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# Influence of cytochrome P450 polymorphisms on drug therapies: Pharmacogenetic, pharmacoepigenetic and clinical aspects

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**Abstract**

The polymorphic nature of the cytochrome P450 (CYP) genes affects individual drug response and adverse reactions to a great extent. This variation includes copy number variants (CNV), missense mutations, insertions and deletions, and mutations affecting gene expression and activity of mainly CYP2A6, CYP2B6, CYP2C9, CYP2C19 and CYP2D6, which have been extensively studied and well characterized. CYP1A2 and CYP3A4 expression varies significantly, and the cause has been suggested to be mainly of genetic origin but the exact molecular basis remains unknown. We present a review of the major polymorphic *CYP* alleles and conclude that this variability is of greatest importance for treatment with several antidepressants, antipsychotics, antiulcer drugs, anti-HIV drugs, anticoagulants, antidiabetics and the anticancer drug tamoxifen. We also present tables illustrating the relative importance of specific common *CYP* alleles for the extent of enzyme functionality. The field of pharmacoepigenetics has just opened, and we present recent examples wherein gene methylation influences the expression of CYP. In addition microRNA (miRNA) regulation of P450 has been described. Furthermore, this review updates the field with respect to regulatory initiatives and experience of predictive pharmacogenetic investigations in the clinics. It is concluded that the pharmacogenetic knowledge regarding CYP polymorphism now developed to a stage where it can be implemented in drug development and in clinical routine for specific drug treatments, thereby improving the drug response and reducing costs for drug treatment.


*Keywords:* Personalized medicine; Warfarin; Antidepressants; CYP2D6; Copy number variation; Tamoxifen

**Contents**



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## 1. Introduction

Pharmacogenetics is a field whereby the genetics of the individual patient is taken into consideration during drug development and for individualized therapies, overall improving the number of responders and decreasing the number of patients suffering from adverse drug reactions. Although factors like poor compliance, environmental factors and drug–drug interactions might affect the therapeutic outcome tremendously, and indeed more than the genetic factors, there are several examples wherein an altered gene constitution will influence the therapeutic outcome to such a large extent that it would not be ethically appropriate not to take these aspects into consideration as a physician. Also, during drug development, it is important to consider these aspects which could explain, or even prevent discarding of drug candidates if appropriate genetic reasons are identified, lack of response or occurrence of ADRs in drug therapy.

In general one can envision important pharmacogenetic variation at the level of

- drug transporters,
- drug metabolizing enzymes,
- drug targets,
- other biomarker genes

As being important for the interindividual differences in drug response. So far, it is apparent that variability in genes encoding drug metabolizing enzymes often affects outcome in drug treatment to a very high extent and that the polymorphism of the cytochrome P450 (CYP) enzymes plays a major role in this respect. Because of such variability, the populations could be classified into 3 major phenotypes:

- the ultrarapid metabolizers (UM), with more than 2 active genes encoding a certain P450;
- the extensive metabolizers (EM), carrying 2 functional genes; and
- the poor metabolizers (PM), lacking functional enzyme due to defective or deleted genes.

In addition, a more subtle phenotype occur that is commonly called

- the intermediate metabolizers (IM), usually carrying 1 functional and 1 defective allele but may also carry 2 partially defective alleles.

By contrast, polymorphism in genes encoding drug transporters and drug receptors do, in some cases, influence therapeutic outcome, but the number of important examples where this variation is of clinical importance are fewer.

Thus, with respect to the penetrance of polymorphic genes on drug disposition and action, it is evident that the genes encoding drug metabolizing enzymes exhibit a prominent role because of the great influence on drug elimination, thereby influencing the effect of drugs in the treatment of many different diseases. In general, it can be estimated that 20–25% of all drug therapies are influenced by such polymorphism to an extent that therapy outcome is affected (Ingelman-Sundberg, 2004) and the CYP play a critical role, as these enzymes are responsible for about 80% of all phase I drug metabolism (Eichelbaum et al., 2006). This makes the field of CYP pharmacogenetics of great importance both for drug development and for drug treatment in clinical practice.

Recently, some reviews have covered the topic regarding the use of pharmacogenetics in drug treatment (Ingelman-Sundberg, 2004; Eichelbaum et al., 2006; Gardiner & Begg, 2006). In the present review, we update the field on CYP pharmacogenetics and focus on novel pharmacogenetic aspects concerning gene copy number variation, epigenetics, as well as the