TOWARDS INDIVIDUALIZED MEDICINE: INSIGHTS GAINED FROM GENOMIC STUDIES

Salman Kirmani*, Dusica Babovic-Vuksanovic

Department of Medical Genetics, Mayo Clinic College of Medicine,
200 First Street SW, Rochester, MN 55905, USA

* Corresponding author

Abstract

Advances in the field of human genetics have made it possible to develop specific management and prevention strategies for rare genetic disorders, and tailor pharmacotherapeutic approaches to anticoagulation and certain cancers. The role that genetic variation plays in influencing the risk and outcome of the most common diseases are still unclear. Data from genome-wide association studies is just beginning to answer these questions. We review the role of genome-wide association studies in the quest towards individualized medicine, and examine the promises and challenges that lie ahead.

KEY WORDS: personalized medicine, genome-wide association studies, single nucleotide polymorphism

Introduction

One size fits all?

One of the biggest challenges in practicing medicine is the variability in phenotypes and responses to applied treatments, leading to different, often unpredictable outcomes. The idea about individualizing medical care and treating each person in the way that will fit them best is very appealing, but is not novel. In daily practice, clinicians routinely tailor diagnostic and therapeutic interventions according to individual patients' characteristics and preferences, and thus have been practicing a form of individualized medicine for many years. The unraveling of the human genome at the turn of the century now promises to revolutionize this entire concept. The terms personalized or individualized medicine as they are understood today refer to the use of preventative and therapeutic interventions to manage the individual's disease or predisposition to disease, based on the patients unique molecular risk profile. We describe here a few examples of the successful application of genetic information to achieve optimal health outcomes in different settings. We also discuss the role of genome-wide association studies in furthering the practice of individualized medicine.

Individualized medicine in newborn screening

One of the examples of successful individualized medicine is newborn screening. Detecting a newborn with phenylketonuria and making an immediate change to a phenylalanine-restricted diet will prevent manifestations of the metabolic disorder and allow for normal psychomotor development in the child who would otherwise be mentally retarded if managed like other children. Currently, genetic screening is available for more than 50 conditions, and great successes have been achieved in preventing adverse outcomes in previously fatal conditions.

Pharmacogenomics

Another example of successful implementation of genomic data is the use of pharmacogenomic information in selecting appropriate therapy and dosage for an individual. Based on genetic markers, one can determine how the person will metabolize a drug, and thus predict response to some medications. This strategy has already been introduced for dosing Warfarin (1) (Figure 1.), some psychotropic medications (2) or for selecting patients with breast cancer who will benefit from chemo-prophylactic therapy with Tamoxifen (3). Warfarin is administered as a racemic admixture of R- and S-enantiomers. The more potent S-enantiomer is metabolized principally by cytochrome P450 (CYP) 2C9. The pharmacologic effect of warfarin is mediated by the inhibition of vitamin K epoxide reductase complex 1 (VKORC1). This results in the decreased concentrations of activated clotting factors (II, VII, IX and X) producing therapeutic anticoagulation. Genetic variations in the above-mentioned genes can lead to inter-individual variation in effective warfarin dose. Profiling an individual based on these genetic variations leads to the choice of the safest and most effective dose, thus preventing significant adverse events.. OH = hydroxy; NAD+ = oxidized form of nicotinamide adenine dinucleotide; NADH = reduced form of NAD; GGCX = γ-glutamyl carboxylase. (*with permission From Yin & Miata, Throm Res, 120 (1), 2007*)

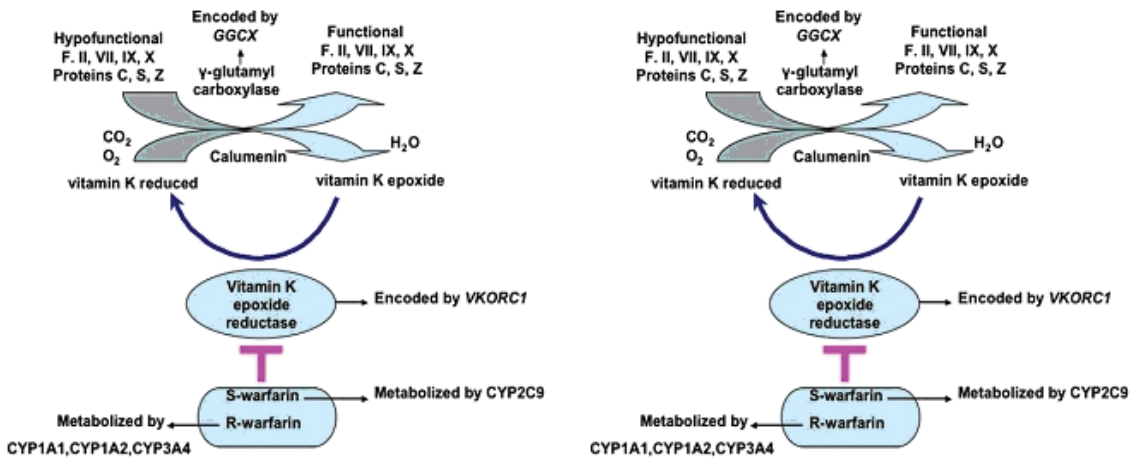

FIGURE 1. Genetic factors influencing Warfarin metabolis

Cancer Genetics

There are emerging examples of the successful use of genetic information in cancer therapeutics. Perhaps the best example is the use of trastuzumab (Herceptin), a monoclonal antibody directed against the extracellular domain of HER-2, for breast cancers with amplification of HER-2[4]. There is promising data emerging for similar generic markers that may have direct therapeutic implications in cancer, for example EGFR mutations in lung cancer, and KRAS mutations in colorectal cancer.

Implications of genomic studies in common diseases

While the above examples represent successful approaches in selected situations, the role that genetic variation plays in influencing the individual expression and outcome of common diseases is unclear. Data from genome-wide association studies is just beginning to answer these questions. As mentioned above, the goal of personalized medicine is to tailor preventative and therapeutic interventions for an individual based on their genetic profile. This is as yet not possible for the most common diseases that we face (such as hypertension, diabetes, sporadic cancers etc). Most researchers agree that common, complex diseases have both environmental and genetic risk factors. The interaction between these risk factors is not well understood, and just how much of a role a single risk factor plays in the development of disease in an individual is not known.

Each small circle above the magnified chromosome (labeled 5′ to 3′) represents one SNP with its two allelic possibilities. At the intersection between any two of these SNPs, the associations between their variants are shown in various shades from white to red, with the deepest red indicating the strongest association. Patterns of triangular blocks of strong association are separated by short nodes with very little association. One SNP (called a tagging SNP) represented above a deepest-red block- block 1 (3t) or block 2 (8t) — can serve as a surrogate for any variant within its block. Testing for one SNP might provide almost complete genetic information for that block. (*with permission from Christensen & Murray, NEJM 356;11, 2007*)

Genome-wide association studies (GWAS) are now making it possible for us to better understand the role of genetic variation in the pathogenesis of these common diseases. The principle on which these studies work is that the human genome contains significant variation within the species, with the most common example being single nucleotide polymorphisms (SNPs) that occur at roughly every 300 base pairs of DNA. If SNPs lie

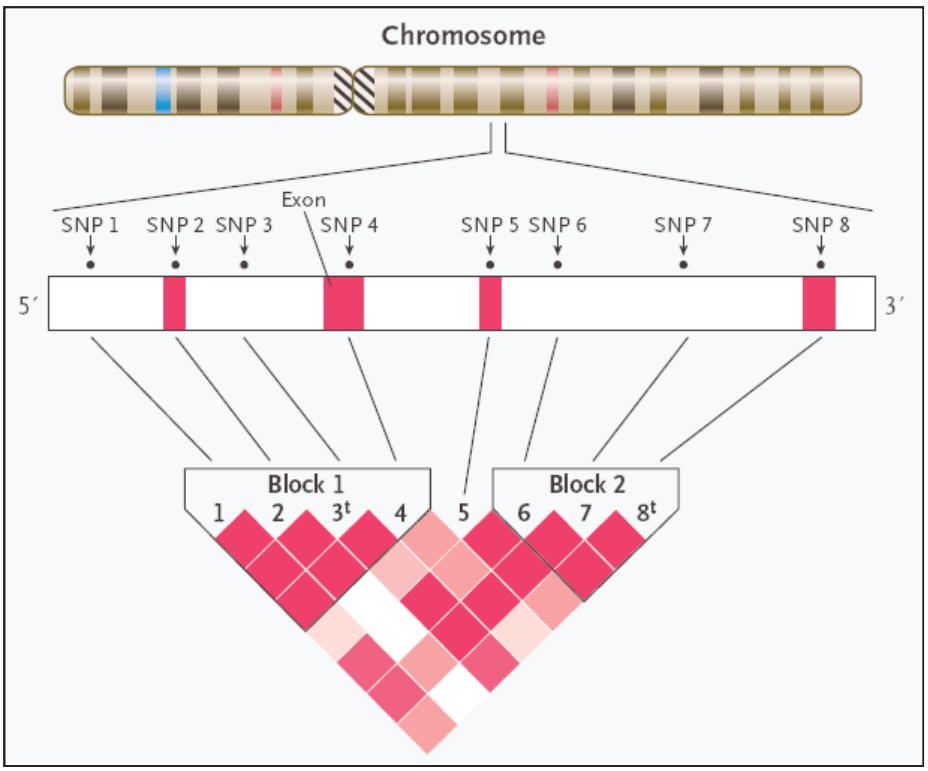

FIGURE 2. Mapping the relationships among SNPs.

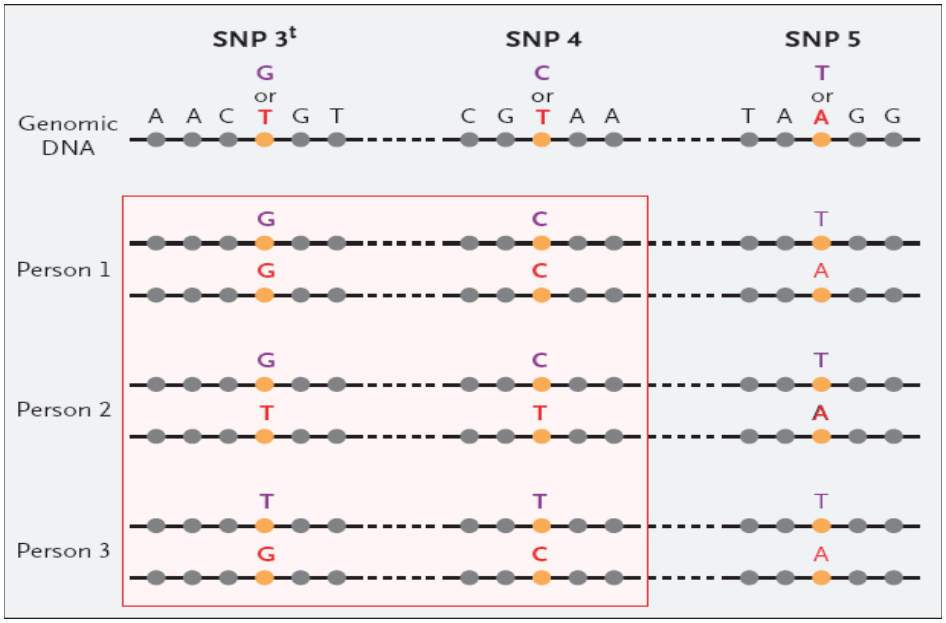

FIGURE 3. The nature of genomic variation

in close proximity to each other, they are more likely to be inherited "en bloc" and travel together down generations. This concept of linkage disequilibrium allows one SNP to act as a surrogate marker for other SNPs or mutations that may be inherited together and contribute to disease pathophysiology (Figure 2). The occurrence of such genetic variants that are inherited en bloc on a chromosome is called a haplotype. With the International HapMap Project delineating the location of certain informative SNPs called "tagging SNPs", it has become possible to identify disease associated SNPs without having to go through the laborious and expensive process of identifying every SNP in the DNA sample under study (Figure 3.).

Invariant nucleotide bases (gray circles) are interspersed with SNPs (orange circles). SNPs lying in close proximity in genome regions that tend to be unaffected by genomic shuffling during meiosis are usually inherited together. The inheritance pattern of SNPs 3 and 4 suggests that they are tightly linked to each other (box) — G travels with C and T travels with T — as well as to SNPs 1 and 2 in Figure 1. One tagging SNP may therefore be used as a surrogate for other SNPs in genome-wide analyses. (*with permission from Christensen & Murray, NEJM 356;11, 2007*).

If an adequate number of cases and controls (usually thousands) are studied, one may then be able to statistically discern which SNPs are more likely to be present in cases vs. controls. If a few SNPs do stand out, the genes on which they occur, or other genes in close proximity may be studied further to explore their role in the pathogenesis of that disorder. It also becomes statistically possible to obtain an odds ratio for the occurrence of a certain SNP in cases vs. controls, leading people to use this information in a predictive fashion in asymptomatic individuals. The "hypothesis generating" role of GWAS is well accepted, and many fruitful candidate genes have been explored and confirmed to have causal relationship with disease, e.g. TCF7L2 in T2DM (5). The "disease prediction" role of GWAS is more controversial and less well accepted. This is mainly because common complex diseases by their very nature result from the combined effects of multiple genetic and environmental factors, with each individual risk factor having only a modest effect on disease occurrence. Thus prediction models generated from such data will typically involve a large number of SNPs or risk genotypes, with the risk from each individual genotype being quite small (Figure 4).

With a large number of genotypes being studied, one will find that each individual genotype may occur frequently in the control population, thus the risk attributed to a particular genotype may be only slightly higher or lower in cases vs. controls. It thus becomes extremely problematic to interpret a profile that may contain both "risk increasing" as well as "protective" genotypes, as the interaction between these individual genetic factors is currently unknown. How much more this type of risk genotyping will

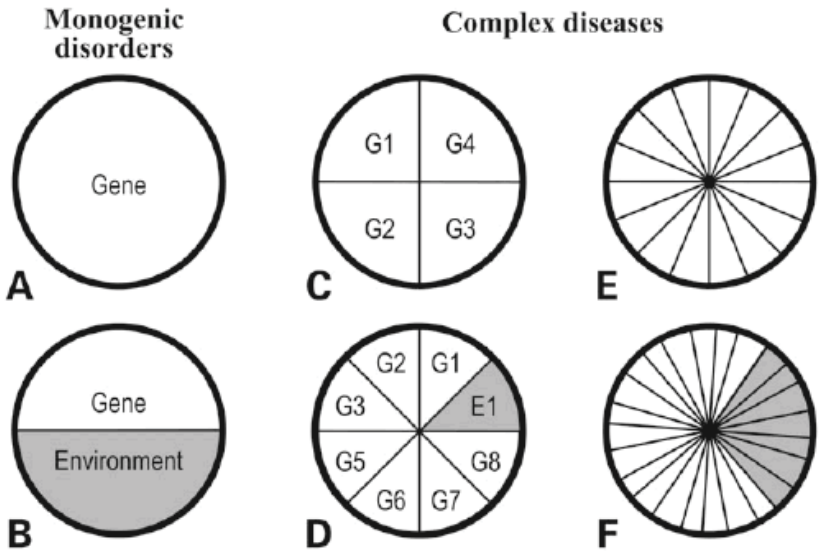

FIGURE 4. Complete cause models or sufficient causes of disease development
Complete causal models for (A) Huntington Disease; (B) Phenylketonuria; (C–F) Hypothetical examples for complex diseases. White areas refer to genetic factors and grey areas to environmental factors. (*with permission from Janssens & van Duijn, Hum Mol Genet, 17;2, 2008*).

add to the information more cheaply gathered from traditional clinical risk factors questions the current role of GWAS in personalized medicine today. With the exception of five susceptibility variants for age-related macular degeneration (AMD) (6, 7) and seven variants in hypertriglyceridemia (8), the predictive value of data from GWAS is in question. Simulation models have been used to compare the predictive value of data from GWAS from traditional clinical risk factors like age, sex, family history and serum markers. Data from these studies indicates that genomic profiling did not substantially improve the prediction of T2DM (9, 10), cardiovascular disease (11) or prostate cancer (12). Thus it seems clear that current prediction models from GWAS have been rather simplistic, identifying a few susceptibility markers that do not explain the complex nature of common diseases.

Conclusion

We conclude that although genomic studies are playing an immense role in identifying novel disease pathways and biomarkers, their role in realizing the dream of individualized medicine is still in its infancy. The predictive data from these studies needs intense scrutiny and review, and is currently not ready for implementation in every day clinical practice or to drive healthcare policy. The urgency in starting to use genomic information for predictive purposes in medicine is understandable and there are several laboratories that offer direct-to-consumer products. However, one needs to be aware of the complexities in interpretation of test results and possible errors in the process that can lead to significant consequences for an individual. So until we are better informed in the future it is prudent to remember, primum non nocere.

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