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Individualized Medicine – Implementation of Pharmacogenetic Diagnostics in Antidepressant Drug Treatment of Major Depressive Disorders

Original Paper

Antidepressant drug therapy is characterized by a high rate of therapeutic failure. There is increasing evidence that genetic factors are contributing to the inter-individual variability in antidepressant drug response. Genetic variability is described in both the pharmacokinetic part of drug action as well as in pharmacodynamic structures mediating drug effects. Genetic polymorphisms in drug metabolizing enzymes are well characterized and have large effects on oral clearances or elimination half-lives of antidepressant drugs. These differences can be compensated by adapting the individual dose to genotype in addition to other factors such as gender, weight, age, liver and kidney function. On the part of drug action, genetic variability is described in molecular structures of antidepressant effects. Several studies on response of antidepressants have revealed influences of polymorphisms in neurotransmitter receptors and transporters changing sensitivity of patients to treatment with antidepressants; however, results were often contradictory. A pharmacogenomic approach to individualize antidepressant drug treatment is recommended to be based on several levels: 1) identifying and validating the candidate genes involved in drug-response; 2) providing therapeutic guidelines; and 3) developing a pharmacogenetic test-system for bedside-genotyping.

Key words
Major depressive disorder · antidepressants · pharmacogenetics · pharmacokinetics · cytochrome p450 enzyme · lab-on-a-chip · individualized medicine

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Introduction

Treatment resistance in antidepressant drug therapy
Major depressive disorder (MDD) is a severe mood disorder associated with significant morbidity and mortality that affects individuals of all ages and ethnic backgrounds. It occurs in about 5 – 10 % of the adult population during any one-year period of time, with women at a two-fold higher risk than men [1]. For the majority of patients, depression represents a chronic or recurrent condition with a recurrence probability of 13 % during the first six months and 87 % after 15 years [2]. Antidepressant drugs constitute the first-line treatment for the acute and long-term treatment of MDD [3]. However, up to 30 – 40 % of patients do not respond sufficiently to the first prescribed antidepressant drug [3,4]. Failure to respond to antidepressant drug therapy, as well as intolerable side effects, imposes not only personal suffering to individuals and their families but also considerable costs on society. At present, there is no possibility to reliably predict the individual's response probability before onset of a certain drug treatment.

Genetic variability influencing drug response

Substantial data assessing genetic influences on response probability to certain drugs already exist [5]. For antidepressants,

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most studies refer to genetic variability in drug metabolism [6,7], since plasma concentrations and efficacy of antidepressants vary considerably among patients even if treated with similar doses. However, drug response is just as complex as disease genetics, and genetic variability will derive not only from genotypes in the translated gene regions but also from variability in gene expression and regulation. Therefore, pharmacogenetic approaches using information on hundreds of genetic variants simultaneously, as well as in vitro models for studying gene expression, are necessary to overcome the limitations of single candidate gene approaches [8]. Genetic mechanisms on the level of drug metabolism, transport and drug target structures, such as neurotransmitter receptors and transporter molecules, have to be systematically studied for their predictive value on antidepressant drug response using a multiple SNP (single nucleotide polymorphism) candidate gene approach.

A future perspective is to optimize individual drug therapy by genetic testing before pharmacotherapy commences. However, this implies clear validation of the response-predictive value of genetic profiles and clear-cut therapeutic strategies depending on the individual profile. Individualized medicine is the general aim of all pharmacogenetic research, and antidepressant drug therapy is the first-line application for this approach, since many pharmacogenetic factors were initially researched in antidepressant drugs [9,10].

Genetic variability in drug response:

The polymorphic enzyme cytochrome P450 (CYP) 2D6
Most antidepressants are metabolized by the polymorphic cytochrome P450 enzyme (CYP) 2D6 which shows high variability in enzyme activity due to genetic variants. Genetic polymorphisms in *CYP2D6* can either lead to complete deficiency of the enzyme or to ultrarapid metabolism which is caused by duplicated active genes.

The group of tricyclic antidepressants undergoes similar biotransformation actions in the liver with CYP2D6 catalyzing hydroxylation reactions [11]. Individuals carrying two deficient alleles of *CYP2D6,* the so-called CYP2D6 poor metabolizers (PM), have largely (50% or more) decreased clearances. This was reported for amitriptyline [12–14], clomipramine [15–17], desipramine [18–21], imipramine [20,22], nortriptyline [9,23–25], doxepin [26] and trimipramine [27,28].

Enantioselective metabolism by CYP2D6 was reported for trimipramine towards the less active (L)-trimipramine [28], and stereoselectivity for doxepin metabolism towards the clearance of the less active E-isomers [26].

In Table **1**, pharmacokinetic data of antidepressants from studies in humans on *CYP2D6* polymorphisms are shown either as area under the concentration time curve (AUC) or steady state concentrations (Css).

Some SSRIs such as fluoxetine, fluvoxamine and paroxetine are potent inhibitors of CYP2D6 activity. Therefore, CYP2D6 activity is decreased after multiple dosing and the metabolism of the

drugs is inhibited. Conversion from extensive to slow metabolizer phenotype and from ultrafast to extensive metabolizers has been described [29,30]. In the case of fluvoxamine, differences in AUCs were described after single doses [31,32], whereas multiple doses result in similar AUCs in PMs as in EMs, indicating a phenotype-conversion from CYP2D6 EM to PM [33].

For fluoxetine, enantioselective metabolism towards the S-enantiomer was described in vivo with impaired demethylation of S-fluoxetine in CYP2D6 PMs [34]. However, since desmethylfluoxetine is regarded as active as an antidepressant, as the parent drug [35], the sum of desmethylfluoxetine and fluoxetine accounts for the active drug moiety, which was the same in CYP2D6 PMs and EMs [34]. For paroxetine, undetectable drug concentrations are described in one ultrafast metabolizer carrying at least three functional *CYP2D6* genes [29], and in CYP2D6 PMs, AUCs were two-fold higher than in EMs [36]. For sertraline and citalopram, no influences of *CYP2D6* polymorphisms on pharmacokinetic parameters were detected.

For other antidepressants (bupropion, maprotiline, mianserin, mirtazapine, moclobemide, nefazodone, reboxetine, venlafaxine) no general assessment on polymorphic drug metabolism can be made.

Bupropion is a substrate of CYP2B6 and apparently not influenced by CYP2D6 polymorphisms [37]. Amino acid polymorphisms in CYP2B6 are associated with about 40% higher blood concentrations of hydroxybupropion, an active metabolite [38].

Contradictory data exist on effects of *CYP2D6* polymorphisms on metabolism of the tetracyclic antidepressant maprotiline: while under monotherapy, no differences in steady state concentrations were detected [39], a study in healthy volunteers receiving 100 mg maprotiline over seven days revealed differences similar to those detected in tricyclics [40].

For mianserin, CYP2D6 mediates enantioselective hydroxylation of the more active S-mianserin (Table **1**).

For mirtazapine, a racemic mixture of the more active S-enantiomer and R-mirtazapine, only one study exists which does not report significant differences in mirtazapine disposition to CYP2D6. For moclobemide, nefazodone, reboxetine and trazodone, *CYP2D6* polymorphisms do not seem to have a major influence on metabolism in humans [41–47].

Venlafaxine is a chiral drug with both enantiomers transformed by CYP2D6 to the equipotent O-desmethyl-venlafaxine [48–50]. A higher risk for cardiotoxic events and severe arrhythmia was reported in four patients admitted to a cardiologic unit who all were PMs according to CYP2D6 [51].

CYP2C19

Much fewer studies than on CYP2D6 polymorphisms were conducted evaluating CYP2C19 mediated differences in drug metabolism. In general, CYP2C19 seems to be involved in demethylation reactions of tricyclic antidepressants as was shown for

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Table **1** Differences in AUCs or steady state concentrations (Css) of antidepressants due to CYP2D6 metabolizer type

Substance	Measured	Parameter	Dose (mg)	UM	EM	IM	PM	Dosage	Participants	Numbers UM/EM/IM/PM	References
Tricyclic antidepressants											
Amitriptyline	P	AUC	50		1.7	2.8	3.0	SD	volunteers	2/4/3	[12]
		AUC	50		1.9	2.8	4.1	SD	volunteers	5/3/3	[13]
	P+DM	AUC	75		3.7		5.6	SD	volunteers	4/0/3	[14]
		Css	150		0.54		1.3	MD	patients	11/0/4	[11]
Clomipramine	P	AUC	100		3.2		5.7	SD	volunteers	15/0/10	[17]
	P+DM	Css	150		0.2		0.57	MD	patients	35/0/1	[16]
		Css	200		1.5		2.34	MD	patients	15/0/5	[15]
		Css	75		0.24		0.62	MD	patients	19/0/3	[15]
		Css	125		0.63		1.25	MD	patients	21/0/2	[15]
Desipramine	P	AUC	25		1.0		8.0	SD	volunteers	5/0/4	[97]
		AUC	25		1.5		6.6	SD	volunteers	8/0/6	[19]
		AUC	100		3.8	6.1	33.0	SD	volunteers	6/6/6	[20]
		AUC	100	1.0	2.0			SD	volunteers	6/6/0/0	[98]
		Css	100		0.30		0.90	MD	patients	29/0/2	[21]
		Css	100		118	530		MD	patients	4/5/0	[99]
Doxepin	P+DM	AUC	75		1.43	1.7	4.15	SD	volunteers	8/8/8	[26]
Imipramine	P	AUC	100		2.3	2.6	4.4	SD	volunteers	6/6/6	[20]
	P+DM	Css	100		0.38		1.8	MD	patients	28/0/2	[22]
Nortriptyline	P	AUC	25	0.8	1.3	3.6	4.3	SD	volunteers	6/5/5/5	[24]
		AUC	29		1.8	3.1	3.9	SD	volunteers	2/3/2	[25]
		AUC	29		1.7	3.0	4.2	SD	volunteers	2/4/2	[9]
		Css	150		0.39	0.5	0.96	MD	patients	7/13/1	[23]
		AUC	25		2.2	4.0		SD	volunteers	10/5/0	[100]
		Css	15–120		0.27	0.56		MD	patients	7/6/0	[101]
Trimipramine	P+DM	AUC	75		0.95	2.38	7.23	SD	volunteers	8/7/6	[27]
	D-P+D-DM	Css	300–400		0.10		0.24	MD	patients	25/0/1	[28]
SSRIs											
Citalopram	P	AUC	40		4.6		4.7	MD	volunteers	10/0/8	[59]
Fluoxetine	P+DM	AUC	60		25.8		53.6	SD	volunteers	6/0/6	[102]
		AUC	20		6.8		8.6	SD	volunteers	9/0/10	[103]
		Css	20		0.32		0.33	MD	patients	8/0/3	[34]
Fluvoxamine	P	AUC	50		1.0		1.3	SD	volunteers	10/0/5	[31]
		AUC	50		1.4		5.3	SD	volunteers	10/0/4	[32]
		AUC	100		2.5		2.1	MD	volunteers	8/0/2	[33]
Paroxetine	P	AUC	30		2.6		4.4	MD	volunteers	9/0/8	[104]
Sertraline	P	AUC	50		1.4		1.5	SD	volunteers	10/0/10	[103]
Other antidepressants											
Bupropion	P	Css	300		0.13		0.15	MD	patients	4/0/3	[37]
Maprotiline	P	Css	150		0.42		0.40	MD	patients	75/0/5	[39]
		AUC	100		8.3		29.0	MD	volunteers	6/0/6	[40]
Mianserin	S-P	Css	30		0.05	0.14		MD	patients	14/1/0	[105]
	P+DM	AUC	30	0.23	0.64		1.1	SD	volunteers	2/8/0/5	[106]
	S-P+DM	Css	10–360		0.28	0.36	0.44	MD	patients	21/7/1	[107]
Mirtazapine	P	AUC	15		2.0		1.9	SD	volunteers	7/0/7	[108]
Moclobemide	P	AUC	600		110.1		84.1	MD	volunteers	2/0/2	[45]
		Css	450		8.6		6.5	MD	volunteers	22/0/5	[44]
Nefazodone	P	AUC	400		13.6		15.9	MD	volunteers	10/0/10	[42]
Trazodone	P	Css	150		1.5	1.8		MD	patients	46/8/0	[47]
Venlafaxine	P	AUC	19		0.7		2.9	MD	volunteers	8/0/6	[51]
		AUC	31		1.2	4.6		SD	volunteers	8/4/0	[49]
		AUC	19		0.58		2.27	SD	volunteers	7/0/5	[109]
	P+DM	Css	225	0.66	1.12	1.24	1.94	MD	patients	2/22/6/3	[50]

Measured: Measured drug component in the studies, if available the active moiety was taken. P+DM: Parent drug + Desmethyl-metabolite; S-P: S-enantiomer, E-P: E-stereoisomer; OHM: Hydroxy-metabolite.
Parameter: Pharmacokinetic parameter taken for calculation (AUC; area under the concentration time curve in $\mu M \cdot h$; Css: concentration at steady state in μM).
Dose in mg: the doses given in the clinical studies are depicted. In cases where different doses were given to patients the dose range is shown.
UM, EM, IM, PM: Mean group values of AUC or Css given for ultrafast metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM).
SD or MD: Single dose (SD) data or data from multiple dosing (MD).
Participants: Either healthy volunteers or patients taking part in the study.
UM/EM/IM/PM: Number of participants for each genotype group. If no UM involved, number of EM is given first.

amitriptyline, clomipramine, doxepin, imipramine, and trimipramine; and poor metabolizers with lacking enzyme activity of CYP2C19 had about twofold higher AUCs than individuals with normal activity (CYP2C19 EMs) [11,17,26–28,52–57]. Moclobemide, sertraline and citalopram are metabolized by CYP2C19 as well, and differences in AUCs in CYP2C19 PMs were about twofold (moclobemide and citalopram) or less (sertraline) [46,58,59].

CYP2C9

Only few data exist concerning other polymorphic cytochrome P450 enzymes: For CYP2C9, carriers of alleles *CYP2C9*2* and **3* have lower enzyme activity compared with carriers of the wild type allele, and an allele (*CYP2C9*4*) with complete deficient enzyme activity was described in a single African-American subject [60]. *CYP2C9*2* and **3* allele frequencies are about 22% and 13% in Caucasians [61].

All currently existing data show only a minor contribution of the CYP2C9 polymorphisms for inter-individual pharmacokinetic variability of tricyclic antidepressants: Data on amitriptyline is based on in vitro studies only, and a small difference in kinetics between carriers of CYP2C9*1/*1 and *3/*3 was shown for trimipramine and doxepin [26,27].

Pharmacogenetic-based dose recommendations

Genetic variants in drug metabolizing enzymes mostly result in an accumulation of a drug and/or its metabolite because of impaired metabolism and elimination. Thus, according to the principles of bioequivalence, dose adaptations can be derived in order to achieve similar concentration-time courses of drugs and metabolites [7,62,63] (Fig. 1). In Fig. 2, the differential doses of antidepressants due to polymorphisms of *CYP2D6* are depicted based on pharmacokinetic data provided in Table 1. Only data on dose related parameters such as clearance, AUC or steady-state concentrations (Css) for different groups of genotypes are used for the calculation of dose recommendations. For further information on methods and references refer to [7,62]. Dose adaptations are given for the poor, intermediate, extensive and ultrafast metabolizer of CYP2D6. For the UM group, extrapolation was made assuming a linear gene-dose effect according to the calculation methods given above. If possible, data on the active moiety of the drug (sum of parent drug and active metabolites) after multiple dosing was taken. Fig. 2 is based on data listed in Table 1.

Dose recommendations based on differences in pharmacokinetics, however, are not automatically helpful for prediction of treatment response, since correlation between plasma concentrations and efficacy is very poor in antidepressant therapy [64]. However, adverse drug effects are at least partly correlated to the amount of drug measured by plasma concentration time courses. Therefore, the drug metabolic capacity predicted by genotyping might rather account for treatment failure due to adverse drug effects than for response prediction.

Additionally, genetic variability in metabolism does not only change the amount of parent drug concentrations but also influences metabolism of the metabolites. Metabolites often have pharmacological activity and might be responsible for adverse drug reactions like, for example, in the case of venlafaxine, in which the metabolite O-desmethylvenlafaxine was associated with arrhythmias [51].

Genetic variability in pharmacodynamics

Individuals with identical plasma and tissue concentrations of a drug may still vary extensively in their responses. Genetic variants exist in molecular targets directly involved in drug action as, e.g., receptor and transporter molecules. Thus far, mostly serotoninergic receptors and transporters have been studied with regard to antidepressant drug response. Systematic exploration of other transmitter systems, downstream intercellular signaling molecules, and neurotrophic factors and their receptors is a major goal for future research.
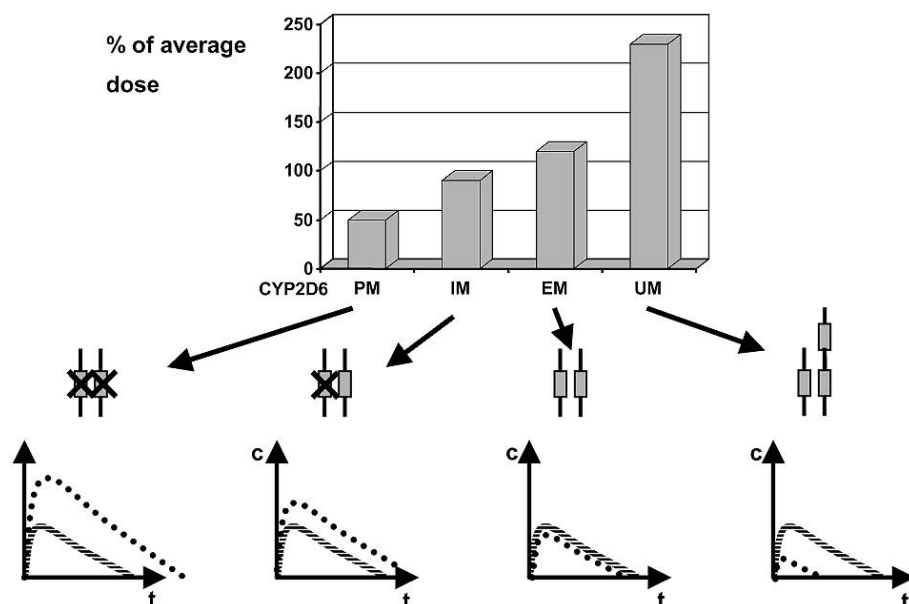

Fig. 1 Schematic adaptations of dosages due to genotypes causing differences in drug metabolism and elimination. By adapting the doses according to *CYP2D6* genotype, similar concentration-time courses can be achieved for each genotype group.
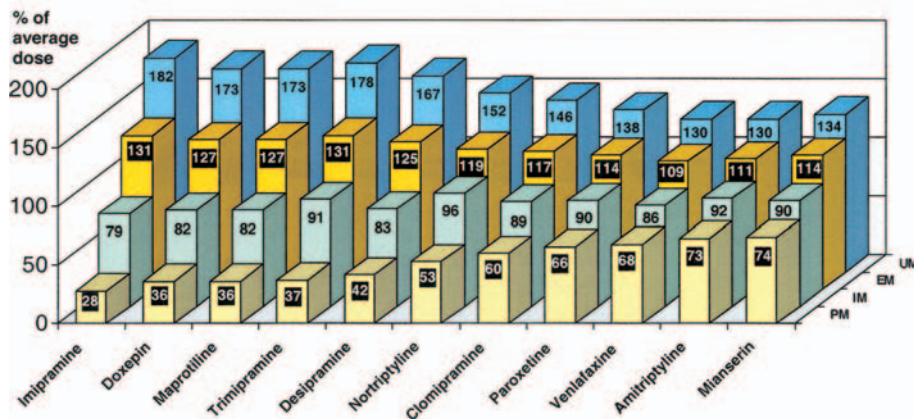
Fig. **2** Genotype based dose adaptations derived from pharmacokinetic studies on *CYP2D6* polymorphisms and effects on clearance of antidepressants in humans. Dose adaptations are provided as percent of a standard dose which is the usual dose recommended by the manufacturer. Figure adapted from [110].

The molecular mechanism of antidepressant drug action involves inhibition of the neuronal serotonin transporter. A functional polymorphism in the 5'-upstream regulatory region of this gene consists of a 44-base pair (bp) insertion/deletion resulting in a long (l) and a short (s) variant, the latter resulting in twofold decreased in-vitro expression and transport activity [65,66]. Several studies have reported a better response to SSRIs in individuals carrying one or two of the long allele (l) of the 44-bp deletion in the promoter of the serotonin transporter (SERT) [67–75].

How can these genotype-based differences in antidepressant drug response depending on SERT be used in psychiatric practice? A theoretically approach would be to prefer noradrenergic agents or tricyclics in patients who are carriers of the s/s genotype, however, such strategy requires confirmation in a clinical study.

Serotonin (5-HT) receptor genes are further candidates for genetic prediction of antidepressant drug response. Two polymorphisms in the serotonin receptor gene *5-HT-2A* have been studied in this context: a silent point mutation 102T > C and the promoter polymorphism –1438G > A which is in strong linkage disequilibrium to 102T > C. Better treatment response to antidepressants in patients carrying the C-allele of the 102T > C polymorphism was reported as compared to T/T homozygotes [76]. In contrast, no significant association between the completely linked –1438G > A polymorphism and therapeutic response to fluvoxamine was observed [77].

Another candidate gene within the serotonin system is the tryptophan hydroxylase which is the rate-limiting enzyme of serotonin biosynthesis [78,79]. A genetic polymorphism (218A > C) is located in a potential transcription factor binding site and may influence gene expression [80]. Significant associations with response to SSRIs were reported in individuals carrying the C variant of the A218C polymorphism [78].

Antidepressant efficacy is mediated not only by serotonin reuptake inhibition but also by inhibition of the norepinephrine uptake. Preclinical and clinical studies have shown that stimulation of the serotonergic system leads to noradrenergic effects and vice versa, which shows that the serotonin and norepinephrine systems are intimately connected in the central nervous system

[81]. The human norepinephrine transporter modulates norepinephrinergic signaling by reuptake and clearing of secreted norepinephrine [81]. Several genetic variants are known in the human norepinephrine transporter gene; however, it has not yet been studied if they influence antidepressant drug response.

Associations with response to various antidepressant drugs were observed with the ACE 287bp insertion/deletion polymorphisms [82,83] and for the G-protein ß3 subunit (Gbeta3) [84]. Both genes play an important role in the regulation of blood pressure. Cerebrovascular disease can be a contributing factor for the development of depression, and it was shown recently by the same authors that the allelic combination of ACE and Gbeta3 is associated with increased risk for myocardial infarction [85] and depressive disorder [86].

Bedside genotyping test: Lab-on-a-chip

Pharmacogenetic testing is a highly potent diagnostic tool for improvement and individualization of drug therapy. However, the time-delay between obtaining genotyping results and onset of drug therapy is the main reason that pharmacogenomic diagnostics is not yet routinely used in clinical drug treatment. An innovative approach of pre-therapeutic genetic testing is the development of a pharmacogenetic bedside-test that can be performed directly in the clinical setting and does not require special laboratory or scientific equipment. Biochemical microsystems, the so-called lab-on-a-chip technology, aim to perform several chemical reactions on a single micro-chip, which can be a silicon based or a polymer based chemical analysis system [87]. Chip-based microsystems have been developed for several aspects of molecular diagnostics [87]. However, despite the progress no complete lab-on-a-chip system exists for bedside genotyping. Below, we will suggest how such a lab-on-a-chip system for genotyping could be realized.

The suggested procedures for genotyping are depicted in Fig. **3**. Genotyping involves collection of full blood samples, cell-lysis, DNA extraction, amplification by the polymerase chain reaction (PCR), and analysis of single nucleotide polymorphisms (SNP).

For full blood samples the first step in this extraction procedure will be a hypotonic lysis of the red blood cells (RBC) which will be
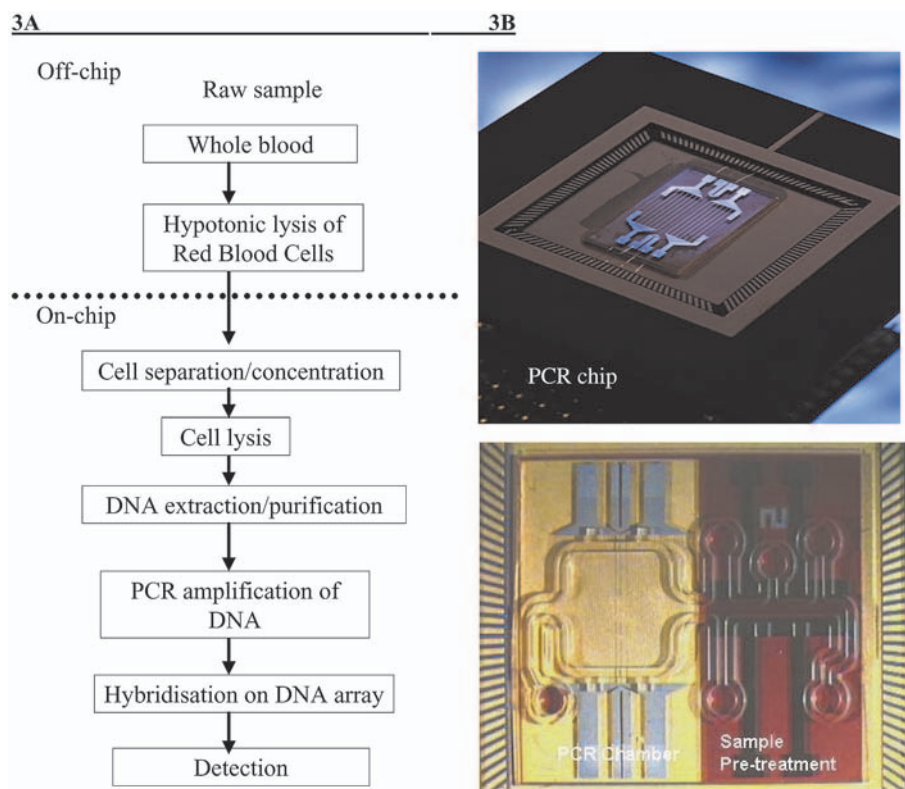
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Fig. **3** Schematic depiction of the single steps for genotyping using DNA amplification and minisequencing techniques. The lysis and separation of the red blood cells must be done "off-chip", all further steps can be included into the chip technology. Further, a "Lab-on-a-chip" prototype is shown in its natural size.

done before preparation of the chip (off-chip). The DNA-containing white blood cells (WBC) will remain intact after RBC lysis. Since haemoglobin is a potent PCR inhibitor, the WBCs have to be separated from the lysed RBCs. The cells can be purified by dielectrophoresis (DEP) which acts as a selective filter and keeps the cells in a microsystem while the PCR inhibitors haemoglobin and heparin are flushed out [88]. The WBCs can be lysed on-chip similar to a method described for thermolysis of yeast and Campylobacter cells [89]. Very limited research has been published on adapting DNA extraction and purification for the microchip format. One on-chip method is based on silica resin binding of DNA [90]. DNA binds to silica in the presence of chaotropic reagents and is released in its absence. DNA can, therefore, be extracted, washed, and eluted for the PCR reaction on the chip. On-chip DNA amplification has already been performed as ultrafast thermocycling with precise temperature control [91–94]. SNP analysis could be performed using a method similar to the solid-phase minisequencing assay developed for detecting multiple mutations [95]. It involves multiplex PCR of genomic DNA, preparation of single stranded templates, annealing of the templates to a primer array and minisequencing reactions on the array with subsequent measurement of the incorporated labelled dideoxynucleotides. Recently such a microarray minisequencing system has been used for pharmacogenetic profiling of antihypertensive drug response [96] and pharmacogenetic profiling of antidepressant treatment response related genes could probably be done in a similar way.

As described above the steps necessary for genotyping have been realized in various microsystems. The main challenge for a lab-on-a-chip system for bedside genotyping will be, to perform all steps on a single chip.

Genetic profiling for individualized drug treatment – future perspective

The role of genotyping in drug therapy is currently limited to the explanation of therapeutic failure or adverse drug effects. Pharmacological therapy of the future will include genotyping to optimize therapeutic strategies for the individual patient. To reach this goal, several steps must be completed. First, the role of the genes involved in drug action and disease progression require improved characterization. Second, therapeutic consequences must be deducted from genetic results and these recommendations should be prospectively validated. This might be in the form of dose recommendations accounting for differences in drug disposition and metabolism; or in the form of therapeutic flow-charts/guidelines for therapeutic strategies reliant upon genetic profiles. Third, methods for tast and cheaper genetic testing have to be developed, validated and brought on the market. Future research in pharmacogenomics is both challenging and promising and can lead to a patient-oriented individualized drug treatment.

Acknowledgment

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