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Review article

Personalized medicine: A paradigm shift in healthcare

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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.

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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

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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-1 β (HNF-1 β) 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

for Kawasaki disease, suggesting that additional genetic factors remain to be discovered.

Recently, two new loci, one at BLK (encoding B-lymphoid tyrosine kinase) and one at CD40, have been found to be associated with Kawasaki disease in Han Chinese [22] and Japanese populations [23]. In another example, a two-stage GWAS was conducted in Han Chinese in Taiwan [24]. The study comprised 2798 patients with T2DM and 2367 healthy controls. The researchers not only confirmed that the *KCNQ1* gene was associated with T2DM but also identified two novel genetic susceptibility loci: *PTPRD* and *SRR*. Interestingly, these two newly identified genes are in pathways that were not previously associated with T2DM. In a recent GWAS comprising 6952 patients with T2DM and 11,865 healthy controls conducted by the Asian Genetic Epidemiology Network consortium, eight additional genetic loci were found to be associated with T2DM, namely, variations in or near the *GLIS3*, *PEPD*, *FITM2-R3HDML-HNF4A*, *KCNK16*, *MAEA*, *GCC1-PAX4*, *PSMD6*, and *ZFAND3* genes [25].

Most GWASs have been designed to find relatively common variants, typically focusing on those with allele frequencies of >5%. This is because studies require very high statistical power (and therefore, a very large sample size) to detect associations with relatively rare alleles. Therefore, it is possible that some rare genetic variants that play critical roles in disease onset or therapeutic response remain undiscovered. A substantial part of the missing heritability could be attributable to variants with large or intermediate effect sizes and relatively low frequencies. Such variants are likely to have escaped detection by current methods, as their low penetration would preclude linkage analysis, and their frequency would be too low for detection in GWASs. The strategies for identifying such variants largely depend on the frequency of said variants in test populations. Some variants with allele frequencies in the range of 1–5% might be identified by increasing the genotype density and cohort sizes. In this regard, the 1000 Genomes Project has extended the catalog of known human variants to include those with frequencies close to or <1%. However, detection of many of these rare or intermediate variants will require next-generation sequencing rather than traditional GWAS or genotyping [26].

2.1. Prediction of disease

In traditional medicine, physicians use different parameters, including patient characteristics and data from laboratory tests and imaging studies to identify an individual's health risk, to predict a patient's response to drugs and to monitor disease status during and following therapy. For example, there is compelling evidence that increasing age, higher body mass index/waist circumference, impaired fasting glucose, impaired glucose tolerance, higher glycated hemoglobin (HbA1c) level, and metabolic syndrome are important risk factors for T2DM. Several scores have been created on the basis of the combination of the clinical features that could predict the risk of diabetes. For example, the Diabetes Risk Calculator includes parameters of age, waist circumference, gestational diabetes, height, race/ethnicity, hypertension, family history of diabetes, and exercise. The value of the area under the curve (AUC) of the Diabetes Risk Calculator [27] was

0.70 for detecting impaired fasting glucose, impaired glucose tolerance, or undiagnosed diabetes. The Framingham Risk Score includes parameters of age, sex, obesity, hypertension, parental history of diabetes, low levels of HDL cholesterol, elevated triglyceride levels, and impaired fasting glucose. The AUC of this risk model was 0.85 for predicting T2DM in middle-aged adults [28].

In recent years, researchers have discovered numerous genes with variations in sequence or expression that contribute to disease susceptibility, and some of those variations provide the basis for targeting the molecular causes of some diseases [22]. The results from other studies have also indicated that genetic variability may be responsible for heterogeneous patient responses to treatment [4,29]. The number of SNPs included in genetic models has increased from three in 2005 to 40 in 2011, and the combinations of genes in each model have differed [30]. Recent studies have compared the predictive ability of risk models that include genetic variants only to those that combine genetic variants with clinical risk factors and found that genetic risk models have lower AUC values (0.55–0.68) than clinical models (AUC, 0.61–0.92) [30]. Incorporation of genetic factors into clinical risk models only marginally improved and in some cases did not improve the AUC value (Table 1) [31–42]. The contribution to disease risk by any one of these genetic factors is small (1.1–1.5-fold increased risk). However, research shows that the discriminative power of genetic risk factors improved as the duration of follow-up increased, whereas that of clinical risk factors decreased [33].

3. Pharmacogenomic studies

Pharmacogenomics is a science that examines the relationships among genetic variations and individual responses to pharmaceutical agents [43]. It has been applied in the field of personalized medicine to develop ways of optimizing drug therapy by stratifying patients into responders, individuals who demonstrate a therapeutic or an adverse response, and nonresponders. Pharmacogenomics technically differs from the science of pharmacogenetics, with the former referring to the general study of all different genes that determine drug behavior, and the latter referring to the study of inherited differences (variation) in drug metabolism and response; however, the distinction between pharmacogenomics and pharmacogenetics is considered arbitrary, and the two terms tend to be used interchangeably. The following are some examples related to the effect of gene variants on drug treatment.

3.1. Warfarin treatment, blood clotting, and the *CYP2C9* gene

Warfarin, an anticoagulant drug, is widely used to prevent thrombosis, but because of interindividual variations in dose requirements, hemorrhagic complications caused by warfarin therapy are common. Two genes, cytochrome P450 2C9 (*CYP2C9*) and vitamin K epoxide reductase (*VKORC1*), are associated with the pharmacokinetics and pharmacodynamics of warfarin, respectively [44]. The metabolism of (S)-

Table 1 – Predict models combined with clinical risk and genetic markers for type 2 diabetes.

Author (year published)	Outcome no. of cases/study population	Clinical risk factors + biomarkers		+ Genetic markers	Different ^a
Balkau et al (2008) [31]	203 i.c./3817 (30–64 y)	Men: smoking, WC, FPG, GGT Women: FH, BMI, FPG, TG	AUC: 0.850 (men) 0.917 (women)	2 genes AUC: 0.851 (men) 0.912 (women)	
Vaxillaire et al (2008) [32]	187 i.c./3442 (30–65 y)	Age, sex, average BMI over 9 y	AUC: 0.82	3 genes AUC: 0.83	
Lyssenko et al (2008) [33]	2201 i.c./18,831	Age, sex, BMI, BP, FH, FPG HDL, TG, WC	AUC: 0.74	11 genes AUC: 0.75	Yes
van Hoek et al (2008) [34]	490 i.c.+545 p.c./5297 (>55 y)	Age, sex, BMI	AUC: 0.66	17 genes (18 SNP) AUC: 0.68	Yes
Meigs et al (2008) [35]	255 i.c. /2377	Age, sex, BMI, FH, FPG, SBP, HDL, and TG	C: 0.900	18 genes C: 0.901	No
Lango et al (2008) [36]	2309 p.c./2598 controls (35–70 y)	Age, sex, BMI	AUC: 0.78	17 genes (18 SNPs) AUC: 0.80	Yes
Schulze et al (2009) [37]	801 i.c. /1,962	Age, height, WC, hypertension, intake of red meat, whole gram bread, coffee, alcohol, PA, smoking, glucose, HbA1c, TG, HDL, CHOL, GGT, ALT	AUC: 0.9000	20 genes AUC: 0.9002	No
Lin et al (2009) [38]	356 p.c./5360 (35–75 y)	Age, BMI, FH, WHR, TG/HDL ratio	AUC: 0.86	15 genes AUC:0.87	Yes
Sparso et al (2009) [39]	4093 cases/5302 g.t.	Age, sex, BMI	0.92	19 genes 0.93	N/A
Talmud et al (2010) [40]	302 i.c./5535 (35–55 y)	Age, sex, BMI, drug treatment, FH, smoking (Cambridge risk score)	AUC: 0.72	20 genes AUC: 0.73	Yes
Talmud et al (2010) [40]	302 i.c. /5535 (35–55 y)	Age, sex, BMI, FH, HDL, TG, FPG (FHOS risk score)	AUC: 0.78	20 genes AUC: 0.78	No
Wang et al (2010) [27,41]	518 i.c./7232 (45–74 y)	Age, BMI,WC, BP medication, history of blood glucose, PA, daily consumption of vegetables, fruits or berries, TG, HDL, adiponectin, ALT	C: 0.772	19 genes C: 0.772	N/A
De Miguel-Yanes et al (2011) [42]	144 i.c. <50 y; 302 i.c. ≥ 50 y /3471	Sex, BMI, FH, FPG, SBP, HDL, TG	C: 0.903	40 genes C: 906	No

ALT = alanine aminotransferase; AUC = area under curve; BMI = body mass index; BP = blood pressure; CHOL = cholesterol; FPG = fasting plasma glucose; FH = family history; FHOS = Framingham Offspring study; GGT = gamma-glutamyltransferase; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; i.c. = incident cases; g.t. = glucose tolerance; N/A = not applicable; PA = physical activity; p.c. = prevalent cases; SBP = systolic blood pressure; pop. = population; TG = triglyceride; WC = waist circumference; WHR = waist/hip ratio.

a Different between model with clinical Risk factors and/or biomarkers and model with genetic markers.

warfarin to its inactive metabolite is mediated by the cytochrome p450 enzyme CYP2C9. Persons with at least one copy of either CYP2C9*2 or CYP2C9*3 require less warfarin for effective anticoagulation compared to the general population [45]. Consistent with this observation, hemorrhagic complications are more common in persons carrying the CYP2C9*2 or CYP2C9*3 allele. The function of VKORC1 is the gamma carboxylation of glutamyl residues, which is required for the activation of multiple vitamin K-dependent clotting factors [23]. A functional variant in the promoter region (.1639G>A) of the VKORC1 gene was found to alter a transcription factor-binding site [46]. *In vitro* studies confirmed that the A (minor) allele reduces transcription of the gene by almost 50% compared with a promoter bearing the wild-type G allele. Several pharmacogenetic warfarin dose-prediction models have been developed [29,47]. These dose-initiation models indicate that the CYP2C9 and VKORC1 polymorphisms account for 18% and 30% of the observed variability of warfarin, respectively. Specifically, the VKORC1 variant predicts warfarin sensitivity, and the CYP2C9*2/*3 variants affect warfarin clearance.

Clinical factors—including age, sex, body size, race/ethnicity, smoking status, and relevant concomitant medications—are responsible for an additional 12% of dose variability, meaning that, overall, VKORC1 and CYP2C9*2/*3 variants as well as clinical factors account for up to 60% of interindividual variability [48].

3.2. Herceptin treatment of breast cancer and the HER2/neu gene

About 18–20% of patients with breast cancer show amplification of the HER2/neu gene or overexpression of its protein product. Those factors are associated with increased risk of disease recurrence and poor prognosis. The mean relative risk for overall survival is 2.74 for patients who are HER2-positive [49]. The development of HER2-targeted therapies for patients with HER2-positive disease has dramatically reduced the risk of recurrence after the initial therapy and has led to improved prognosis. Various HER2-targeted drugs are approved or in development, such as monoclonal antibodies

that are directed against its external domain (e.g., trastuzumab and pertuzumab), small molecule tyrosine kinase inhibitors (e.g., lapatinib and neratinib), anti-HER2 antibodies conjugated to toxic molecules (e.g., trastuzumab-DM1 or T-DM1), and chaperone antagonists (e.g., geldanamycin) [50]. Herceptin (trastuzumab) is a recombinant humanized IgG1-kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of HER2. Based on results from randomized clinical trials, trastuzumab-containing regimens are now recommended for women with HER2-positive metastatic breast cancer [51]. Data from trials of first-generation adjuvant regimens combining trastuzumab with various chemotherapeutic drugs showed significant improvements in disease-free and overall survival rates [49]. Studies on second-generation adjuvant regimens comprising other HER2-targeted agents such as lapatinib and pertuzumab are underway, and newer drugs such as T-DM1 and neratinib are being actively tested in the metastatic setting.

3.3. Carbamazepine therapy and the HLA-B*1502 allele

Carbamazepine is an important treatment for seizure disorders, bipolar disorder, trigeminal neuralgia, and chronic pain. However, carbamazepine is also associated with hypersensitivity reactions that range from benign urticaria to life-threatening cutaneous disorders, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Both conditions (SJS–TEN) are associated with significant morbidity and mortality. The incidence of SJS in Han Chinese is higher than that in Caucasians (8 cases per million person-years in the Han Chinese population compared with 2–3 cases in Caucasians) [52]. Recently, pharmacogenomic studies have found a strong association between carbamazepine-induced SJS–TEN and the HLA-B*1502 and HLA-B*5801 alleles in the Han Chinese populations in Taiwan [52,53] and in other Asian countries [54,55]. Furthermore, the incidence of SJS–TEN among people treated with the drug is substantially reduced when individuals carrying HLA-B*1502 are excluded from carbamazepine therapy [53]. Patients of Han Chinese descent with molecular evidence of that allele should, therefore, be treated with other classes of anti-epileptic drugs. However, the allele frequency of HLA-B*1502 is markedly lower in Caucasians (1–2%) than in Han Chinese (8%). In addition, no association between HLA-B and carbamazepine-induced SJS–TEN has been found in Caucasian patients. Therefore, the United States Food and Drug Administration recommends genetic screening for patients of Asian ancestry before initiation of carbamazepine therapy.

3.4. Antidiabetic drugs

Blood glucose control is a priority in the treatment of T2DM. Pharmacogenetic studies have been performed on three classes of drugs commonly used in the treatment of diabetes: metformin, sulfonylureas, and thiazolidinediones [56]. Metformin suppresses hepatic gluconeogenesis by activating AMP-activated protein kinase, which inhibits the expression of hepatic gluconeogenic genes PEPCK and Glc-6-pase by increasing the expression of the small heterodimer partner. It was recently found that variations in the organic cation

transporter 1 and 2 (OCT1 and OCT2), proteins responsible for the hepatic transport of metformin, might affect metformin response [57]. Sulfonylureas bind to ATP-sensitive potassium channels in pancreatic β cells, thereby stimulating insulin release in a glucose-independent manner [58]. Recently, polymorphisms in drug target genes (ABCC8, KCNJ11) and diabetes risk genes (TCF7L2 and IRS-1) have been shown to be associated with variability in the response to sulfonylurea drugs in patients with T2DM [59]. Pearson et al [60] found that patients with hepatocyte nuclear factor-1 α (HNF-1 α) gene mutations were supersensitive to treatment with sulfonylureas but responded poorly to treatment with metformin. In addition, research has shown that individuals with the TCF7L2 risk genotype respond poorly to treatment with sulfonylureas [61]. Variations in CYP2C9, an enzyme involved in sulfonylurea drug metabolism, KCNJ11, K⁺ inward rectifier Kir6.2, and the sulfonylurea receptors SUR1 and ABCC8 are all genetic modifiers of the response to treatment with sulfonylurea. For thiazolidinediones, the focus has been on PPAR- γ variants, although the results are currently inconclusive. Despite these associations, the genetic data currently available are insufficient to support management decisions for the common forms of T2DM [62].

4. Conclusion

Results from large cohort studies will provide fundamental data that can be used to profile risk factors and discover novel therapeutic targets for patients. Tailoring therapy based on pharmacogenomic testing results may save lives and improve patient care. Finally, the decreasing price of new technologies that gather personal genomic information will facilitate their transition from basic research settings to the clinical setting, thereby reshaping clinical diagnostic paradigms. The challenge to healthcare teams is to consider how the new genomic information may be leveraged to influence management decisions and to fulfill the promise of personalizing medical care.

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