Table 1. The prototype for the genome basis of drug efficacy

Pharmacogenomic: An era to shift from generalized to personalized drug therapy.

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Back-ground

To develop rationale means through genomically guided research in all drug development and treatment programs to improve efficacy, avoid life threatening side effects and promote cost effectiveness. It could act as a tool for individuals to change their way of life and adopt precautionary ways for future better life.

Introduction

In order to achieve differential drug response we need to identify genomic variants of individual patients. Until recently very limited data has been known(1).As a result patient and Pharmaceutical industries experiencing financial burden , only in USA at least one third of prescription drug amount is wasted .The reason is major proportion of patients received medications which at individual level either ineffective or produce serious adverse drug reactions. Same challenges exist in the development of new drugs. Pharmaceutical industries now focus at point that study of genetic information of diseases is prerequisite for effective new drug development. Several studies highlighted the importance of genomically guided research in making personalised decision for medicines(2-5).The studies used to identify DNA sequence like GWAS(Genome wide association studies) determined > 250 disease traits (including heart attack, diabetes, most cancers, Alzheimer's disease and most autoimmune diseases) with an Odd ratio in the range of 1.05-1.15. Such ratio indicate a small effect and most of these studies remained unresolved but on the other hand pharmacogenomic studies achieve odd ratio of > 3.0(equivalent to >300% increased efficacy or safety) compared with common disease GWAS(6). Before the GWAS era, many candidate gene studies suggested associations between sequence variation and responses to drugs such as codeine, abacavir and nortiptyline. With rare variants estimated to frequently occur in drug target genes (1 every 17 bases), it is highly probable sequencing will yield further insights into drug responses. A prime example for the lack of efficacy in drugs today is for tumor necrosis factor (TNF) α-receptor blockers, the leading group of prescription drugs worldwide by gross sales(7-9) (Table 1).

The application of pharmacogenomic studies to determine genetic (DNA) variants responsible for serious adverse drug reactions GWAS have been shown to be an extraordinarily powerful tool for finding sequence variants tied to key drug side effects. Mainly these adverse effects include drug-induced liver injury, drug-induced renal injury and serious skin rashes. In the past various drugs withdrawal from market due to their serious life threatening adverse reactions e.g. rofecoxib and rosiglitazone were never subjected to state-of-the art pharmacogenetic investigations. Then Several candidate gene studies performed to determine association between variation among alleles of human leucokocyte antigens(HLA) triggered by wide variety of structurally different therapeutic agents(Table 2).These studies are origin specific , but it emphasize on the strong need to extend these studies across all ancestries ,races and regions.The integration of GWAS within drug development pipelines to reduce drug attrition and development costs but it must be recognize by FDA and European Medicine Agency that there should be systemic assessment for all new drug development programe for all clinical trials that are being conducted (http:// www.clinicaltrials.gov/). This will reduce the bias in the literature resulting from unpublished studies. Genomically guided trials require fewer patients to be monitored over a shorter time frame but with sufficient statistical power, thereby markedly reducing costs for biotech/pharmaceutical companies or other providers operating trials.

Limitations in the pathway of Clinical Pharmacogenetics

Currently major barriers for effective clinical pharmacogenetic testing include:

- ➢Time consuming and costly process
- ➢Lack of knowledge among physician about pharmacogenomic studies.
- ➢Lack of proprietary status of commercially available drugs so less interest to evaluate pharmacogenomics of the drug's efficacy and safety.

Conclusions

The future is for Pharmacogenomics and gene sequencing for individualization of not only for prescription medicines but also for future development of drugs. No one can conflict about the influence of human genomes on drug efficacy and safety but unfortunately such studies are still far away from routine practice.This could be only overwhelm by mutual efforts of stake holders of life sciences industry and medical community.

Table 1. The prototype for the genome basis of drug efficacy

Drug	Indication	Population response	GWAS
Polyethylene glycol– modified (pegylated) interferon-α	Standard drug used in the treatment of chronic infections of hepatitis C virus (HCV)	Injectable pegylated interferon-α and oral ribavirin, costing ~ $50,000 per patient per year but the treatment is effective in less than 50% of patients.	GWAS have been carried out in various HCV-infected populations, and the results indicate that three single nucleotide polymorphisms (SNPs) in IL28B are mainly responsible for an individual's responsiveness to pegylated interferon-α/ ribavirin.[10,11]
Clopidogrel	Standard adjunctive anti-platelet agent	With >2 million coronary stenting procedures performed annually, variants that determine the differential responsiveness to clopidogrel	GWAS validated previous candidate gene studies and implicated CYP2C19 loss-of-function (LOF) polymorphisms with reduced anti-platelet effects and a threefold increased risk of stent thrombosis.[12-14]
Metformin (Glucophage)	Top-selling drug for glycemic control,	25% of individuals receiving the top-selling drug for glycemic control, contradicted previous pharmacogenetic evidence and showed nonresponsiveness	GWAS suggested that a SNP close to the ataxia telangiectasia gene was involved in drug response, which disappointingly accounted for only 2.5% of the total glycemic variability observed.[15,16]

Table 2. Therapeutic agents with their possible variation among HLA alleles

Therapeutic agents	ADR accounts	Possible association (Allele name)	Targeted population
Ximelagatran[17]	Hepatotoxicity	HLA DRB 1 gene (P= 6.0x 10^{-6}) HLA –DRB 1 *0701 (P = 4 x 10^{-5})	Swedish ancestry population
Floxapen[18]	Hepatotoxicity	HLA B*5701 (OR, 80.6; 95% CI, 23–285)	European ancestry
amoxicillin-clavulanate[19]	Hepatotoxicity	DRB1*1501-DQB1*0602- DQA1*0102	European ancestry
Carbamazepine[20,21]	Hypersensitivity reactions	HLA-A*3103	European ancestry
Carbamazepine[22]	Stevens-Johnson syndrome	HLA-B*1502	Asian ancestry
Statins[23]	Rhabdomyolysis	SLCO1B1 (OR, 17.4; 95% CI, 4.8– 62.9)	European ancestry
Lumiracoxib[24]	Hepatotoxicity	HLA-DQA1*0102	European ancestry

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