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Swynghedauw B

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Cardiovascular Pharmacogenetics and Pharmacogenomics

B. Swynghedauw

The recent developments of genome-based technology provide to the pharmacologists and therapists new tools that allow genotypings 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

Therapeutic efficacy is a complex issue that obviously includes in the first line a good diagnosis, but even if the diagnosis is unquestionable, every clinician and every participant of a clinical trial knows that there is always, for any drug, a group of non-responders. Geneticians have tried for a long time, to bring their solution to the problem and to help the therapist to better adapt a treatment to a given patient by trying to link various genotypes and drug efficacy. This review aims to define the basis of both pharmacogenetics and of pharmacogenomics, and then to show examples of linkages between either therapeutic efficacy or therapeutic accidents and single nucleotide or insertion/deletion polymorphisms.

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].

Pharmacogenomics 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 'drugable 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

From the U127-INSERM Hôpital Lariboisière, Paris, France
Correspondence to: Bernard Swynghedauw, PhD, MD, FESC, U127-INSERM Hôpital Lariboisière, 41 Bd de la Chapelle 75475 Paris Cedex 10 France; e-mail: bernard.swynghedauw@inserm.lrb.ap-hop-paris.fr

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, CYP2D6, is a drug-metabolizing polymorphic enzyme that belongs to the first two categories. This enzyme is able to both inactivate drugs such as mercaptopurine and to activate opioids. A rather historical example is the activation of codeine by CYP2D6. O-demethylation transforms codeine into an active derivative, morphine. Mutations on CYP2D6 render 2-10 % of the population insensitive to opioids. In these patients, codeine does not have its normal psychomotoric, respiratory and papillary pharmacological effects and is not transformed into morphine as it normally is [4]. The desibroquine range comprises at least 30 drugs including antidepressants and antipsychotics, which are major targets for pharmacogenomics [5], such as clozapine [6] and several cardiovascular drugs such as antiarrhythmics and β-blockers. 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 deshydrogenase 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

Drug	Enzyme	Consequences
Losartan	CYP2C9	Not documented
Flecainide	CYP2D6	Inconsistent β-blockade
Benzodiazepines	CYP2C19 & CYP3A4	Not documented
Carvedilol	CYP2D6	Variations in α1 / β2 blockades
Metoprolol	CYP2D6	Variations in β-blocker activity
Warfarin	CYP2C9	Variations in anticoagulant effect

Antiarrhythmics

(R, S)-propafenone is a widely utilised class 1C antiarrhythmic drug, which is hydroxylated by CYP2D6 to 5-hydroxypropafenone. The drug 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 metabolite 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 anticoagulat properties and bleeding complications. Slow metabolizers have the CYP2C0 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 isogenes (ADH 1, 2, 3) nevertheless ADH 3 is the only locus that give different alleles with different kinetic properties. Pharmacokinetics show indeed that the homodimere γ1γ1 is associated with a fast rate of oxidation as compared to γ2γ2. Homozygoty for γ2γ2 is associated with the highest level of plasma HDL and a reduced risk of myocardial infarction as compared to homozygoty 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 polycyclic 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 GSTT-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 discovered 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 aggression, 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 aetiology 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, xanomeline or tacrine response [5]. Cardiovascular pharmacology is full of similar examples (Tab. 2).

Statins

The cholesterol ester transfer protein (CETP) is a polymorphic protein that plays an important role in regulating the plasma levels of high density lipoproteins (HDL). CETP polymorphism includes two different variants, TaqIb B1 and B2. B1B1 homozygotes have low plasma concentrations of HDL and high concentrations of CETP. Conversely, the B2B2 homozygotes have high HDL and CETP. B1B1 have more severe and more rapidly progressing coronary atherosclerosis. Pravastatin reduces the size of atherosclerotic plaques, but the reduction is significantly more pronounced in patients with the B2B2 polymorphism, as shown by coronarography [17].

A sub-study of the Scandinavian Simvastatin Survival Study, the 4S Study [18] examined whether the risk of death or a major coronary event depends on apolipoprotein E genotype in 966 myocardial infarction survivors. Myocardial infarction survivors with the apolipoprotein E ε4 allele have a nearly 2-fold increased mortality risk as compared to patients with ε2 or ε3. These alleles result from C/T transitions in position 112 and 158. They are functional and have specific activities. Allele ε4 is a risk factor for arteriosclerosis. The 4S Study also demonstrated that patients with the allele ε4 were more sensitive to simvastatin than others and that such a treatment improves mortality and abolishes the excess mortality observed in patients with the ε4 as compared to the other genotypes. Interestingly, such an effect is independent of the plasma cholesterol level strongly suggesting that the protective effects of statins are better linked to its angiogenic properties [19] than to its hypocholesterolaemic effect.

Diuretics for Hypertension

Interindividual variations in antihypertensive therapy are likely to reflect heterogeneity in pathogenic mechanisms [20]. α-adducin is a cytoskeletal protein, and experiments in rats evidenced a mutation at this locus that could explain the increased sodium reabsorption and arterial hypertension. The Gly460Trp genotype of α-adducin is equally linked to hypertension in human and Trp460 heterozygotes were more sensitive to diuretic therapy and had lower plasma renin than Gly460. It is then possible to predict salt-sensitivity, ie the blood pressure response to diuretics, for a given group of hypertensive patients and thus to better select the therapeutic options [21].

Table 2. Predicting drug efficacy from genotyping in cardiovascular pharmacology

Drug	Gene polymorphism	Effect	Reference
Statines			
Pravastatin	CETP	Improved mortality	[17]
Simvastatin	Apolipoprotein E (ε4)	Improved mortality	[18]
Diuretic	α-adducin	Hypotensive effect	[21]
	G-protein	Diuretic effect	[20]
Converting Enzyme	Angiotensinogene	Hypotensive effect	[23]
Inhibitors	Angiotensin II receptor	Debatable	[23]
	Deletion/Insertion on ACE	None Renoprotection controversial	[20, 27, 28, 35] [37, 38]
β-blockers	α-subunit of Gs protein	Hypotensive effect	[33]
	β1 & β2-adrenergic receptor	None	[31]

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 DD/ID/II 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 a large meta-analysis which found no differences between the different genotypes [28]. Several articles have unsuccessfully tried to correlate the insertion/deletion polymorphism with the effects of CEI on blood pressure or on renal function.

Beta-Adrenergic Antagonists and Agonists

β-blockers are now a major tool for treating heart failure, and the large utilisation of the drug enabled us to identify a group of non-responders [29]. It has been suggested that non-responders have functional mutations on one of the genes encoding the adrenergic receptors or on one of the components of the transduction system.

On the β1-adrenergic receptor, several polymorphisms, (C1165G, A145G) have been reported, some, such as C1165G are functional and are transcribed into inactive receptors and could represent a risk factor in patients with heart failure (discussed in [30]). They obviously would constitute a rational basis for non-responses to β-blockers. Three mutations have been discovered on the β2-adrenergic receptor, two of them, in positions 16 and 27, result in alterations of the down-regulation. The third one (Thr/Ile in position 164) modifies the coupling capacity of the receptor to adenylate cyclase, and, in heart failure, has prognosis significance that has been attributed to the fact that these mutated receptors cannot anymore play their compensatory role [31]. The Arg 16 form is less sensitive to the down-regulator effects of β-agonists than the Gly16 allele, and it has been demonstrated that, in asthma, albuterol, a known β2-agonist, has a significantly attenuated efficacy in homozygotes of the variant Arg16 [32]. Several studies are currently trying to resolve this issue in cardiology. A report has suggested that a silent polymorphism (FokI +/–) in exon 5 of the gene of the α-subunit of G_s protein (which is the coupling protein for the adrenoceptors) is associated with pressure response to β-blockers [33]. Several publications aim to predict patient response to antihypertensive drugs using genetic polymorphisms and have failed to evidence any linkage between sensitivity to β-blockers and polymorphisms on either the angiotensin converting enzyme or angiotensinogen [23, 34].

Genetic Polymorphisms in Cardiovascular Drug Targets: Drug Toxicity

Genotyping sometimes succeeds in revealing silent mutations at the occasion of accidents during treatment which were unrelated to the disease (Tab. 3).

Cough During Converting Enzyme Inhibition

Cough occurs in approximately 10 % of patients who are treated with converting enzyme inhibitors. Such a treatment not only inhibits angiotensin II synthesis, but, also, bradykinin degradation and results in a pronounced elevation of the plasma level of bradykinin. Treatment with angiotensin II receptor inhibitors such as losartan never give rise to cough, and it is generally accepted that cough results from the effects of bradykinin on histamine that activates histamine receptors of the respiratory tract. Mukae et al. [39] have identified a point mutation T/C in position -58 on the promotor of the gene encoding the

Table 3. Predicting drug toxicity from genotyping

Drug	Gene polymorphism *(mutation)*	Accidents	Reference
Converting Enzyme Inhibition	**Bradykinin receptor** *T58C*	Cough	[39]
PTCA with stent	**Converting Enzyme** *Deletion / insertion*	Restenosis	[40, 41]
Oral contraceptives			
	Prothrombin gene *G20210A*	Cerebral-vein thrombosis	[42]
	Factor V *G1691A*	Cerebral-vein thrombosis	[42]
K^+ blockers			
	K^+ channel KCNE2/HERG (I_{Kr})		
Clarithromycine	*Q9E-MiRP1*	Torsade de pointe	[44]
Procainamide, Oxatomide, quinidine	*M54T, I57T, A116V-MiRP1*	Arrhythmias	[45]
Bactrim	*T8A-MiRP1*	Arrhythmias	[45]
	K^+ channel KvLQT1 (I_{Ks})		
Cisapride	*Y 315C*	Torsade de pointe	[46]

bradykinin receptor B2. This mutation is functional and 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 persons (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 economical point of view, expensive complication of PTCA. Several studies attempted to establish a linkage between restenosis 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 immobilisation and genetic factors such as inherited abnormalities of the coagulation system. Several polymorphisms that cause hypercoagulability 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 coagulation 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 repolarisation time [43]. In addition, recent reports have shown that, in some cases, these drugs can reveal latent long QT syndrome and that serious accidents including torsade de pointe and severe 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 (I_{Kr}) current, and thus enhance the sensitivity to drugs like clarithromycin or potassium blockers, such as oxatomide (which antagonizes histamine 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 component of Bactrim) [45].

The recent concept of 'formes frustes' of the long QT syndrome 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 I_{Kr} current, whereas KvLQT1 encodes another potassium channel (I_{ks}) 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 slowly leaving the bench 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 polymorphisms directly or indirectly associated to drug-metabolizing enzymes or drug-targets.

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