Cardiovascular Pharmacogenetics and Pharmacogenomics

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The recent developments of genome-based technology provide to the pharmacologists and therapists new tools that allow genotyping focused on polymorphic drug-metabolizing enzymes, such as the cytochrome P450 enzyme, CYP, family, or polymorphic drug targets proteins, such as lipoproteins or ion channels. Amongst the different allelic isoforms, there is evidence that several of these isoforms are functionally different and can metabolize drugs at different speeds or react to drug binding in a different way. In addition, drug metabolizing enzymes are frequently associated with a more general detoxification function, functionally different isoforms could then provide some interesting information concerning several toxic agents, which are cardiovascular risk factors such as tobacco or alcohol. J Clin Basic Cardiol 2001; 4: 205–210.

Key words: pharmacogenetics, pharmacogenomics, genetics, drug-metabolising enzymes

Pharmacogenetics Versus Pharmacogenomics

Pharmacogenetics was born in the 1950s when it was reported that several therapeutic accidents could be hereditary. Probably the first description was that of haemolysis after antimalarial therapy occurring in persons who expressed deficiency in glucose-6-phosphate-dehydrogenase, G6PDH. Another rather historical example is that of isoniazide-induced peripheral neuropathy due to a deficiency of the enzyme in charge of isoniazide acetylation [1].

Pharmacogenetics is a child of the Human Genome Program. It utilizes both the > 30,000 gene sequences discovered during this program and the genome-based technology that has been developed for this purpose [2]. Pharmacogenomics aims also to explore the genetic basis of therapeutic efficacy, just like pharmacogenetics but with more powerful tools, it also aims to discover new ‘druggable targets’, and as such it represents one of the major challenges of industrial pharmaceutical research.

Genome-based technology is now able to provide tools that allow individual determination of genotypes, making possible the adaptation of a given therapy to a given person. DNA microarrays, which are the most popular, can indeed target onto a specific group of proteins such as, for example, polymorphic drug-metabolizing enzymes that could influence a patient’s response to chemotherapy for acute lymphoblastic leukaemia. Automated systems can then be developed to determine an individual genotype for genes involved in the pathogenesis of a given disease [1].

The therapeutic ratio, which is the efficacy/toxicity ratio, depends upon non-genetic factors as well as genetic factors. From a genetic point of view, the therapeutic ratio is a polygenic trait and is determined by the expression of two groups of polymorphic genes: drug-metabolizing enzymes which may either activate or inactivate drugs and toxic substances and proteins that are targets for drug action, such as receptors, enzymes, or proteins involved in signal transduction or cell cycle control. Drug-metabolizing enzymes belong to a broader family of enzymes that is in charge of detoxification and which also plays a role in maintaining or lowering the eventual toxicity of several components that are cardiovascular risk factors.

Drug-Metabolizing Enzymes in Cardiovascular Pharmacology

Several dozen human drug-metabolizing enzyme genetic polymorphisms have been identified so far, including the cytochrome P450, mainly CYP2D6, N-acetyltransferase 2, NAT2, glucose-6-phosphate dehydrogenase, G6PDH, glutathione S-transferase, alcohol dehydrogenase and so on [3]. Drug detoxification represents < 1 % of their normal function, and in fact these enzymes mainly play an important physiological role in metabolizing non-peptides that are involved in ligand-modulated processes that are involved in growth, apoptosis, homeostasis and so on. Good examples are found in the activation of the ligand for the vitamin D receptor or in the arachidonic cascade. Most of these genes encode alleles, which express isoforms with different metabolic activities (slow, intermediary, fast metabolizers) [3, 4].

There is some evidence that the evolution of these enzymes occurred because of the interaction between animals and plants. During evolution, plants have to maintain defense systems for survival and have to defend themselves by evolving new genes to make them different or more toxic and, naturally, in response, animals have to evolve new genes, which are more adapted to changing plants. For example, cytochrome P450 genes that are human and animal drug-metabolizing enzymes are evolution products from enzymes that metabolize plant metabolites and belong to a larger family that detoxify pollutants and carcinogens as well as drugs. There are striking geographic differences between these polymorphisms and, for example, poor metabolizers of debrisoquine are ≈ 5 % in African populations and < 1 % in Asians, which may reflect two kinds of selective pressure, including diet habits and the evolution of balanced polymorphisms (balanced polymorphisms reflect the fact that there are several inherited diseases in which the...
The desibroquine range comprises at least 30 drugs including into an active derivative, morphine. Mutations on CYP2D6 opioids. A rather historical example is the activation of co-belongs to the first two categories. This enzyme is able to homozygotes bear the risk while the heterozygotes retain a distinct survival advantage [3].

Debrisoquine (debrisoquine is an antihypertensive agent that has never been approved in the USA) hydroxylase, (R, S)-propafenone is a widely utilised class 1C antiarrhythmic drug, which is hydroxylated by CYP2D6 to 5-hydroxypropafenone. The dose is both a β-blocker and a sodium channel blocker. The β-blocking activity of (R, S)-propafenone is mostly due to the S-enantiomer whereas the sodium channel blocking activity is due to both enantiomers, R and S. The metabolic product, 5-hydroxypropafenone, has a different pharmacological activity to propafenone, and is mainly a sodium channel blocker with a minor β-adrenergic antagonist effect. In vitro, the β-blocking effect of propafenone is readily demonstrable, while in vivo clinically significant β-blockade occurs inconsistently. Genotyping has shown that poor metabolizers have more β-blockade and severe side effects as compared to extensive metabolizers [9].

The usual form of converting enzyme inhibitors (CEI), such as enalapril, is inactive and needs to be activated to be transformed by an esterase, but, for the moment, no functional mutation affecting this esterase has been reported, and genetics did not bring a response for explaining the non-responders to CEI.

Conversely, severe neuropathy may occur during treatment with 5-Fluorouracil. This, in fact, reveals familial deficiencies in dihydropyrimidine dehydrogenase with an autosomal recessive pattern of inheritance. These patients are unable to metabolize the drug, which accumulates in the cerebrospinal fluid and plasma and is excreted into the urine as unchanged fluorouracil [7].

Most of the works on this topic have concentrated on cytochrome P450 enzyme (CYP) which is a highly polymorphic enzyme that plays a key role in metabolizing the majority of drugs in the human body (Tab. 1). The decision about drug-metabolizing enzyme genotyping is based on preclinical data showing that the compound is metabolised by a polymorphic enzyme such as CYP or NAT2 and that, for example, there is quite a large group of persons that are slow metabolizers because they have the slow response allele. Genotyping is currently becoming quite cheap (especially if the company has a large list of volunteers with a ‘CYP-Passport’ [8]), and, at least cheaper than developing a drug that has not been correctly optimised. Surprisingly, despite the high economic incidence of the problem, very few papers have so far dealt with the cardiovascular system and while genotyping usually has been carried out during the preclinical stage of drug development, it should be interesting for the clinician to know the drugs whose metabolism could be modified by such a polymorphism. The following list is obviously not exhaustive (Tab. 1).

### Table 1. Polymorphic drug-metabolizing enzymes in cardiovascular pharmacology

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enzyme</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>CYP2C9</td>
<td>Not documented</td>
</tr>
<tr>
<td>Flecainide</td>
<td>CYP2D6</td>
<td>Inconsistent β-blockade</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>CYP2C19 &amp; CYP3A4</td>
<td>Not documented</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>CYP2D6</td>
<td>Variations in α1 / β2 blockades</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>CYP2D6</td>
<td>Variations in β-blocker activity</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CYP2C9</td>
<td>Variations in anticoagulant effect</td>
</tr>
</tbody>
</table>

### Antiarrhythmics

(R, S)-propafenone is a widely utilised class 1C antiarrhythmic drug, which is hydroxylated by CYP2D6 to 5-hydroxypropafenone. The dose is both a β-blocker and a sodium channel blocker. The β-blocking activity of (R, S)-propafenone is mostly due to the S-enantiomer whereas the sodium channel blocking activity is due to both enantiomers, R and S. The metabolic product, 5-hydroxypropafenone, has a different pharmacological activity to propafenone, and is mainly a sodium channel blocker with a minor β-adrenergic antagonist effect. In vitro, the β-blocking effect of propafenone is readily demonstrable, while in vivo clinically significant β-blockade occurs inconsistently. Genotyping has shown that poor metabolizers have more β-blockade and severe side effects as compared to extensive metabolizers [9].

Flecainide is a 1C antiarrhythmic drug which is also metabolized by CYP2D6, but the metabolic products are inactive. The dose recommendations are valid only for the dose range given in the studies to take into account the differences in metabolizing activity [10].

### Beta-Blockers

Carvedilol is a racemic drug whose α1-blocking activity is mainly supported by the (S)-enantiomer, while the β1-blocking activity is a property of the two enantiomers. The (R)-enantiomer is better metabolized by CYP2D6, which explains the differences in α1/β1 relative activities, depending on the genotype and the expressed alleles [11]. Metoprolol is also metabolised by CYP2D6 and treatment has to be adjusted to take into account patients’ responsiveness [12].

### Anticoagulants

Warfarin is also a racemic drug with a 3–5 times higher anticoagulant effect of the (S)-enantiomer than the (R)-form. Detailed genotypings have shown strong correlations between the CYP2C9 alleles and the anticoagulant properties and bleeding complications. Slow metabolizers have the CYP2C9 3/3 allele and show bleeding complications as compared to fast metabolizers CYP2C9 1/1 [13].

### Toxic-Metabolizing Enzymes and Risk Factors

An interesting application of research on genetic polymorphisms concerns toxic-metabolizing enzymes, which detoxify alcohol and tobacco products, two well-identified risk factors in cardiology and cancerology.

### Alcohol

Moderate alcohol consumption is consistently associated with reduced risk of myocardial infarction (the so-called ‘french paradox’), nevertheless, still, it is not clear whether the apparent benefit of alcohol is due to constituents of the alcoholic beverages other than ethanol or in fact reflects lifestyle factors (such as the Provencal lifestyle, of course) that are usually associated with moderate alcohol consumption.

Alcohol dehydrogenases, ADH, isoenzymes are also drug-metabolizing enzymes that oxidize ethanol and play a major detoxification role after alcohol consumption. There are several ADH isoforms (ADH 1, 2, 3) Nevertheless ADH 3 is the only locus that give different alleles with different kinetic properties. Pharmacokinetics show indeed that the homo-dimere γ1γ1 is associated with a fast rate of oxidation as compared to γ2γ2. Homozygosity for γ2γ2 is associated with the highest level of plasma HDL and a reduced risk of myocardial infarction as compared to homozygosity with γ1γ1. An interesting conclusion from this type of study is that it is possible to eliminate confounding factors by using specific geno-
typings [14]. It is indeed unlikely that ADH3 allele is associated either with the lifestyle status or with constituents of alcoholic beverages other than ethanol. More generally speaking, associations observed between a risk factor and the existence of functional variants in genes that encode enzymes, which specifically metabolize the factor, add substantial support to the hypothesis that the factor is really at risk [14].

**Tobacco**

Glutathione S-transferase, GST, belongs to the drug-metabolizing enzymes that detoxifies or activates several drugs and also chemicals in cigarette smoke. GST can eliminate the products of oxidative stress and also carcinogenic compounds such as benzo[a]pyrene, other poly cyclic aromatic hydrocarbons, monohalomethanes or ethylene oxide. The gene exists as two different main forms, GST M1 and GST T1 with different capacities to detoxify tobacco compounds. There is available evidence that one of these isoforms, GST T1-1, increases the mutagenicity of several chemicals. Several of these alleles are associated with various types of cancer: GST M1-0 with increased risk of smoking-related cancers, GSTT1-0 with bladder cancer among smokers and GST T1-1 with kidney cancer in workers with long-term exposure to trichlorethene.

In a case-cohort study of 400 coronary patients and 924 controls, ever-smokers with GST M1-0 were at a nearly 2-fold higher coronary risk relative to ever-smoker with GST M1-1 or never-smokers with GST M1-0, just as for cancer. Rather paradoxical results have been found concerning GST T-1 that is correlated with smoking-induced coronary risk, as with renal cancer despite the fact that GSTT1-1 is the functional isoform opposed to GST T-0 which is not functional. One of the explanations which have been proposed is that GST T1-1 can synthesise deleterious compounds [15].

**Genetic Polymorphisms in Cardiovascular Drug Targets: Drug Efficacy**

Molecular studies have shown numerous genetic polymorphisms on genes encoding targets for drug action. A good recent example is genetic polymorphisms that have been described in the Interferon γ system and may explain inherited cases of tuberculosis and leprosy. There are indeed at least eight different mutations on this system. These mutations render the Interferon γ receptors unable to bind their own ligand, thus these people were unable to react to any mycobacterial infection, although their immunosensitivity remained unaltered [16].

There are diseases whose pathogenesis are unknown and in which attempts were made to establish links between a given polymorphism on a simple marker for the disease and drug efficacy. A good example is Alzheimer’s disease, whose etiology is presently unknown. Research has established that the ε4 allele of apolipoprotein E confers a significant risk for late onset, sporadic Alzheimer’s disease, the most common form of the disease. Accordingly, this allele has served as the primary target for pharmacogenomics and several large studies have established a strong linkage between such a polymorphism and either acetylcholinesterase inhibitors, sotaxemibe or tacrine response [5]. Cardiovascular pharmacology is full of similar examples (Tab. 2).

**Table 2. Predicting drug efficacy from genotyping in cardiovascular pharmacology**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene polymorphism</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>CETP</td>
<td>Improved mortality</td>
<td>[17]</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Apolipoprotein E 4</td>
<td>Improved mortality</td>
<td>[18]</td>
</tr>
<tr>
<td>Diuretic</td>
<td>α-adducin</td>
<td>Hypotensive effect</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>G-protein</td>
<td>Diuretic effect</td>
<td>[20]</td>
</tr>
<tr>
<td>Converting Enzyme</td>
<td>Angiotensinogen</td>
<td>Hypotensive effect</td>
<td>[23]</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Angiotensin II receptor</td>
<td>Debatable</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>Deletion/Insertion on ACE</td>
<td>None</td>
<td>[20, 27, 28, 35]</td>
</tr>
<tr>
<td>β-blockers</td>
<td>α-subunit of Gs protein</td>
<td>Hypotensive effect</td>
<td>[33]</td>
</tr>
<tr>
<td></td>
<td>β1 &amp; β2-adrenergic receptor</td>
<td>None</td>
<td>[31]</td>
</tr>
</tbody>
</table>

ACE: angiotensin converting enzyme
The C825T polymorphism on the exon 10 of the G protein is linked to hypertension with volume expansion, sodium sensitivity, low renin, obesity and abnormalities in the sodium–proton antiport. A study on nearly 400 persons has evidenced higher sensitivity to thiazide diuretics in patients with the 825T allele [20].

Converting Enzyme Inhibition (CEI)
CEI is obviously related to the efficiency of both the circulatory and tissue renin-angiotensin systems, and, during aging, for example, the plasma level of angiotensin II is strongly reduced. In these persons CEI efficacy is caused by the tissue system that is overexpressed [22]. The genes of this system have a pivotal role in arterial hypertension and were the first candidates for genetics studies on hypertension.

The angiotensinogen gene is linked to essential arterial hypertension and several variants have been reported so far. In addition, the T235 genotype positively influences the sensitivity to CEI. This is, for the moment, the only polymorphism whose linkage to CEI response is not controversial. The polymorphism A1166C of the gene of the type 1 angiotensin II receptor is not functional and is thus only a marker. In addition the corresponding polymorphism is unrelated to CEI efficacy [23].

There are two types of sequence polymorphisms. Single nucleotide polymorphisms are single base mutations leading, in some cases, to a functionally inactive protein. Insertion/deletion polymorphisms are insertions or deletions of whole stretches of sequence giving rise to allelic variants. The insertion/deletion polymorphisms D/D/VII of the angiotensin converting enzyme gene is located in position 287 on the intron 16 and follows Mendelian laws. Such a polymorphism is in linkage disequilibrium with the gene locus involved in the control of the plasma angiotensin converting enzyme levels, and several studies showed that the serum level were significantly lower in II genotype than in DD. Since the pioneer work of François Cambien [24], there are conflicting data regarding the association between this polymorphism and myocardial infarction [25, 26] with at least twelve articles supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and several studies showed that the serum level were significantly lower in II genotype than in DD. Since the pioneer work of François Cambien [24], there are conflicting data regarding the association between this polymorphism and myocardial infarction [25, 26] with at least twelve articles supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studies, including a study by Agerholm-Larsen et al. with 7,300 patients [27] and supporting such an association, and five studie...
bradykinin receptor B2. This mutation is functional and re- results in an increased transcription which enhances the bradykinin receptor density and consequently could explain cough. The genotype CC is more frequent in hypertensive patients (33 %) than in normotensive patients (18 %), but the CC genotype is nearly absent in patients who are under CEI and suffer from cough suggesting that such a genotyping could help in prescribing another treatment.

Coronary Restenosis

Restenosis is a frequent, well-documented and, from an eco- nomical point of view, expensive complication of PTCA. Several studies attempted to establish a linkage between re- stenosis and gene polymorphism. Now, the linkage found by Amant [40] between restenosis and the insertion/deletion polymorphism of the angiotensin converting enzyme has not been confirmed in a rather extensive trial recently published in Hypertension [41].

Risk of Vein Thrombosis and Oral Contraceptives

The risk of vein thrombosis is increased by numerous factors including non-genetic factors such as prolonged immobilisa- tion and genetic factors such as inherited abnormalities of the coagulation system. Several polymorphisms that cause hyper- coagulability have been identified, including the G1691A polymorphism on the gene encoding factor V – the mutation causes resistance to activated protein C – and the G20210A polymorphism on the non-coding sequence of the prothrombin gene, which is a new form of thrombophilia. Both deep- vein and cerebral-vein thrombosis are associated with these mutations. In addition, a recent work has shown that use of oral contraceptives is also strongly and independently linked to the diseases, the presence of both a mutation on the coagu- lation system and oral-contraceptive use increasing the risk of cerebral-vein and deep-vein thrombosis to an extremely high level that requires a careful revaluation of the therapy [42].

Torsades de Pointe and Long QT Syndrome

Several drugs have a pronounced direct effect on repolarisa- tion [43]. In addition, recent reports have shown that, in some cases, these drugs can reveal latent long QT syndrome. In patients with long QT syndrome, these drugs can induce episodes of T orsades de Pointe and Long QT Syndrome. The recent concept of 'formes frustes' of the long QT syn- drome initially rises from one observation that concerns a heterozygotes Y315C of the pore region of the KvLQT1 gene and which was revealed during treatment with potassium blockers, such as cisapride. Interestingly, cisapride is a blocker of the IKr current, whereas KvLQT1 encodes another potassium channel (IKs) showing that indeed the QT interval duration does not depend on a given channel, but is determined by a 'repolarisation reserve' and could be modified by the two currents and that the effects are additive [46].

To conclude, genotyping is slowing leaving the bend to reach the bedside, and there are now convincing data that strongly suggest that therapeutic prescription could better be adapted to a given patient by knowing a few selected poly- morphisms directly or indirectly associated to drug-metabo- lizing enzymes or drug-targets.

References

17. Kuivenhoven JA, Jukema JW, Zwinderman AH, de Knijff P, McPherson R, Kuivenhoven JA, Jukema JW, Zwinderman AH, de Knijff P, McPherson R. Risk of vein thrombosis is increased by numerous factors including torsades de pointe and se- vere arrhythmias, may occur accordingly. There are, for the moment, only five (amongst several, probably more than ten mutations on the genes encoding, at least, three ion currents [43]) mutations that have been detected [44, 45] (Tab. 3). Table 3 also shows that there are roughly two groups of mutations: mutations, such as the Q9E-hMiRP1 or M54T, I57T and A116V-MiRP1, that reduce the basal (IKr) current, and thus enhance the sensitivity to drugs like clarithromycin or potas- sium blockers, such as oxatomide (which antagonizes histo- mine receptors), procainamide or quinidine, and mutations (type T8A-MiRP1) that do not influence basal ECG at rest but sensitize patients to drugs as sulfamethoxazole (a compo- nent of Bactrim) [45].

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