Pharmacogenetics – impact on future medical treatment and healthcare

It has long been known that responses to pharmaceuticals vary widely within the general population. Some individuals may experience adverse drug effects while others may not, and drugs that are therapeutic in some individuals are ineffective in others. For example, it is estimated that in the US more than 100,000 deaths occur each year due to side effects of frequently prescribed medication. Age, nutrition, health status, environmental exposure, and concurrent therapy can contribute considerably to this phenomenon. However, inherited differences are one of the most important factors in predicting drug response. Over the last few years human genome research has improved the understanding of these genetic factors. Variants in genes could be identified that are associated with processes such as the metabolism of pharmaceutical compounds and nutriments. This has led to an improvement of knowledge in a segment of genetic research that focuses on studies of genes involved in drug metabolism including resorption and detoxification, as well as drug target genes: Pharmacogenetics. Identified genetic variants - polymorphisms - could be shown to be associated with the variation in drug responses between individuals. This variation can result from numerous defects ranging from deficiency of drug metabolising enzymes with a consequently increased risk of concentration-related toxicity, to enhanced enzyme activity resulting in lower drug concentration and decreased response to therapy (see Box1).

- Extended pharmacological effect
- Adverse drug reactions
- Lack of pro-drug activation
- Increased effective dose
- Metabolism by alternative, deleterious pathways
- Exacerbated drug-drug interactions

Box1: Polymorphic drug metabolism and potential consequences

One example of a very common variation with functional consequences that was shown to be associated with a genetic variation is the response to the substance codeine: 6-10% of Caucasians carry an inherited polymorphism in the gene coding for the enzyme CYP2D6 that causes a deficiency of this activating enzyme and therefore a markedly reduced response to the drug. In addition to polymorphisms in genes of drug metabolising enzymes, targets such as drug receptors, transporters and other mediators of cell signalling can be major determinants of clinical response.

By enabling prescription of more efficient treatments according to patients´ genetic profiles, pharmacogenetics opens the door to personalized medicine with a reduction of the individual risk for adverse toxic side effects as a consequence. Furthermore, pharmacogenetics will enable a better understanding of effects generated by new medication, the development of new therapeutic molecules, and finally reduces costs related to clinical trials. With a more accurate dosage of drugs and less development costs, pharmacogenetics can produce substantial savings for the public health system in addition to personal benefits of an individually optimized medical therapy.

Pharmacogenetic diagnostic service

Bioscientia offers pharmaceutical and biotechnology companies including Clinical Research Organisations (CRO´s) a comprehensive package of pharmacogenetic assays. The advantage of such an approach is the improvement of clinical studies and drug treatment by a preselection of patients based on their genetic profiles. This allows for a more focused selection of new drugs for clinical phase studies, or the ability to trace patients' histories retrospectively for genetic alterations which may explain observed unexpected effects or failure of treatment. Integrating pharmacogenetics into drug development means significant cost reductions in R&D and an increased likelihood of drug approval and patient safety.

Physicians will be provided with the most comprehensive information on their patient's pharmacogenetic background enabling them to select the most effective medication and optimal dosage thereby reducing possible adverse drug reactions to a minimum. An update on latest research about how specific genetic variants will influence individual drugs, complements each pharmacogenetic profiling report.

Pharmacogenetically relevant drugs and their major metabolic pathways

Psychiatry/Neurology

Drug class	Drug	Enzyme/Gene
Antiepileptics	Phenobarbital	CYP2C9
	Phenytoin	CYP2C9
Neuroleptics	Haloperidol	CYP2D6
	Clozapine	CYP2D6
Tricyclic antidepressants	Nortriptyline	CYP2D6
	Amitriptyline	CYP2D6/CYP2C19
Other antidepressants	Fluoxetin	CYP2D6/CYP2C9
	MAO-Inhibitors (Moclobemide)	CYP2C19
Analgetics	Codeine	CYP2D6
Benzodiazepines	Diazepam	CYP2C19
NSARs	Diclofenac	CYP2C9
	Ibuprofen	CYP2C9

Oncology/Haematology

Drug class	Drug	Enzyme/Gene
Thiopurines	Azathioprine	TPMT
	6-Mercaptopurine	TPMT
Topoisomerase-1-Inhibitors	Irinotecans	UGT1A1
Cytostatics	Anthracycline	MDR1
	Taxans	MDR1
	Vinca alkaloids	MDR1
	5-Fluorouracil	DPD

Cardiology

Drug class	Drug	Enzyme/Gene
Antiarrhythmics	Mexiletine	CYP2D6
	Procainamide	NAT2
Beta-Blocker	Propranolol	CYP2D6/CYP2C19
	Carvedilole	CYP2D6
	Irbesartan	CYP2C9
Beta-2-Receptor Agonists	Salbutamol	ADRB2
Statins	Fluvastatine	CYP2C9
Vitamin K Antagonists / Coumarine derivatives	S-Warfarin	CYP2C9 VKORC1
	Marcumar	CYP2C9

Endocrinology/Gastroenterology

Drug class	Drug	Enzyme/Gene
Antidiabetics	Glibenclamide	CYP2C9
	Tolbutamide	CYP2C9
	Troglitazone	CYP2C9
Diuretics	Torasemide	CYP2C9
	Tienilinic acid	CYP2C9
Hormones	Estrogen	COMT/CYP2C9
	Tamoxifen	CYP2D6/CYP2C9
Neurotransmitter	L-Dopa	COMT
Proton Pump Inhibitors	Omeprazole	CYP2C19
	Lansoprazoel	CYP2C19
	Pantoprazole	CYP2C19

Pharmacogenetic Assays/Analyses

Enzyme	Alleles
CYP1A1/CYP1A2	*2A, *2B, *2C / *1F
CYP2C9	*1, *2, *3, *4
CYP2C19	*1, *2, *3, *4; *5
CYP2D6	*1, *2, *3, *4, *5, *6, *7, *8, *9,*10,*11, *14, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *36, *40, *41, *1XN, *2XN, *4XN,*10XN, *17XN, *35XN, *41XN
CYP3A4	*1B
DPD	*2A (Exon 14 Skipping)
NAT2	*4 -7, *10-14, *17-19
GST-M1	*0 (Gene Deletion)
GST-T1	*0 (Gene Deletion)
GST-P1	*A, *B, *C, *D
TPMT	*2, *3A,*3B,*3C,*3D
UGT1A1	*28 (TA-Expansion Promoter), *6 (G71R), *7 (Y486D), *27 (P229Q), *60 (-3279T>G Promoter), *62 (F83L)
COMT	V158M
VKORC1	*1, *2, *3, *4

Other drug targets

Gene	Alleles
MDR-1	C3435>T
APOE	E2, E3, E4
APOB	R3500Q, R3500W
MTHFR	C677>T
PAI-1	-4G/-5G
ADRB-2	R16G, Q27E, T164I

Further targets on request

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Pharmacogenetics

State of the art solutions
in modern genetic diagnostics