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Personalized medicine: Genetic risk prediction of drug response

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ABSTRACT

Pharmacogenomics (PGx), a substantial component of "personalized medicine", seeks to understand each individual's genetic composition to optimize drug therapy –– maximizing beneficial drug response, while minimizing adverse drug reactions (ADRs). Drug responses are highly variable because innumerable factors contribute to ultimate phenotypic outcomes. Recent genome-wide PGx studies have provided some insight into genetic basis of variability in drug response. These can be grouped into three categories. [a] *Monogenic* (Mendelian) *traits* include early examples mostly of inherited disorders, and some severe (idiosyncratic) ADRs typically influenced by single rare coding variants. [b] *Predominantly oligogenic traits* represent variation largely influenced by a small number of major pharmacokinetic or pharmacodynamic genes. [c] *Complex PGx traits* resemble most multifactorial quantitative traits –– influenced by numerous small-effect variants, together with epigenetic effects and environmental factors. Prediction of *monogenic drug responses* is relatively simple, involving detection of underlying mutations; due to rarity of these events and incomplete penetrance, however, prospective tests based on genotype will have high false-positive rates, plus pharmacoeconomics will require justification. Prediction of *predominantly oligogenic traits* is slowly improving. Although a substantial fraction of variation can be explained by limited numbers of large-effect genetic variants, uncertainty in successful predictions and overall cost-benefit ratios will make such tests elusive for everyday clinical use. Prediction of *complex PGx traits* is almost impossible in the foreseeable future. Genome-wide association studies of large cohorts will continue to discover relevant genetic variants; however, these small-effect variants, combined, explain only a small fraction of phenotypic variance –– thus having limited predictive power and clinical utility.

Contents

Abbreviations: ADR, adverse drug reaction; GRR, genotypic relative risk; GWAS, genome-wide association study or studies; LD, linkage disequilibrium; MAF, minor allele frequency; OR, odds ratio; PD genes, those encoding proteins involved in pharmacodynamics; PGx, pharmacogenetics or pharmacogenomics; PK genes, those encoding proteins involved in pharmacokinetics; SNP, single-nucleotide polymorphism or variant; WES, whole-exome sequencing; WGS, whole-genome sequencing.

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1. Introduction

How successful will we be in predicting drug responses caused by inherited genetic variation? This is the primary question addressed herein. *Inter-individual variability in response* is defined as an "effect of varying intensity occurring in different individuals receiving a specified drug dose", or a "requirement of a range of doses (concentrations) in order to produce an effect of specified intensity in all patients." Patients are well known to vary widely in their responses to drugs (Brunton, Chabner, & Knollman, 2011).

A substantial subset of *personalized medicine* comprises *personalized medication*. Over the past six decades, this field of study began by being called *pharmacogenetics*; however, since the Human Genome Project started in 1990, the term *pharmacogenomics* has become more popular. Although the terms are often used interchangeably –– for many of us in the field, there are subtle differences, *i.e.* effect of individual genes (pharmacogenetics) *vs* total genomic expression (pharmacogenomics), in response to a drug. Pharmacogenomics aims to develop rational methods to *optimize drug therapy* with respect to the patient's genotype, as well as to *ensure maximum efficacy* with *minimal adverse effects in each individual*. Any drug capable of producing a desired therapeutic effect –– can also produce unwanted, or adverse, side effects (Edwards & Aronson, 2000).

All the above-mentioned drug responses (therapeutic effect, adverse effect and toxic effect) are regarded in the field of genetics as *phenotypes*, or *traits*, which herein we collectively call "*pharmacogenetic* or *pharmacogenomic traits*" (PGx traits). Most drug responses are expressed as *multifactorial traits* –– similar in many ways to human complex diseases (*e.g.* type-2 diabetes, schizophrenia, cancer), as well as quantitative traits such as height, blood pressure or serum lipid levels. One major difference between drug-response and complex-disease is obvious: any individual not challenged with a particular drug will never know his or her phenotype for that drug.

The degree of success in predicting outcome of a drug before treating the patient will depend on the "genetic basis of the PGx trait" (*genotype*), *i.e.* number of genetic variants contributing to that *phenotype*, allele frequency and *effect-size* of each contributing genetic variant, and interactions between them and with other environmental factors (Park et al., 2011). This review examines the *genetic architecture* (genetic basis) of various drug responses (PGx traits) and discusses statistical feasibility of genetic prediction.

2. Brief history of genetics

2.1. Gregor Mendel

Principles of "dominant-*versus*-recessive" classical genetics began in the 1860s by Mendel, using garden peas as his experimental model system (*e.g.* red flower color *dominant*, white *recessive*). Whereas the F_1 cross yields all red flowers, the F_2 generation yields three red (two are *R*/*r* heterozygotes, and one *R*/*R* homozygote) and one white flower color, *r*/*r*; this F_2 population represents the "Mendelian pattern of inheritance", or distribution (Fig. 1A).

Recent advances have greatly expanded Mendel's studies, *e.g.* showing in the garden pea (*Pisum sativum*) at least two genes involved in red flower color: the *A* gene codes for a bHLH transcription factor that regulates anthocyanin pigmentation. The white-flowered mutant allele most likely used by Mendel is a simple G-to-A transition in a splice-donor site –– resulting in a mis-spliced mRNA and premature stop codon; the *A2* gene encodes a WD40 protein, which is part of an evolutionarily highly conserved regulatory complex (Hellens et al., 2010).

2.2. Garrod's "inborn-errors-of-metabolism"

In the first decade of the 1900s, Sir Archibald Garrod described "inborn-errors-of-metabolism": albinism, alkaptonuria, cystinuria and pentosuria. Each of these distinct clinical *autosomal recessive* traits show a pattern of inheritance similar to that of white flower color of Mendel's garden pea. Garrod is credited with ushering in the era of human genetics; the predominant underlying tenet was "one gene, one disease", or "one wild-type (healthy) allele, and one disease allele". For each pregnancy, two healthy parents, "carriers" heterozygous for a disease allele, bring a 25% chance of producing a child having both disease alleles and, hence, inheriting the unwanted disorder.

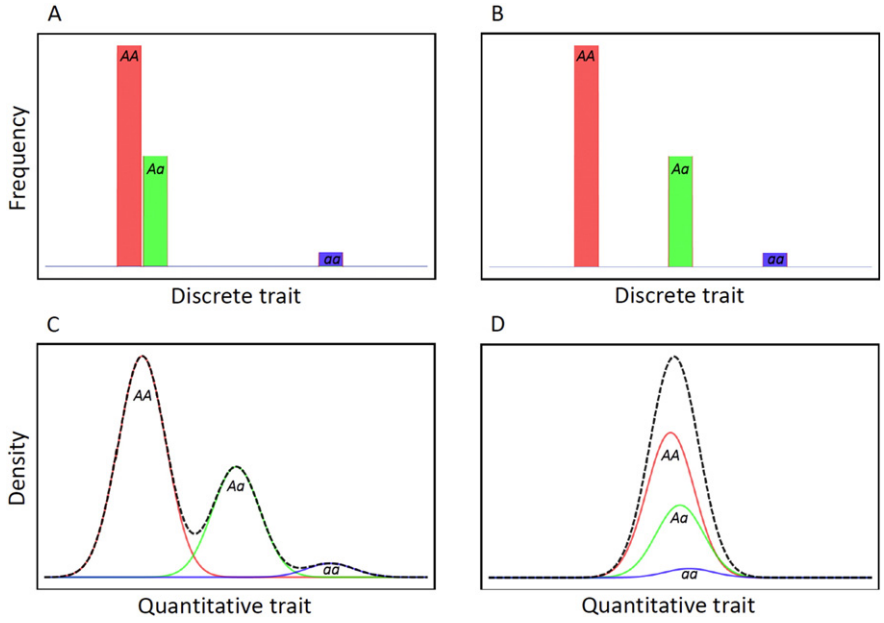

Fig. 1. Phenotype distribution of different traits. A: a recessive Mendelian trait with two discrete phenotypes; B: a distinct codominant Mendelian trait with three discrete phenotypes; C: a quantitative trait –– controlled predominantly by a large-effect gene, and undoubtedly additional modifiers showing continuous distribution, with three distinct modes; D: a quantitative trait influenced by numerous genetic and environmental factors, *i.e.* a polygenic trait that follows a normal distribution.