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Review article

Personalized medicine: A paradigm shift in healthcare

Wen-Ling Liao [a], Fuu-Jen Tsai [b,c,d,e,*]

[a] Center for Personalized Medicine, China Medical University Hospital, Taichung, Taiwan
[b] Department of Medical Research and Medical Genetics, China Medical University Hospital, Taichung, Taiwan
[c] School of Chinese Medicine, China Medical University, Taichung, Taiwan
[d] Department of Pediatrics, China Medical University Hospital, Taichung, Taiwan
[e] Department of Health and Nutrition Biotechnology, Asia University, Taichung, Taiwan

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ABSTRACT

Personalized medicine is based on the established principle that each individual is born with unique biological characteristics. Genomics, the science of studying the genes in a genome and their interactions with each other, forms the foundation of personalized medicine. Several genomic methods are currently used to identify susceptibility loci for diseases or phenotypic traits, namely, linkage analysis, candidate gene association studies, and genome-wide association studies. The success of personalized medicine depends on having accurate diagnostic tests capable of identifying patients who can benefit from targeted therapy. Larger cohort studies plus the application of genome-wide association studies offer great potential for identifying the genetic factors that influence the pharmacology of specific drugs. By combining these approaches, physicians can predict health risks, determine and quantify the dynamics of disease development, and tailor therapeutic protocols to the needs of the individual. In this review, we focus on the effect of genetic profiling on disease outcomes as well as the potential of genomic methods to predict disease and drug response.

1. Introduction

Traditional clinical diagnosis and management focuses on the patient's clinical symptoms and signs, medical and family history, and data from laboratory and imaging studies to diagnose and treat illnesses. Personalized medicine is a relatively new paradigm of evidence-based medicine that is based on the established principle that each individual is born with unique biological and genetic characteristics. Also known as P4 medicine, personalized medicine takes into account the patient's genetic profile (personalized medicine), anticipates health-related problems and focuses on wellness, not disease (preventive medicine), directs appropriate treatment using predictive models (predictive medicine), and encourages patients to take more responsibility for their health and healthcare (participatory medicine) [1,2]. In this article, we

* Corresponding author. Department of Medical Genetics, Pediatrics and Medical Research, China Medical University Hospital, Number 2, Yuh-Der Road, 404 Taichung, Taiwan.
E-mail address: d0704@mail.cmuh.org.tw (F.-J. Tsai).

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review the personalization aspect of the four-part paradigm by focusing on the effect of genetic profiling on disease outcomes as well as the potential of genomic methods to predict disease and drug response.

There is considerable variation between patients with the same disease. For example, some patients show no response to treatment, whereas others rapidly respond to therapy. Underlying this variation are alterations in the coding sequence or expression of hundreds of genes that confer disease susceptibility. A number of these genes are associated either with disease etiology or with clinical response to treatment. Therefore, it is believed that analysis of the genomic, proteomic, and metabolomic profiles of patients for the presence of drug targets and biomarkers will lead to improvements in diagnostic accuracy, prevention measures, and targeted therapies.

Genomics, the science of studying the genes in a genome and their interactions with each other [3], forms the foundation of personalized medicine [1,2,4,5]. The sequence of the 3 billion base pairs in the human genome has been publicly available since the completion of the International Human Genome Project in 2003. Recent advancements in technology, such as next-generation sequencing and improved computational methods to handle the huge amount of data generated by the new sequencing platforms, have changed the way we perceive medicine. Advances in genomic and high-throughput technologies will soon have a profound impact on the management of diseases. Such platforms will enable presymptomatic diagnosis, stratification of disease, assessment of disease progression, evaluation of patient response to therapy, and identification of relapses [6,7].

2. Human disease and genes

Genetic disorders are classified into several major groups. The first group comprises chromosomal disorders such as Down syndrome, which is caused by an extra copy of chromosome 21. The second group consists of single gene disorders, such as cystic fibrosis and sickle cell anemia. The majority of genetic diseases, however, are multifactorial in nature. Indeed, rather than being associated with changes in only one or a few genes or proteins, many diseases are likely a manifestation of multiple interconnected aberrant pathways and numerous molecular abnormalities. Many birth defects such as cleft lip and neural tube defects as well as many adult disorders, including heart disease, diabetes, and cancer, result from a combination of multiple genetic and environmental causes [6].

Several methods are currently used to identify phenotypic features of diseases and disease-susceptibility loci, including linkage analysis, candidate gene association studies, and genome-wide association studies (GWASs). Linkage analysis is useful for identifying familial genetic variants that have large effects and has been successfully used to discover several mutations responsible for monogenic forms of disease, such as maturity-onset diabetes of the young (MODY). In this disease, heterozygous mutations in the Glucokinase (*GCK*) gene were shown to cause MODY2 [8], whereas mutations in the hepatocyte nuclear factor-1β (*HNF-1β*) gene were shown to be related to the development of MODY5 [9]. Furthermore, linkage studies of type 2 diabetes mellitus (T2DM)-linked chromosomal regions have identified potential causative genetic variants in genes, including calpain-10 (CAPN10) [10], ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) [11], hepatocyte nuclear factor 4 alpha (HNF4A) [12,13], and adiponectin (ADIPOQ) [14]. Disease-related genes can also be identified on the basis of association testing in populations rather than in families. The methods include candidate gene association studies and GWASs. Candidate gene association is based on measurements of selected biomarkers from relevant pathophysiological pathways. For example, of the scores of candidate genes related to T2DM that have been investigated using this approach, the *PPARG* and *KCNJ11* genes were found to be directly linked to the development of the disease. The *PPARG* gene encodes the peroxisome proliferator-activated receptor γ, a type II nuclear receptor that plays a fundamental role in adipogenesis and insulin sensitivity by regulating the transcriptional activity of various genes. The *KCNJ11* gene, located on the short arm of chromosome 11, encodes the pore-forming subunit of the ATP-sensitive potassium channel Kir6.2 in pancreatic β cells. Gain-of-function mutations in *KCNJ11* open the potassium channel and inhibit the depolarization of β cells, leading to a defect in insulin secretion.

However, significant interethnic differences occur in the risk allele frequency at discrete loci. Variants of the *KCNQ1* gene were first identified in Asians, and it was found that the frequency of the minor allele in that population (30–40%) was much higher than the frequency in Europeans (<10%). In addition, linkage analysis has demonstrated that the presence of the *TCF7L2* gene increases the risk of developing T2DM in almost all ethnic groups. However, risk allele frequencies of single-nucleotide polymorphisms (SNPs) in TCF7L2 in European populations were shown to be higher than those in Japanese (40% vs. 5%), indicating that TCF7L2 variants have little effect on T2DM susceptibility in the Japanese population.

The HapMap project demonstrated that genotyping of approximately 500,000 SNPs is sufficient to cover about 75% of the common variants (MAF of >5%) in the genome. Furthermore, improvements in high-throughput technology for SNP genotyping, which allows for the simultaneous genotyping of hundreds of thousands of SNPs and the development of biostatistical methods to handle the large volumes of data being produced, have opened up new possibilities for GWASs. GWASs are used to compare, in an unbiased manner, the genomes of individuals with or without a disorder of interest (such as T2DM) and to identify differences among a large number of common SNPs. Through such studies, many genetic variants have been identified and placed in pathways that were not previously associated with a particular disease. In addition, disease-associated SNPs have also been ascribed to genes with currently unknown functions [15]. For example, the results of a genome-wide linkage analysis conducted in Japanese sibling pairs [16,17] and GWASs in individuals of European ancestry and in Korean and Taiwanese populations [18–21] have identified the candidate loci for Kawasaki disease. However, these loci do not fully explain the genetic risk