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Mini Review

PERSONALISED MEDICINE: THE RISING SUN

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Abstract

Inter individual genetic variation contributes to both disease susceptibility and response to drugs. The genetic makeup of every individual is distinctive, henceforth there are variations in the gene products. It is also responsible for the phenotypic diversity, which results in the different capacity of each individual to respond to exogenous substances, such as drugs and xenobiotics, and in the different propensity to induce undesirable health effects. So, the aim of personalised medicine is to increase the possibility of therapeutic efficiency and to decrease the drug toxicity risk for an individual patient.

Keywords: Pharmacogenetics; Epigenetic; Xenobiotics; Pharmacokinetics; Pharmacodynamics.

Pharmacogenetic variation in drug response

As a rule, humans vary in their responses to environmental factors because of variability in their genes and their genes' epigenetic modification. The same level of chemical exposure may give rise to different biological effects in different individuals. For example, it has been shown earlier (Marsh and McLeod, 2004) that, severe life-threatening toxicities can occur in some individuals treated with irinotecan, an anticancer drug. Although multiple genes play a role in irinotecan activity, polymorphisms in the UDP glycuronosyltransferase 1 family, polypeptide A1 (UGT1A1), enzyme have been strongly associated with irinotecan toxicity.

Factors that are Relevant to Understand Human Variability

Variation in Gene Sequence

Gene-environment interactions refer to effects in which human genetic variability governs differential responses to environmental exposures. This variation in DNA sequence influences individual characteristics such as physical appearance, susceptibility to disease and response to medical treatments. A central goal of medical and population genetics is to understand the patterns and determinants of sequence variation in the human population. The paraoxonase 1 gene (PON1) encodes an enzyme involved in the metabolism of chlorpyrifos, an organophosphate pesticide, widely used in agricultural settings to protect crops from insects. Organophosphate pesticides affect the nervous system of animals and acute toxicity is characterized by nausea, diarrhea , impaired muscle function and respiratory illness due to the effects on respiratory muscles (Blondell, J, 1999). There has been extensive research on the relationship between pesticide toxicity and variations in the PON1 gene. Variations in the PON1 gene have been associated with both the amount and the type of paraoxonase 1 enzyme produced as part of the body's normal detoxification system. Specifically, a mutation in the amino acid sequence of the gene at position 192 changes a glutamine to arginine (Q192R) and is associated with variable enzyme activity in the population. In addition, at least one mutation in the promoter region of the gene has been associated with a two fold increase in gene expression and consequently, enzyme production (Li WF *et al.*, 1993).

Gene-gene interactions

Gene-gene interactions are another important area of research for understanding human susceptibility to chemical sensitivity. This refers to situations in which one gene modifies the effect of another gene on disease or other adverse effects. In a recent study, it has been shown (McKeown-Eyssen GC *et al.*, 2004) that, a gene-gene interaction between Arylamine-N-Acetyl Transferase (NAT2) and Cytochrome-P450-2D6 (CYP2D6) enzymes has multiple chemical sensitivity. These results suggests that individuals with the rapid-metabolizing forms of both these enzymes were 18 times more likely to have chemical hypersensitivity than individuals with normal metabolizing forms of these enzymes. Also, it has been studied (Le Corre P *et al.*, 2004) that, gene-gene interactions between CYP2D6 and another P450 enzyme (CYP3A4) have also

been found to influence the metabolism of commonly used pharmaceutical agents.

Epigenetic Variability

Variations in susceptibility are not only due to polymorphisms in DNA sequence. Epigenetics refers to the study of reversible heritable changes in gene function that occur without a change in the sequence of nuclear DNA. These changes are major regulators of gene expression. It has been shown earlier that, differences in gene expression due to epigenetic factors are increasingly recognized as an important basis for individual variation in susceptibility and diseases (Scarano MI *et al.,* 2005). Epigenetic phenomena include DNA methylation, imprinting, and histone modifications. Among all the three, DNA methylation is the most easily measured and amenable to the efficient analysis characteristic of toxicogenomic technologies. DNA methylation refers to addition of a methyl group to the 5^{th}-carbon of cytosine in an area of DNA, by the enzyme DNA methyltransferase. It has been shown (Jaenisch R and Bird A, 2003) that, epigenetic regulation of cell phenotypes is DNA methylation, which turns off a gene or gene region by changing the chemical structure of the DNA.

Gene Expression Variability

Another way to assess human variability is to look downstream of the gene sequence or its epigenetic modification to the amount of mRNA expressed by the genes, examining differences in the amount expressed rather than just differences in what is expressed.

It has been illustrated, by Single Nucleotide Polymorphism (SNPs) variation, that how both gene expression and genetic sequence together could be used to study human variation in drug responsiveness.

Human carboxylesterases 1 and 2 (CES1 and CES2) catalyze the hydrolysis of many exogenous compounds and play an important role in the metabolism of toxic chemicals in the body. Alterations in carboxylesterase sequences could lead to variation in both the activation and inactivation of drugs. A study (Marsh S *et al.,* 2004) in individuals of European and African populations, identified novel SNPs in CES1 and CES2 and showed that, at least one SNP in the CES2 gene was associated with reduced CES2 mRNA expression. Analysis of genetic variation between individuals involves first the discovery of SNPs and then the analysis of these variation in populations. Current advances in statistical genetics analysis methods, sequencing technologies and clinical trial designs have shown promise for the discovery of variants associated with drug response.

Components of Personalised Medicine

There are four essential components of personalized medicine. As the first component, personalized medicine requires standard health risk assessment (HRA) tools capable of evaluating an individual's possibility of developing a certain disease. One well-known HRA tool is the Diabetes Risk Calculator (Heikes KE *et al,* 2008), the purpose of which is the calculation of the probability that an individual has either diabetes or prediabetes. The second component is family health history (FHH), which is a complex combination of shared genetic, environmental and life style risk factors (Hariri S. *et al.,* 2006) FHH has tremendous potential for improving preventive healthcare in a personal manner. Regarding the third component, personalized medicine needs to integrate information on genomes and their derivatives, such as the transcriptome, proteome and metabolome. Upon completion of the reference human genome sequence, sequence variation was discovered among individuals, and it is estimated that 10-15 million common sequence variants (minor allele frequency $>5\%$) are polymorphic in humans (Willard H. 2009).The fourth component is the clinical decision support (CDS) system. CDS systems are interactive computer programs intended to assist clinicians in their decisions regarding disease care.

Some instances of Drugs that have potential for personalisation, have been summarised

Thiopurines

The thiopurine drugs, Azathiopurine (AZA), 6-Mercaptopurine (6-MP) and thioguanine (TG) are generally used in the clinical practices, such as childhood acute lymphoblastic leukemia (ALL), organ transplant rejection and rheumatic diseases. The polymorphic thiopurine S-Methyl-Transferase (TPMT) catalyses the S- methylation of 6-MP and AZA, with genetically deficient TPMT causing increased production of 6- thioguanine nucleotides (6-TGNs) that exerts therapeutic and toxic hematologic effects. Thus, of clinical significance is how to balance a lower risk of drug toxicity (such as serious and life threatening) myelosuppression and an increased risk of therapy failure or disease relapse (such as ALL). A large number of studies have shown that several common defective TPMT variant alleles (TPMT*2, *3A and *3C) results in an impaired capability to metabolise AZA and 6MP (Van Aken J *et al.,* 2003)

Since there is a significant co-relation between TPMT genotype and TPMT activity considered in the peripheral erythrocytes, individualization of drug dosing could be enhanced by determining genotype or more frequently phenotype (Mc leod H.L, Siva C, 2002).Compared with the carriers of the TPMT*1 allele who have normal activity, patients who have intermediate activity or are heterozygous for TPMT*1 allele, requires 65% of the conventional dosage, whereas TPMT-deficient patients requires 5-10% of the above dose. Currently this genetic polymorphism is widely thought to be one of the best examples of the translation of the genomic information into clinical practice. For example, it was estimated that TPMT genetic tests were

performed over 4000 times throughout Australia and New Zealand in 2003 (Gardiner SJ, Begg EJ, 2005). Prospective genotyping or phenotyping in able to improve TPMT-associated drug therapy and avoid drug toxicity (Gardiner SJ *et al*. 2005;Marshall E, 2003; Corominas H, Baiget M, 2004)

Oral Anticoagulants

The coumarin anticoagulants, including warfarin, acenocoumarol and phenprocoumon, are a class of extensively prescribed oral anticoagulants each having a narrow therapeutic index and a wide interindividual variations in dose requirements. A large number of pharmacogenetic studies have revealed that the genetic polymorphisms in the genes encoding drug-metabolizing enzyme CYP2C9 (Daly AK, 2007) the warfarin target protein Vitamin-K Epoxide Reductase Complex1 (VKORC1) (D'Andrea G *et al.*, 2005; Rieder MJ *et al*, 2005;Veenstra DL *et al*, 2005) and Vitamin-K dependent proteins (Shikata E *et al.*, 2004) such as clotting factors II (prothrombin) and VII, as well as γ-glutamyl carboxylase (GGC), may affect the response to these drugs. For the CYP2C9 gene, some evidence indicated that CYP2C9*2 was associated with reduced warfarin dose requirement, whereas all studies demonstrated that individuals carrying at least one CYP2C9*3 allele required a lower than normal dose for all three coumarin anti-coagulants than those without this variant (Daly AK, 2007; Schalekamp T *et al*., 2004; Xie HG *et al.*, 2002). More importantly the carriers of these variants (particularly CYP2C9*3 allele) appeared more likely to experience bleeding events due to overanticoagulation after taking conventional doses. This is because the variant enzymes exhibits a markedly impaired ability to catalyze the metabolism of the pharmacologically more active S-enantiomers of these drugs, leading to increased plasma drug levels. For the target gene VKORC1, ten common polymorphisms were identified in its promoter region and five main haplotypes inferred, in which haplotypes1 & 2 were shown to be associated with a low dose requirement of warfarin, whereas haplotypes 7-9 were responsible for a high dose requirement (Rieder MJ *et al.*, 2005; Veenstra DL *et al.*, 2005).

Conclusion

An obstruction in applying Personalised Medicine to risk reduction in humans is the difficulty in conducting large population studies to understand the distribution of gene-environment interactions in the population at large. Without adequate method of exposure, studies of gene-environment interactions the risk reduction cannot be carried out effectively and as genomic data is the driving force behind personalized medicine, it will not change traditional medicine but instead will make healthcare more safe and successful for individual patients.

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