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Contribution of allelic variations to the phenotype of response to antidepressants and antipsychotics

Abstract Individualized medicine through molecular pharmacogenetics is one of the major future goals in clinical medicine. In psychopharmacology, pharmacogenetics became an expanding research component. Major research results were already attained: first, it is now feasible to predict a major proportion of the interindividual variation of plasma levels of most antidepressants and antipsychotics by using the DNA-sequence variation in genes for crucial CYP P450-enzymes as CYP2D6. Second, it is now possible to relate serious side effects (tardive dyskinesia, weight gain) of antipsychotics to specific genetic variants of genes for target proteins. Third, a long list of mainly functional variants in target protein genes was explored for their predictive power for the beneficial and adverse treatment outcome. Although specific results transferable into clinical practice were not yet obtained in this respect, the proof of principle could be demonstrated.

Key words pharmacokinetics · pharmacodynamics · antidepressants · antipsychotics · side effects

Individualized medicine was one of the great promises of molecular medicine at the turn of the last century [8]; the adaption of therapies to the individual patient by means of genetic and other molecular tools. There are large differences of drug effectiveness from one patient to the next, which cannot be attributed to dosage, co-medication, specific disease variants or apparent clinical features; thus, this predicted possibility would be a benefit of utmost

importance. This possibility is of particular relevance for psychiatry as:

1. medications are still allocated to an individual by a trial-and-error principle in absence of known clinical predictors of response;
2. a substantial proportion of patients (at least 20% in depression or schizophrenia) cannot profit sufficiently from any specific medication and are therefore at a high risk to develop enduring complaints and impairments and a chronic course of the disorder;
3. a major proportion of patients experience serious side effects compromising compliance and inducing termination of needed treatment.

The DNA sequence variation hosts such an enormous degree of variability that two subjects (who are not monozygote twins to each other) are genetically not identical; therefore, molecular genetics offers an opportunity to explain and predict interindividually variable drug response patterns. A precondition for realizing this goal with pharmacogenomic/-genetic tools is that genetic factors determine the therapeutic response and the emergence of side effects by psychotropic drugs. The classical phenotypic tools (e.g. analysing familial resemblance of drug effects by family or twin studies) were only rarely used; in order to prove this assumption, only very few studies, mainly on prognosis under lithium therapy or on the occurrence of extrapyramidal side effects under classical neuroleptics, were performed. Thus, the empirical a priori evidence for strong genetic forces influencing psychotropic drug effects in individuals is slim. Yet, it is generally believed that major genetic factors are operating because of the enormous DNA sequence variability in target sites, metabolizing enzymes and transport proteins of drugs [37].

Pharmacogenetics in treatment of acute episode focuses on various phenotypes:

1. Primary pharmacodynamic response measures are beneficial treatment effects mediated through target

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sites and resulting in remission and recovery or—as a substitute—in changes in measures of efficacy or effectiveness during treatment or at the endpoint; other derived phenotypes are time to response or processes impacting on delivery of drugs to the primary targets, which mediate the response pattern (i.e., receptors in the brain).

- Another primary pharmacodynamic response measure are side effects either as specific side effects or as global, i.e., combined measures of side effects at any time during treatment.
- Intermediate measures are pharmacokinetics, which can be attributed to biotransformation (metabolization) into metabolites or transport processes, moving active substances or active metabolites to the target sites. Plasma levels of substances or of active metabolites are the most widely studied phenotypes in this respect; they are of particular interest as they trigger elevated risks of side effects or of ineffectiveness.

Pharmacodynamics and pharmacokinetics are driven by very different tissues and systems. Thus, it does not come as a surprise that they reveal distinct genetic architectures. Pharmacodynamic targets display a genetic influence of unknown magnitude emerging from the activity of multiple genes, each with assumably only a small effect; on the other hand, pharmacokinetics reveal a documented strong genetic determination, which is mainly influenced by variants in a few genes (Fig. 1).

Currently, psychopharmacogenetic results that translate into clinical practice were mainly or even exclusively obtained for pharmacokinetics. We exemplify the current status of knowledge by antidepressant and antipsychotic treatment of acute episode. When reporting empirical results, we will focus only on those gene–drug–response relationships,

which turned out to be at least partly reproducible and to be of current or future clinical interest.

Genes influencing pharmacokinetics

Most drugs are biotransformed by enzyme systems [15]. Metabolizing enzymes frequently reveal genetic variation with functional relevance resulting in different enzyme activity. An enzyme with a reduced activity is called “poor metabolizer”. The relevance of poor metabolism of drugs for adverse effects was convincingly demonstrated by a recent systematic review on those medications, which are frequently cited in adverse drug reaction studies: 59% of drugs with major adverse effects are metabolized by at least one enzyme with allelic variants known to cause poor metabolism; in contrast only 7% of randomly selected drugs are biotransformed by enzymes with genetic variants causing poor metabolism [34].

■ The CYP P450-system

The main focus of previous research was on the CYP P450-systems, which metabolizes the majority of antidepressants and neuroleptics in the first phase in the liver to mainly inactive metabolites (exception e.g., risperidone with an active metabolite). The speed of biotransformation determines the plasma levels of the active substances. Other biotransformation systems are less well investigated.

The CYP P450-system [21] hosts about 50 enzymes with CYP2D6, CYP 2C19, CYP 3A4 and CYP 1A2 as the most important ones for antidepressants and antipsychotics. Drugs can be metabolized by one or several of these enzymes. Most of the drugs (~50%),

Fig. 1 Pharmacokinetics and pharmacodynamics are determined by different underlying genetic architecture

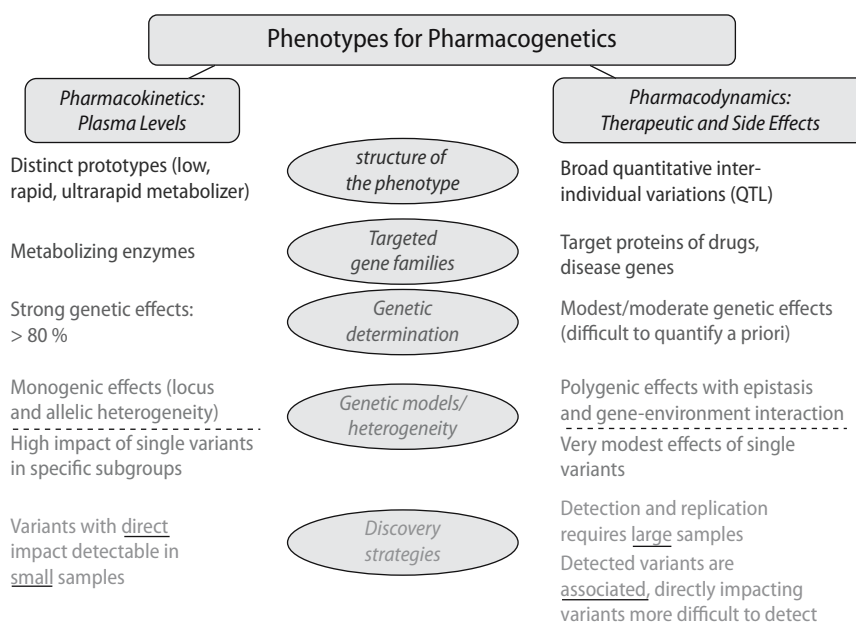
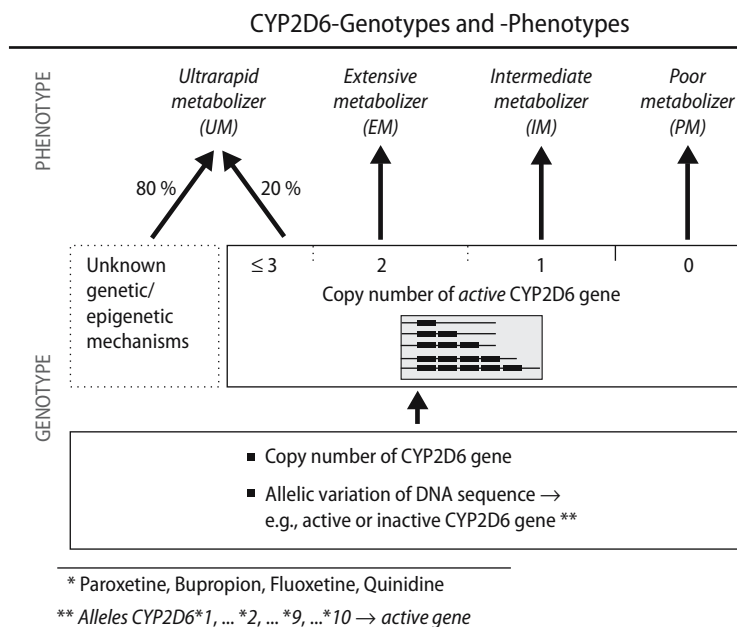


Fig. 2 Genetic variability in the CYP2D6-gene determines distinct phenotypes of drug metabolism



including 80% of antidepressants and antipsychotics, are degraded by CYP2D6, although this enzyme is less prevalent in the liver compared to other members of the CYP P450-family. Drugs not metabolized by CYP2D6 are citalopram, reboxetine, moclobamide and amisulpride. The degree of dependence of plasma level of mirtazapine from CYP2D6-enzyme is controversial [16]. The second major CYP P450-enzyme is CYP2C19, which also degrades a substantial proportion of drugs in clinical use. Among antidepressants, citalopram and moclobamide are degraded by the CYP2D19-enzyme; common antipsychotics are not affected by this enzyme.

The CYP2D6-gene hosts an enormous genetic variability: there are more than 70 functionally relevant alleles; 15 loss-of-function alleles deliver inactive isoenzymes; duplications of active alleles deliver overactive isoenzymes (Fig. 2). Functionally relevant genetic variants in 2C19 have less impact on plasma levels; therefore, we will not further discuss this enzyme.

Another major enzyme, CYP3A4, metabolizes about 50% of all currently used medications including selected antidepressants and antipsychotics. The CYP3A4 gene is not submitted to relevant functionally relevant DNA-sequence variations.

■ CYP2D6

The broad genetic variation of the CYP2D6-enzyme induces a broad interpersonal variability of the CYP2D6-enzyme activity, which can be measured by the ratio of the CYP2D6-dependent-probe drug (e.g., dextrometorphan) to its metabolite (dextrorphan). The distribution of the CYP2D6-enzyme activity can be split into three or four qualitative components, which were initially discriminated on the phenotypic

level in an easy way by the so-called spartein test: poor (PM), intermediate (IM), elevated (EM) and ultrarapid metabolizer (UM); intermediate (IM) and elevated (EM) metabolism status may be combined into one component. Poor metabolizer results from homozygotes with two inactive alleles and ultrarapid metabolizer from at least one gene duplication of an active allele. In Europe, 7% of the population are PM and about 5% are UM.

CYP2D6 polymorphisms and particularly the frequency of variants coding for accelerated metabolism (UM) reveal a high degree of variation across populations. The reason is that the duplication and expansion of active CYP2D6-alleles provide an evolutionary advantage under conditions of starvation: these variants have an increased potential of detoxification of certain food components (fruits), thus providing more energy for subjects with UM. As a result, duplications of active alleles and the UM-phenotype were under selection pressure during evolution with functionally overactive CYP2D6-variants being favored during periods and at places of food restriction. Those places were preferentially located in Africa, where the UM phenotype became more common (≥ 10 –20%) compared to Northern Europe (≤ 5 %) [22]. One consequence of this DNA sequence variation across population might be ethnic-specific, beneficial and adverse drug responses, which were indeed observed in clinical trials of drugs with a CYP2D6-dependent metabolism [14].

Today, the most important function of CYP2D6 for humans lies in lessening the detoxification of food components, but much more in the metabolism of drugs. Poor metabolism produces high plasma levels of the prescribed substance with an increased risk for toxicity and serious side effects if the substance is the active component. Ultrarapid metabolizers reveal a

substantially reduced plasma level of the substance of the same oral dose. The lack of effectivity may be a consequence if the substance is the active component because of the failure of therapeutic plasma levels. Therapeutic windows are particularly established for the classical tricyclic antidepressants (TCAs), whereas the serotonin reuptake inhibitors (SSRI) display a flat plasma level—response curve and “therapeutic windows” cannot be established in a robust manner. Thus it can be predicted that the ultrarapid (UM) metabolizer status is especially associated with inefficient drug levels under TCA treatment [7]—at least if the prescribed dosage is not adapted for accelerated drug metabolism. SSRIs are less prone to inefficacy in UM subjects because of accelerated metabolism, given the flatter dose response curve. Yet, the majority of pharmacogenetic studies focusing on the CYP2D6-gene deal with SSRIs; thus, the very likely major impact of UM-status on TCA is not well documented.

Pharmacoepidemiological studies in commonly used CYP2D6-metabolized antidepressants confirm these predictions: The variability of plasma levels are nearly exclusively determined by the CYP2D6-genotype after control for oral dosage and interactions. The majority of serious adverse effects occurring in clinical routine with treatment when prescribing CYP2D6-dependent SSRIs can retrospectively be traced back to functionally inactive or overactive genetic CYP2D6-variants on a casuistic level [9, 17]. However, the CYP2D6 polymorphism was in comparison to other genes not always the major genetic determinant for SSRI-related side effects or treatment discontinuations [32]. Several reports also demonstrate extrapyramidal motor symptoms and drowsiness emerging under classical CYP2D6-dependent neuroleptic drugs as haloperidol, thioridazine or perphenazine are going together with PM-status [6, 11, 44].

The reverse pharmacokinetic pattern occurs if the metabolite emerging from CYP2D6 biotransformation is more active than the substance itself. This is the case with codein, which is transformed to its more active metabolite, morphine: UM results in exaggerated side effects, and PM in reduced efficacy. This response pattern, however, does not occur among antidepressants or antipsychotics (risperidone presents, however, partly an exception, as this active substance is degraded by CYP2D6 to an also active metabolite).

Predictive CYP2D6 genotyping is therefore proposed to improve drug dosing in the individual patient: Individualizing dose escalation schemes have been developed both for antidepressants and antipsychotics, which are based on the distinction of PM, UM and others. Depending on the impact of the CYP2D6-enzyme activity on the metabolism of a specific drug, dosage recommendations propose to prescribe 30–70% dose reduction on PM and 135–180% dose elevation in UM patients for the CYP2D6-

dependent antidepressants and neuroleptics [24]. Another practical consequence in identified poor metabolizers (due to 2D6 or 2C19-gene variants) might be in selecting drugs, which are not metabolized by the CYP450-system as reboxetine, amisulpiride or sulpiride [12].

Yet, it is noteworthy that up to now no prospective randomized controlled study has proven the clinical superiority of genotype—adjusted dosing in antidepressants or neuroleptics compared to the current clinical practice. A more conservative procedure identifies poor and rapid metabolizers retrospectively in a therapeutic drug monitoring (TDM)-approach by plasma level measurement and subsequent readjustment of prescribed dosages if needed.

Despite this current lack of evidence, a commercial chip array was recently introduced to identify UM and PM based on the DNA-sequence variation in the CYP2D6-gene. The metabolism status can thus be quickly recognized, and genotype adjusted dosing becomes clinically feasible before starting treatment. This strategy is clearly more convenient than the classical genotyping approach for determining genetic variants of CYP2D6. This approach, however, is less sensitive than the classical spartein test in identifying UM-variants on a phenotype level, as only 80% of the carriers of the UM-phenotypes can be identified by known allelic variants.

In practice, the CYP2D6-enzyme and its genetic variants are particularly relevant for combined treatment with those drugs, which also interact with CYP2D6. Several SSRIs inhibit CYP2D6 (particular strong inhibitors are fluoxetine and paroxetine): thus, co-administration of one of these drugs might change a person with the status of UM, IM, or EM into a PM status independent of the individual genotype. This is particularly the case if the additionally administered drug is exclusively metabolized by CYP2D6 and by no other enzyme. If a CYP2D6-dependent drug is additionally administered under this condition, its plasma levels will increase and adverse drug effects might occur under the unadjusted dosage.

Promising new candidate genes for pharmacogenetics of psychotropic drugs are coding for transport proteins at the blood–brain–barrier. First consistent results from clinical trials and animal models were obtained for genetic variants of the transport protein MDR1 (now called ABCB1/p-glycoprotein). Yet replications for the targeted drugs in humans are needed to draw valid conclusions [5].

Genes influencing pharmacodynamics

■ Antidepressants

Drug effects are mediated by a vast variety of pathways and systems hosting substantial genetic varia-

tion. This scenario offers a large bulk of hypotheses of specific polymorphic genes influencing drug response through differential effects of their functional genetic variants. Genes coding for polymorphic target sites of an effective substance received priority attendance in this respect.

Among antidepressants, particularly genes coding for receptors or transporters in the serotonergic system received most study. In particular, the potentially functional promoter repeat polymorphism of the serotonin-transporter gene—5HTTLPR—was examined as modulator of response to antidepressant treatment with SSRI: A “short” variant “s” of this promoter component causes an underexpression of the receptor *in vitro* compared to the “long” allele “l”. The short variant is postulated to go together with inferior response to SSRI treatment and the “long” variant (or homozygote with long variant) goes together with more beneficial outcome under SSRI. This hypothesis is, however, somewhat paradoxical, as underexpression of the transporter is mediated by the short promoter variant, which is like having an inbuilt serotonin-transporter inhibitor. Thus, it is difficult to understand that SSRI-treatment under this specific genetic conditions (“s”-variant) should result in a less beneficial antidepressant response.

Despite this lack of plausibility of homozygosity, a recent meta-analysis combining all publications till 2006 suggested that homozygosity for the short promoter variant (s, s) of the 5HTTLPR is associated with a reduced (OR = 2,4) remission rate and that homozygosity for the long promoter version (l, l) is associated with increased response rates within 4 weeks to antidepressant SSRI treatment (OR = 1,75) among Caucasians (combined sample size up to $n = 750$) [42]. However, the biggest study in this field—the STAR *D study in a non-Hispanic sample ($n = 1131$) and a Hispanic sample ($n = 524$) in the US – was published later in 2007 and did not find an effect of this polymorphism on the antidepressant effect under the tested SSRI citalopram [20]. This result was also obtained in the Hispanic subsample of the same study. Given the enormous sample size of this study, a remake of the meta-analysis in 2007 would probably come out without a significant advantage for l/l or a disadvantage for s/s with regard to the antidepressant SSRI-effect. Thus, currently there is no equivocal evidence for 5HTTLPR-polymorphism to modulate the antidepressant effects of SSRI treatment in the Caucasian population.

However, this conclusion might depend on the ethnic background: First the non-Hispanic STAR*D-sample combines white and black patients and does not provide a separate analysis for Caucasians and thus comparability to Serretti’s meta-analysis is hampered. Second, the meta-analysis by Serretti detected an even stronger impact of s/s and l/l on remission and response in Asians (same direction as among Caucasians in Serretti’s study) than among

subjects with European descent. This conclusion for Asians is currently not challenged by an additional major study.

In contrast to the wanted, beneficial antidepressive effect, the STAR*D study found the short variant of the 5HTTR-promotor polymorphism to be predictive for the global burden of side effects. Unfortunately, the relationship between 5HTTLPR-polymorphism and side effects under SSRI-treatment is not as extensively studied as the antidepressant effects in other studies. Yet, a few exceptions report for “s”-carriers an increased discontinuation rate under SSRI-treatment [13]. Altogether, it remains a possibility that both outcome components i.e., antidepressant effect (measured by change in severity of depression) and side effects get mixed in the repeated assessments during treatment. Thus, an ambiguity of results may be obtained and might explain the controversial results among Caucasians.

Another possible reason for this blend of mixed results is that the 5HTTLPR-polymorphism only insufficiently covers the functionally relevant DNA-sequence variability at this site. And, indeed, recently two SNPs in or in close neighborhood to the promoter region were identified, which might be functionally relevant by themselves [19, 25].

An additional common SNP allele in the long 5HTTLPR allele reduces RNA expression of 5HTT on a level comparable to “s” [19]. It is postulated that the G allele of this SNP changes the functional status of the “l” allele in the 5HTTLPR; thus, the combined lg variant should be associated with SSRI non-response if underexpression of the 5HTT goes together with a worse outcome. Yet, this refinement of the polymorphic 5HTTLPR site did not change the negative STAR*D result with regard to antidepressant SSRI response [20]. Additional studies taking this additional DNA sequence variation into account are currently not published. Another SNP rs25531, detected just upstream of the 5HTTLPR, is of putative functional relevance and found in association with SSRI response [33].

Therefore, additional variation at this promoter site has to be considered. Thus, the impact of the 5HTTLPR polymorphisms on the treatment response under SSRI remains under discussion and requires further study. An application of these results to designing individual antidepressant treatments is currently not viable.

Another repeatedly investigated polymorphic gene coding for a serotonin-related target site of antidepressives is the 5HT2a-receptor gene. Downregulation of this postsynaptic and widely distributed receptor was postulated as a common feature of all antidepressants. This receptor is similarly antagonized by a majority of classical and atypical neuroleptics. This receptor gene receives particular attention through exciting results emerging from the STAR*D study [30]. The sizeable sample of this study allows to be

split in a sufficiently powered discovery subsample and a distinct validation subsample. By these means, 68 competing genes with 768 tested variants could be explored for prediction of response and a single anonymous variant in the 5HT2a (rs7997012) came out as the only one with replicable significant predictive power for response to citalopram in unipolar depression among the white patient population. A further validation of this unexpected finding is that the allele going together with less favorable response at this specific site is more common among blacks, who respond less well to citalopram than whites. However this polymorphism was not related to the treatment outcome in blacks. Instead, another 5HT2a variant, rs6311 (alternative name: marker 102T/C), revealed a trend of association to treatment outcome in blacks. Markers rs7997012 and rs6311 are, however, not dependent on each other (i.e., not in linkage disequilibrium) [19]; thus, the findings for the white and the black subsample are not related to each other. Previous pharmacogenetic investigations of the 5HT2a-receptor gene with regard to antidepressant treatment response never investigated the marker rs7997012; instead functional variants as marker 102T/C (rs6311 in exon1) were tested for impact in response to antidepressants and to antipsychotics (particularly to clozapine). The C variant at 102T/C was found to be associated with less favorable antidepressant response [10, 31, 38] and with treatment discontinuation under SSRIs, but not so for mirtazapine [32]. As mentioned before, these findings were not supported by the biggest study in this field (STAR*D). Currently, it remains difficult to draw valid conclusion on the relationship between variants in the 5HT2a gene and antidepressant response. This gene, however, remains a most relevant target for future pharmacogenetic research. In this respect, it is also noteworthy that the C-variant at rs6311 (resp 102T/C) was detected as predicting an increased rate of tardive dyskinesia in response to neuroleptics treatment [41], but not consistently so [4].

Further genes, which were initially shown to be implicated in the modulation of antidepressant response received a few replications: TPH1 and G-protein $\beta 3$; however, the evidences are still too limited to draw definite conclusions [5]. All other genes explored for prediction of response to antidepressant treatment did not deliver consistent or replicated results. Some genetic polymorphisms are “hot candidates” with promising initial results, but without published replications (e.g., FKBP5, Glucocorticoid-receptor gene) [5].

■ Antipsychotics

Pharmacogenetics of antipsychotics is the most extensively investigated area in psychopharmacogenetics. The genes coding for target proteins of neuroleptics were extensively studied since 1995: genes

for D2-, D3-, and D4-receptor and for the 5HT2a- and 5HT2c-receptor. Response to clozapine received most interest in the past.

As all antipsychotics are D2-receptor blockers, the highly polymorphic D2-receptor gene attracts priority interest. A specific polymorphic site in the D2-receptor gene, the 141-Ins/Del was explored in several studies and populations (Asians, Caucasians): the Del-allele predicts less beneficial response [26, 46], but not consistently so [29]. The Del-variant is putatively functionally relevant, as it goes together with increased striatal receptor density and as it might modify the expression of D2-receptor in an area-specific fashion [23].

Another functional polymorphism is located in the D3-receptor gene Ser9Gly. The Gly variant predicts less improvement [36] in several, but not all, enquiries [3]; the same variant also goes together with tardive dyskinesia in a majority of studies, as evidenced in a meta-analysis [27]; the reported odds ratio was 1.8. This Gly-variant might have a functional meaning in vitro (higher dopamine binding to the receptor), which is, however, difficult to reconcile with its relationship to an unfavorable outcome in antipsychotic treatment [28].

In the 5HT2a receptor gene, different polymorphisms were explored, 102T/C and 1438 G/A, which are both in linkage disequilibrium. Another most frequently explored polymorphism is Hrs452Tyr. The most consistent result emerged from a previous meta-analysis for the Hrs425Tyr site with a relatively high odds ratio (5, 5) for the Tyr variant with regard to poor response to clozapine [1]. Functionally, this allele has been proposed to lower calcium release of cell, which might limit the effect of antipsychotics. Other 5HT2a polymorphisms were either not predictive (as 102T/C) or not sufficiently studied in the context of antipsychotic treatment.

The strongest predictive power ever found in pharmacogenetics of antipsychotic response emerged already in 1995 at the 5HT2 C-235 site in the 5HT2c-gene: Ser was associated with good response to clozapine (OR = 6,4) [43]. This finding, however, was never replicated. Interestingly, in further investigations the ser variant was observed to interact with the Gly allele at the D3-receptor Ser 9Gly site to induce tardive dyskinesia [40].

These two strong associations between 5HT2a and 5HT2c receptor gene polymorphisms and clozapine response created together with other less strongly associated variants the basis for a composite score, which should reveal a very high predictive power for beneficial response to clozapine [2]. Yet this prototype failed to be confirmed in independent samples [39]. Despite this negative conclusion, the principle to combine genetic variants each with moderate effect on treatment outcome into a combined score with a stronger predictive power will probably be very useful in the future.

A very strong, at least partly replicated, pharmacogenetic finding related to the pharmacodynamics of antipsychotics is reported for the phenotype weight gain. The 5HT2c receptor gene (located on the x chromosome) is apparently a very “hot” candidate in this respect: knockout of this gene in mice results in obesity and increased feeding [45]. Furthermore, genetic studies in patients with diabetes mellitus type II and obesity found associations between this phenotype and sequence variants in the promotor area of 5HT2c-gene. This constellation prompted [35, 47] to investigate the promoter polymorphism 5HT2c-759C/T in relationship to weight gain under antipsychotics. The maximal risk for antipsychotics-induced weight gain was described for the wild-type variant C in a Chinese population with an odds ratio of 6 [35]. Although not consistently so, the majority of subsequent eight investigations (also in European populations) proposed qualitatively the same result with lower odds ratios [3]. This finding is particularly interesting in the light of previous investigations in other non-promotor-related DNA sequence variations of the 5HT2c-gene (including the C23S variant), which were not associated with induced weight gain (review in: [18]). Thus, there is considerable evidence that the promoter region in the 5HT2c-gene and its DNA-sequence variation is involved in antipsychotics-induced weight gain. As gene expression is regulated through promoter sites, it can be speculated that the underlying mechanism is mediated through differential expression of the 5HT2c-gene. It is tempting to speculate if a similar constellation is also observed for weight gain under antidepressants as TCA or mirtazapine. Unfortunately, those studies are currently not available.

Taken together, specific genetic variants provide a stronger predictive power for serious side effects as tardive dyskinesia or weight gain under neuroleptics than for the general psychopathological outcome.

Conclusion

The molecular era in psychopharmacogenetics started 15–20 years ago. The main results of impact for clinical practice obtained during this period are related to pharmacokinetics:

- a) identification of DNA-sequence variation in enzymes of the CYP P450-system as determinants of plasma levels for the vast majority of antidepressants and antipsychotics;
- b) genetic determinants in the CYP P450-system causing low or exaggerated plasma levels account for a practically relevant proportion of failures to respond and of serious side effects and lack of compliance; yet, other genetic determinants are also relevant in this context;
- c) the availability of first commercial chip arrays allows the translation of genotype-based individualized

treatment planning in clinical practice, in order to optimize prospectively antidepressant and antipsychotic treatment through control of plasma levels.

Prediction of beneficial and adverse outcomes by genes involved in the pharmacodynamics of drugs turned out to be substantially more difficult than prediction of plasma levels by pharmacokinetically relevant genes. One reason for this discrepancy might be that in pharmacokinetics genes, with major effects, the CYP2D6-gene operates, whereas the contribution of each of the involved pharmacodynamically relevant genes might be of only minor magnitude. In agreement with this suggestion, very modest, confirmed risk ratios were obtained for all replicable effects of alleles on the treatment outcome. This is particularly true for the general psychopathologically defined outcome, and less so for the serious side effects. Although it was evident that prediction of response by genetic information was feasible, the results for pharmacodynamically relevant genes (beyond pharmacokinetics) that can now be implemented in clinical practice or clinical prototypes have not yet been obtained. It is also to be conceded that appropriate prospective clinical studies designed for these specific pharmacogenetic purposes are currently very limited. Meta-analyses are currently used as a substitute in order to increase power and to explore gene effect of moderate to minor magnitude; yet, the retrospective combination of initially not standardized studies also introduces biases and losses of power. The application of the emerging, more effective tools to identify outcome-related DNA-sequence variants (as genome-wide association analysis) requires those extended, prospectively investigated samples, which were missing in the past. Fortunately, those samples and studies are now being established. The combination of pharmacogenetically informative prospective clinical studies and the expanding tools to identify predictive genetic variants will soon create new opportunities for individualized medicine in pharmacopsychiatry.

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