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Genotyping of Drug Targets
A Method to Predict Adverse Drug Reactions?

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Abstract

In the last decades, advances in molecular biology have led to modern pharmacogenetics, which started as a science that focused on investigating drug metabolising enzymes and genetic determinants of pharmacokinetic variability. As more evidence has become available on the structure of drug targets and the genes coding for them, increasing attention has been directed towards pharmacodynamic explanations of variability in therapeutic response as well as in the risk for adverse drug reactions.

Traditionally, genetic drug safety research has focused on variations in single genes whose functions are known to be related to given adverse drug reactions. A few such examples, malignant hyperthermia, the long QT syndrome, venous thromboembolic disease, tardive dyskinesia, and drug addiction, are presented in this article. In the future, results from the Human Genome Project together with tools such as DNA microarray technology, high-output screening systems and advanced bioinformatics, will permit a more thorough elucidation than is currently possible of the genetic components of adverse drug reactions. By screening for a large number of single nucleotide polymorphisms (SNPs), SNP patterns associated with adverse drug reactions can be discovered even though the functions of the SNPs as such are completely unknown.

On the basis of these findings, it can be expected that pharmacogenetic research will identify situations where a drug should be avoided in certain individuals in order to reduce the risk for adverse drug reactions. If so, it will be feasible to use molecular diagnostics to select drugs that are safe for the individual patient.

Pharmacogenetics started as a science that focused on investigating drug metabolising enzymes and genetic determinants of pharmacokinetic variability. Among the first known such examples were prolonged muscle relaxation after suxamethonium chloride (succinylcholine), which was found to be caused by a mutation on the gene coding for the enzyme pseudocholinesterase (butyrylcholinesterase), and peripheral neuropathy related to isoniazid, which was found to occur at a higher frequency in individuals with a genetic defect in the ability to acetylate this drug. More recently, research in the field of pharmacokinetic variability has been focused predominantly on the cytochrome P450 (CYP) enzymes (table I).

However, even with identical plasma concentrations of a drug across individuals, the variability in drug response is considerable. In some cases, the interindividual variability in drug effects is as high as 10- to 20-fold although the plasma concentrations of the drug are the same.[1] Mutations in genes coding for drug targets are expected to cause much

Table I. Some examples of genetic polymorphisms of metabolic enzymes and drug targets that increase the risk of adverse drug reactions

Enzyme/target/gene	Drug	Adverse drug reaction
Metabolic enzymes		
Pseudocholinesterase (butyrylcholinesterase)	Suxamethonium chloride (succinylcholine)	Prolonged apnoea
N-acetyltransferase 2 (NAT2)	Sulphonamides	Hypersensitivity
	Hydralazine	Lupus erythematosus
	Isoniazid	Neuropathy
Dihydropyrmidine dehydrogenase (DPD)	Fluorouracil	Myelotoxicity
Thiopurine methyltransferase (TPMT)	Azathioprine	Myelotoxicity
	Mercaptopurine	Myelotoxicity
UDP-glucuronosyltransferase 1A1 (UGT1A1)	Irinotecan	Diarrhoea, myelotoxicity
Cytochrome P450 (CYP) 2C9	Warfarin	Haemorrhage
	Glipizide	Hypoglycaemia
	Phenytoin	Increased toxicity
CYP2C19	Diazepam	Prolonged sedation
CYP2D6	Some antiarrhythmics	Proarrhythmic effects
	Some antipsychotics	Extrapyramidal symptoms
	Metoprolol	Bradycardia
Drug targets and related structures		
Ryanodine receptor (RYR1)	Suxamethonium chloride	Malignant hyperthermia
	Inhalational anaesthetics	Malignant hyperthermia
Cardiac ion channels	See section 1.2	Torsade de pointes
Coagulation factor V	Oral contraceptive pills	Thromboembolic disease
Prothrombin	Oral contraceptive pills	Thromboembolic disease
Dopamine D_3 receptor (DRD3)	Antipsychotics	Tardive dyskinesias
Various (see section 1.5)	Opioids	Addiction

UDP = uridine diphosphate.

of this variability, thereby quantitatively or qualitatively altering the sensitivity to drugs. Consequently, interindividual variability in pharmacodynamics could also be expected to increase the risk of experiencing an adverse drug reaction (table I). A recent meta-analysis found that the incidence of serious and fatal adverse drug reactions in the US was 6.7 and 0.32%, respectively, indicating that the clinical consequences as well as the costs of adverse drug reactions are considerable.[2] The high incidence of adverse drug reactions could, at least in part, be caused by the fact that adequate information on the pharmacodynamic variability is often lacking during routine pharmacotherapy.

1. Current Status

Today, very limited knowledge exists about genetic polymorphisms for drug targets and how this would affect the susceptibility for adverse drug reactions. However, the area is witnessing a rapid growth, and information has emerged for several drug/adverse drug reaction combinations. Based upon our own knowledge of the field completed by a literature search, some illustrative examples are presented below.

1.1 Malignant Hyperthermia

Exposing an individual with mutations in the gene coding for the skeletal muscle ryanodine receptor (*RYR1*) gene to suxamethonium chloride or halogenated inhalational anaesthetics may cause the life-threatening condition malignant hyperthermia.[3,4] Traditionally, susceptible patients have been diagnosed by the caffeine halothane contracture test in a fresh muscle biopsy.[5] However, certain obstacles and shortcomings of this

test, such as transportation of the patient to a centre in which the sample can be obtained, inconvenience caused by the muscle biopsy, and a relatively low specificity of the test, places malignant hyperthermia as a difficult condition to diagnose. To date, numerous mutations in the *RYR1* gene are known to cause susceptibility to malignant hyperthermia; the malignant hyperthermia phenotype.[4,6] A better understanding of the genetic factors behind this condition would certainly improve the situation for patients under the threat of malignant hyperthermia, and genetic testing would be expected to be a helpful tool in this respect.[6]

1.2 Long QT Syndrome

Mutations in genes coding for potassium or sodium channels in the heart may cause the congenital long QT syndrome (LQTS).[7] The three most common genes involved are presented in table II.[8-10] Individuals with LQTS have an increased risk for developing the potentially fatal ventricular tachycardia torsade de pointes. Some of the mutations identified markedly prolong the QT interval whereas others affect it only to a minor degree or not at all. However, in addition, individuals with apparently silent mutations might be at risk for developing torsade de pointes when exposed to provoking factors.[11]

Numerous drugs are known to cause the acquired LQTS and provoke torsade de pointes, usually by affecting the rapid component of the delayed potassium rectifier current (I_{Kr}). These drugs include antiarrhythmics such as quinidine, disopyramide, procainamide, sotalol, ibutilide and dofetilide as well as non-cardiac drugs such as thioridazine, pimozide, halofantrine, terfenadine and cisapride.[12] Patients with LQTS mutations most likely have an increased risk for developing drug-induced torsade de pointes. For example, an increased frequency of some of the LQTS mutations has been found in patients with torsade de pointes induced by disopyramide, mefloquine, and clarithromycin.[13-15] Although currently it is not possible to quantify the excess risk of drug-induced torsade de pointes in individuals with LQTS mutations, it has been suggested that individuals having a mutation (or having a prolonged QT interval in an electrocardiogram investigation) should be provided with lists of which drugs to avoid. Updated lists are available, for example, on the Internet.[12]

1.3 Thromboembolic Disease

Mutations both in the coagulation factor V gene and in the prothrombin gene are known to be risk factors for venous thromboembolic disease. The mutation best studied is the factor V Leiden mutation, causing activated protein C resistance. The frequency of this mutation varies from 2 to 15% in different populations, whereas the frequency of the prothrombin G20120A mutation is about 1 to 4%. Although these proteins are not drug targets *per se*, the risk of drug-induced thromboembolic disease is increased when individuals with either mutation are treated with drugs that may induce clotting. For example, being a heterozygous carrier of one of these mutations increases the risk of having a venous thromboembolism by 5-fold to 10-fold irrespective of any drug therapy.[16-18] This risk excess is approximately the same as not having any of

Table II. The three most common types of congenital long QT syndrome (LQTS)

Disease	LQT1	LQT2	LQT3
Gene	*KCNQ1/KVLQT1*	*KCNH2/HERG*	*SCN5A*
Chromosome	11p15	7q35	3p21
Ion channel	KVLQT1	HERG	SCN5A
Electric current affected	I_{Ks}	I_{Kr}	I_{Na}
Percentage[a]	>50%?	30-40%	<5%

a Percentage with this particular LQTS subtype in relation to all congenital LQTS types.

HERG = human ether-a-go-go-related gene; I_{Kr} = rapid component of the delayed potassium rectifier current; I_{Ks} = slow component of the delayed potassium rectifier current; I_{Na} = sodium current.

these mutations, but being treated with a combination oral contraceptive pill.[16-18]

In contrast, when an individual being heterozygous for one of these mutations is treated with a combination oral contraceptive pill, the risk increases 20-fold to 150-fold.[16-18] It could be expected that there is an excess risk also when such individuals are exposed to other drugs known to cause venous thromboembolism, e.g. tamoxifen and clozapine, but this has not yet been systematically studied. Routine testing for the factor V Leiden mutation is available in many countries, but to screen oral contraceptive users for this mutation is usually considered not justified.[19]

1.4 Tardive Dyskinesia

Tardive dyskinesia is a potentially irreversible movement disorder that occurs after long-term treatment with antipsychotic drugs. As the dopamine D_3 receptor is thought to play a role in locomotion, the D_3 receptor (*DRD3*) gene has been investigated in tardive dyskinesias. In three studies,[20-22] the Ser9Gly polymorphism was associated with an increased risk for tardive dyskinesias. However, although these results are encouraging, the predictive value of a positive test is low, so the clinical usefulness of such testing would be very limited. Nevertheless, it might well be the case that a higher predictive value can be achieved when mutations in genes coding for other receptors, such as the serotonin 5-HT_{2A} and 5-HT_{2C} receptors, are included.[23,24] Such combination testing has been shown to be successful in other situations, e.g. in the prediction of the therapeutic response to clozapine.[25]

1.5 Drug Addiction

Several studies have addressed the possible association between addiction and mutations in genes coding for neurotransmitter receptors. Receptors in which mutations have been found to be associated with opiate dependence include the D_2, D_3 and D_4 receptors (*DRD2*, *DRD3*, and *DRD4* genes, respectively) as well as the opioid delta (OP_1) receptor (*OPRD1* gene) [for a review, see Lichtermann et al.[26]). The associations are, however, weak and partly inconsistent, so it remains speculative whether these findings will be shown to have any clinical significance. In fact, a recent study of almost 1500 different mutations not associated with any of these receptors clearly indicates that the genetic contributions to the vulnerability to substance abuse are very complex.[27]

2. The Future

In the last decades, the origin of information for drug discovery has shifted towards molecular biology research. New tools have provided us with a chance to design drugs for the targets, and consequently, variations in the structure of the targets have not gone unnoticed.

These advancements could be used as a basis for the development of safer drugs in general.[28] The specific examples presented in section 1 represent mutations in genes whose function is known to be related to a given adverse drug reaction ('candidate genes') and are therefore relatively easy to recognise and study. It is likely that for many adverse drug reactions, the susceptibility trait is even more complex, and that mutations in other genes, whose function is still unknown, are also associated with the susceptibility of having an adverse drug reaction.

2.1 Screening for Single Nucleotide Polymorphisms

It is estimated that at least 80% of the top 20 pharmaceutical companies are now collecting more or less complete genetic data during clinical trials.[29] Most of the information gathered is, however, used to determine drug responses rather than exploring adverse drug reactions. Thus, the new paradigm is expected to be that the human genome is screened for single nucleotide polymorphisms (SNPs) that may be associated with a drug response, instead of using the conventional candidate gene approach.[30] Although novel methodology is being developed for how SNP knowledge should be employed for the determination of the therapeutic effects of drugs, very little is known

how it should be applied for the study of adverse drug reactions in clinical trials.[31]

As SNPs are expected to occur in about one of every 1500 to 2000 base pair if two unrelated individuals are compared, any two individuals would on average be expected to differ by 1.4 to 1.5 million base pairs.[32] The occurrence of these SNPs can thus be correlated to the appearance of adverse drug reactions, and an individual's SNP 'fingerprint' can be used to calculate the risk of an adverse drug reaction. For example, the drug manufacturer GlaxoSmithKline is collecting DNA from 150 patients who are hypersensitive to the anti-HIV drug abacavir and from 150 controls, analysing 200 000 SNPs throughout the genome in order to find a set of SNPs that distinguish the 3 to 5% of patients who are hypersensitive, from those who are not hypersensitive to abacavir.[28] The functions of these SNP patterns will most likely be completely unknown; they will just be markers that indicate intolerance. A few years ago, this would have been a daunting task to accomplish. However, new genomic technology, which in part has already been established and in part is currently being further developed, makes such tasks possible.[33,34]

If this approach is found to be successful, it can be anticipated that all pharmaceutical companies will follow the same route in order to identify patients at risk for developing adverse drug reactions. It is, however, an open question as to what cost the pharmaceutical manufacturers would be prepared to put into such research, and how such testing would affect the manufacturers' income. Prior knowledge of genetic determinants of safety may perhaps allow testing the drug in a smaller number of individuals, thus reducing research and development costs. Moreover, drugs that have a genetic safety predictor may also gain a marketing advantage. On the other hand, the number of individuals to be treated with the drug will be reduced. Seen from a health economical point of view, it is also an open question whether the costs for genetic testing, if found to be clinically useful, would be favourable in comparison to the expenditures evoked by the adverse drug reactions thereby prevented.

2.2 Proteomics

The purpose of proteomics is to reveal the structure of all human proteins, which would make it easier to develop specifically targeted drugs. With genomics, proteomics is promising to be the next Rosetta Stone of biological sciences and will provide a helpful shortcut in deciphering the gene function. Even though in its initial state, it is clear that proteomics will provide us with information on many new drug targets. In fact, the number of current drug targets is expected to multiply by almost a thousand. New discoveries, especially on signal transduction in addition to receptors and enzymes as targets for drug action, is likely to define new 'diseases' as well as 'cures'. Currently, the first step in proteomics research is to improve our understanding of cellular mechanisms in order to identify suitable targets. Steps to follow are discovery of new drugs to modify these new targets as well as utilisation of the knowledge in order to try to predict adverse drug reactions.

2.3 Microarray Technology

As biological functions are a complex network of many different gene products in which the overall gene expression profile determines the phenotype of a cell, it is difficult or even impossible to predict the function of a gene or a protein purely from its genomic sequence. A much-needed solution to this problem is provided by microarray technology, which gives global information about a cell's response to stimuli in regard to gene expression. Since the information gathered is not restricted to a single gene or process, microarray technology has a potential to broaden our understanding of cell function and pathology, and might well change the overall picture in drug discovery and adverse effect profiling.[35-37]

2.4 Gene/Environment Interactions

It is obvious that for almost all mutations eventually found to be associated with an increased risk for an adverse drug reaction, the association will be less than 100%. In many cases, it can be anticipated that the predictive value of finding a certain mutation or a set of mutations will be rather low. For example, the factor V Leiden mutation is fairly common (on average 5% in the population), and the risk of thromboembolic disease when having this mutation and being treated with an oral contraceptive drug, is increased approximately 10-fold when compared with taking the oral contraceptive pill without having the mutation. Nevertheless, although these numbers are relatively high, approximately 350 factor V Leiden mutation carriers would have to be denied oral contraceptives in order to prevent one thromboembolic episode, and a total of 7000 individuals would have to be screened in order to identify these carriers. Thus, massive testing would be required, and the costs associated with such testing would be considerable.[19] To overcome this problem, a possibility could be to refine the methodology, e.g. by restricting testing to individuals with known additional risk factors. In the case of thromboembolic disease, such risk factors could include e.g. cigarette smoking, thromboembolic disease among family members, age above a certain limit, etc.

Also for the LQTS, several environmental factors may modify the genetic predisposition. For example, the drug dose (or specifically, the drug concentration) is a risk factor, as shown, e.g. for terfenadine combined with CYP3A4 inhibitors such as erythromycin.[38] Moreover, electrolyte perturbations such as hypokalaemia increase the risk of torsade de pointes. Conversely, for tardive dyskinesias, factors such as the receptor profile of the specific drug used, the cumulative drug dose, gender and patient age would be expected to modify the genetic risk.[39]

In fact, it might well be the case that if the genetic predisposition is strong, the provoking factor can be minimal in order to develop the adverse drug reaction, whereas if the genetic predisposition is weak, a stronger provoking factor (such as a higher drug concentration or the existence of additional environmental risk factors) is needed.

One well-known factor recognised even before the discoveries of complex genetic analyses is ethnicity. Subsequently, it has been shown that genetic variations occur at different frequencies among different ethnic subpopulations. Although most studies in this field have been carried out with respect to drug-metabolising enzymes,[40] it can be expected that such diversities also exist for drug targets. This variability implies that ethnicity is an important factor to be considered both in pharmacogenetic studies and in the case when the results from such studies are being applied on different clinical populations.

3. Conclusions

The success of pharmacogenetic approaches in determining the impact of genetic polymorphisms causing adverse drug reactions is to a large part dependent on the possibility to investigate specific candidate genes coding for drug targets. On the other hand, with the Human Genome Project, virtually every gene in the genome can be studied. Thus, an alternative approach to the candidate gene approach, SNP mapping, is also attractive because it offers an unbiased look at the whole genome not restricted to a specific hypothesis. Consequently, with SNP mapping, not only can mutation patterns for the prediction of adverse drug reactions be explored, but it might also be possible to locate hitherto unknown causative genes for the adverse drug reaction phenotype. One major challenge for the future will be to reveal the function of such genes in relation to adverse drug reactions.

Considering the variability in human behaviour and the complexity of our environment, it could be a difficult task to fulfil the high expectations with regard to genetic testing in order to predict, and thereby avoid, adverse drug reactions, and to facilitate the development of safer drugs. On the other hand, rapid developments in research techniques have the potential of generating fundamental changes in our understanding of the genome and

drug targets. DNA microarray technology, high-output screening systems and advanced bioinformatics will permit a more thorough elucidation than today of the complex genetic components of adverse drug reactions. The importance of this area of research is now beginning to be recognised, predominantly within the pharmaceutical industry, but also in clinical practice.

Awareness of inherited variations of adverse drug reaction responsiveness will most likely, at least for some drugs, lead to situations where the drug should be avoided in certain individuals in order to reduce the risk for adverse drug reactions. If so, it will be feasible to use molecular diagnostics to select drugs with an improved safety profile for the individual patient.

4. Note Added in Proof

Very recently, it was published that in patients from Australia treated with abacavir, the presence of *HLA-B*5701*, *HLA-DR7*, and *HLA-DQ3* had a positive predictive value of hypersensitivity to abacavir of 100% and a negative predictive value of 97%.[41] In another study from the US, the sensitivity of *HLA-B5701* for identifying patients hypersensitive to abacavir in Caucasians was 55%, but the sensitivity dropped to 33% when *HLA-DR7* was added.[42]

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