocomplex—together with other proteins as the heat-shock co-chaperon FKBP5. The FKBP5 gene carries a large variety of non-coding polymorphisms; their pharmacogenetic implications were explored and five polymorphisms were observed to predict the response to 5-week antidepressant treatment conditions in a sample of patients with unipolar depressive and bipolar disorder under naturalistic antidepressant treatment in Germany ($n = 294$); a second independent sample ($n = 170$) was investigated by the same group and the initially obtained associations turned out to be replicable [7]. The antidepressant drug treatment protocols were, however, not standardized in both samples and applicated drugs varied across multiple substances. In the STAR*D study using only citalopram over 12 weeks two of the associated FKBP5 markers could be confirmed as predictive for better response (rs1360780, rs4713916) in the white non-hispanic subsample; the same markers also predicted remission in the STAR*D study [29].

The prediction of short-term response by marker rs1360780 was also corroborated in a smaller German sample [22], but not so in another German sample [63]. Convergent evidence for the functional relevance of the associated variant rs1360780 was also obtained in gene-expression studies: an associated variant is accompanied by increased FKBP5 expression in a lymphocyte-based in vitro model [7].

Other "hot" candidates are the genes coding for the GR and for the corticotropin-releasing hormone receptor 1 (CRHR1); both structures have been recognized as modulators of the response to antidepressive drugs (probably for all effective substances). The CRHR1 gene hosts a three-SNP haplotype that predicted response to antidepressant treatment, particularly for anxiety-related outcome measures in two independent studies [32, 33]. Further confirmations are required.

Functional GR-gene variants with an influence on gene expression were identified and explored for their impact on drug response. Indeed, variants coding for a reduced GR-gene expression were found to be associated with a beneficial response to antidepressants in one study [58]; results emerging from previous smaller studies are not fully consistent; the underlying sample sizes are too small to draw valid conclusions. The recently published GENDEP study did not support the initial findings by van Rossum et al. [58] in a more extensive sample—albeit nominal association were found for other variants in this gene [56].

Glutamatergic receptors

The STAR*D study selected 68 candidate genes with a large number of SNPs and detected two genes with variants

(a) showing significant association with (categorically defined) response and/or remission in the discovery sample, as well as
(b) confirmation in the replication sample, and
(c) maintaining significance after control for multiple testing.

Besides the aforementioned 5HT2A-receptor gene variants only one other SNP, an intronic SNP of the glutamate receptor subunit Kinate 4 (GRIK4), met these requirements [42]. This result supports the speculation of the involvement of the glutamate receptor in the action of antidepressants. Yet, further replications are needed.

Conclusion

The conclusion is disappointing given the early hopes in the pharmacogenetics approach [24]. Meta-analyses uncovered only three predictive DNA-sequence variants for clinical response/remission (5HTTLPR, TPH1 218C/C, BDNF 66 val/met) each with only a modest effect size; in addition, recent large-scale studies highlight 5HT2A intron2 markers as replicable predictors. Higher rates of side effects go together with specific variants in 5HTTLPR and 5HT2A promoter. Yet, these results have to be considered on the background of broad design heterogeneity.

Several reasons account for the currently sparse knowledge on the pharmacogenetics of antidepressants with regard to pharmacodynamic endpoints:

(a) *Lack of standardization:* consensus is needed for length of treatment, endpoint definition, adjunct treatment, time points of measurement, handling of dropouts, and adjunct treatment compliance/control.
(b) *Lack of specifically designed studies:* studies specifically designed for pharmacogenetics and standardized treatment protocols are extremely rare.
(c) *Lack of power:* the obtained multiple associations always reveal an only modest effect size; the sample sizes which are able to detect a signal of this magnitude with sufficient certainty should exceed $n = 400$ under monotherapy; only two studies dedicated to antidepressants meet this requirement (GENDEP, STAR*D).
(d) *Lack of hypothesis-free genomic approaches:* the currently exclusively practiced candidate-gene approach in published pharmacogenetic studies only explored the impact of a relatively small number of genes (substantially less then 100 among 20,000 genes) and might have missed the most important genes.

Alternative unbiased, hypothesis-free approaches recently became feasible. Particularly genome-wide association studies (GWAS) and the search for influential copy-number variations provide possibilities but were not yet published. Yet, at least two GWAS on response to antidepressants are currently under way [18].

Up to now, the understanding of the genetic influence on pharmacodynamics of antidepressants has just started. All available replicated genetic associations remain uncertain and are of very limited effect size. Therefore, these findings are unable to guide clinical decisions. Thus, the genetic prediction of the pharmacokinetics of antidepressants currently remains the only relevant field of clinical applications of pharmacogenetics.

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