Pharmacogenomics: A Pathway to Individualized Medicine

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Abstract

Since the 1950s, the field of pharmacogenomics has rapidly expanded, yielding valuable evidence of the link of genetics and drug response whether due to alterations in drug metabolism, transport, target proteins, or genetically determined disease severity. The patient genome is postulated to account for 20–95 % of the variability of drug response. The impact of pharmacogenomics transcends the individual, with major repercussions upon drug discovery and development in pharmaceutical industry as well as the economics of health care. This chapter summarizes important principles and relevant examples.

Keywords

Pharmacogenomics • Pharmacogenetics • DNA • RNA • Drugs • Metabolism • Genome

Introduction

The history of pharmacogenetics dates from the 1950s with the observation of primaquine-induced hemolysis in the presence of glucose-6-phosphate dehydrogenase deficiency, establishing that drug-related toxicity may occur in genetically predisposed individuals. Since then, the field of pharmacogenomics has rapidly expanded, yielding valuable evidence of the link of genetics and drug response whether due to alterations in drug metabolism, transport, target proteins, or genetically determined disease severity. The patient genome is postulated to account for 20–95 % of the variability of drug response. The analysis of DNA sequencing and variation in single-nucleotide polymorphisms (SNPs) brings the hope of personalizing drug therapy for an individual. However, the impact of pharmacogenomics transcends the individual, with major repercussions upon drug discovery and development in pharmaceutical industry as

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well as the economics of health care [1–3]. The following summarizes important principles and relevant examples [1–21].

Definitions and Overview

Pharmacogenomics, which is inclusive of the field of pharmacogenetics, may be defined as the study of variations in DNA and RNA characteristics in relationship to drug response reflecting the variation in the entire genome, describing often a more population-based focus [1–8]. *Pharmacogenetics* is the study of the role of genetic variations affecting an individual patient and the drug-specific response, often focused on a single or on a few gene analyses. The concept of "personalized medicine" is the extension of these studies intended to optimize drug therapy while limiting toxicity based upon genetic patterns or to choose therapy that is most likely to be effective and safe [1, 2].

The "genotype" refers to the genetic pattern of an individual, while the "phenotype" refers to the outcome of the interaction of genes with environmental factors (such as diet, drugs, and other exposures). Single-nucleotide polymorphisms (SNPs) constitute 90 % of all human genome variation with over four million mapped in the human genome [4]. These differences in one base pair in DNA may affect biotransformation pathways as demonstrated for many key hepatic isoenzyme families. Genetic copy-number variations (CNVs) also account for genomic variation. SNPs occurring within the same DNA region may be inherited in concert as haplotypes.

The term *genetic polymorphism* refers to naturally occurring differences in DNA sequence in individuals, usually present in a frequency of at least 1 % [4, 6]. These polymorphisms may affect enzymes, drug transporters, and/or receptors, with changes resulting in increased, decreased, or unchanged drug activity [5]. Polymorphisms may affect individuals or reflect pattern within ethnic groups. A given genetic polymorphism may significantly determine drug pharmacokinetics or pharmacodynamics and/or disease activity and severity.

Pharmacogenetics and Biotransformation

Although pharmacogenetics is perceived as a relatively recent area of study, there is extensive retrospective history of the impact of genetics upon biotransformation and toxicity. Examples include isoniazid-related peripheral neuropathy in patients with *N*-acetyltransferase deficiency ("slow acetylators" in 50 % African-Americans and Caucasians) and glucose-6-phosphate dehydrogenase deficiency with subsequent risk of hemolysis with multiple drugs [2].

In the 1970s, variability of drug metabolism was first documented through evidence of reduced metabolism in up to 10 % of Europeans for debrisoquine [6]. Subsequent research into cytochrome P450 isoenzyme families resulted in identification of this pathway as CYP2D6. Extended knowledge of drug-metabolizing enzymes provided the early foundations of pharmacogenetics. Variation in individual genotypes may correspond to observed phenotypic presentations, with characterization of drug metabolism varying from "poor" to "ultrafast" [8].

Of the over 57 different CYP isoenzymes and 42 involved in metabolism [4], polymorphisms leading to absence of enzyme activity exist in four major families: CYP2D6, CYP2C19, CYP2A6, and CYP3A5 [4, 6]. Limited relevance of CYP3A4 variants has been proposed, despite extensive variation in CYP3A4 activity and the large number of drugs undergoing biotransformation through this system. However, polymorphisms of CYP3A5 may be present in 60 % of African-American and 33 % of Caucasians [4].

As over 25 % of all drugs undergo metabolism via CYP2D6, genetic influences may exert more dramatic effects upon these drugs. Over

80 unique allelic variants in CYP2D6 have been determined, with patterns of "poor metabolism," "intermediate metabolism," and "ultrafast metabolism." [7] Alleles associated with impaired metabolism include CYP2D6*10 (East Asia), CYP2D6*17 (Africa), and CYP2D6*9 and CYP2D6*41 (Europe). However, ultrarapid metabolism has also been detected in subjects with CYP2D6*1 or CYP2D6*2 alleles. For example, lack of effective codeine conversion to the active component morphine in CYP2D6*4 homozygous individuals (so-called "slow metabolizers") results in little or no analgesia. However, "rapid metabolizers" may risk excessive opioid toxicity due to higher than usual morphine generation [1, 2, 4]. Conversion of tramadol to *O*-desmethyltramadol may also be affected by CYP2D6 polymorphism in a similar manner [4]. The conversion of tamoxifen via CYP2D6 to endoxifen is required for biologic activity in breast cancer so that patients showing reduced metabolism may show increased tendency to relapse [4, 6].

There are over 16 variations in CYP2C19 activity, ranging from deficient, reduced, normal, to increased [7]. CYP2C19*17 is associated with ultrarapid metabolism, while CYP2C19*2 and CYP2C19*3 identify poor metabolism [7]. Polymorphisms in CYP2C19 SNPs, for example, have been correlated with altered activity of proton pump inhibitors such as omeprazole, with higher blood levels and acid suppression in poor metabolizers and lower blood concentrations and resulting drug effects in the ultrarapid metabolizers [6, 7]. Other substrates for CYP2C19 include citalopram and select benzodiazepines including diazepam [6]. There are at least 27 variant alleles for CYP2C19, with frequency reflecting ethnicity: 15 % Caucasians, 30 % Asians, and 17 % African-Americans.

Over 33 variant alleles for CYP2C9 have been noted, mostly related to decreased activity. Either or both of two common alleles, CYP2C9*2 or CYP2C9*3, are found in 30 % of Northern Europeans and associated with reduced enzyme activity [7]. These polymorphisms may be of greatest importance with drugs such as warfarin, explaining 10–20 % variability in dose requirements [6] with increased risk of anticoagulation and lower daily dose needs [7].

Other CYP isoenzymes of potential importance in discussion of pharmacogenetics include CYP2B6 which may predispose to efavirenz-associated central nervous system toxicity and CYP2A6 which may be of clinical significance in nicotine dependency [4].

Pharmacogenetics of Other Reactions

Polymorphisms of conjugation reactions with reduced or absent activity have been documented for methylation reactions such as thiopurine *S*-methyltransferase (TPMT; 1 in 300 Europeans) and glucuronidation as for UDP-glucuronosyl transferase (uridine diphosphoglucuronosyl transferase). Assessment of genotype is recommended for TPMT when mercaptopurine or thioguanine may be prescribed, screening for TPMP homozygous or individuals at increased risk of severe hematologic toxicity who may benefit from dosage adjustment or who should not be treated with these agents [8]. UGT1A1*28 allele determination is also recommended when irinotecan use is proposed [6].

Transporter gene pharmacogenomic studies for ABCB1 gene and *p*-glycoprotein response have yielded conflicting data. As discussed by Cavallari and Yam, drugs that are substrates for *p*-glycoprotein-facilitated transport may also be subject to CYP450 biotransformation, leading to more complex impacts of genetic variations [4].

Pharmacogenetics and Drug Targets Including Receptors and Enzymes

Pharmacogenetics of drug target molecules may also determine drug responses independent of or in addition to biotransformation [2, 4–8]. Polymorphisms of drug receptors including beta-adrenergic receptors have been the source

of extensive research, given importance in diseases including hypertension, heart failure, and asthma. Beta-adrenoreceptor genes ADRB1 and ADRB2 provide targets for catecholamines and other medications, with SNPs associated with altered responsiveness of the receptor [8]. Reduced responsiveness to beta-agonist therapy and loss of asthma control has been observed in patients with beta-2 receptor arginine genotype as compared to glycine genotype, with 15–20 % of African-Americans and Caucasians possessing the arginine genotype.

Genetic polymorphisms for other drug receptor genes are also relevant to cardiovascular pharmacotherapy including angiotensin-converting enzymes, angiotensinogen, apolipoprotein E, and cholesteryl ester transfer protein [7]. Polymorphisms in the ACE gene may be linked to plasma concentration of ACE but results of study of ACE inhibitor response are conflicting. However, it is possible that multiple genetic variants determine ACE inhibitor responsive, rather than a single gene [4].

Genetic variation in target enzymes is also of importance for warfarin and statins. Variability in the gene encoding vitamin K epoxide reductase (VKORC1) has been demonstrated, with four haplotypes that contribute to variation in warfarin dose requirements. HMG-CoA reductase is the target enzyme for the statins; two polymorphisms of the gene coding this enzyme are documented.

Pharmacogenetics of Toxicity

Drug toxicity may occur as an extension of deficiency of drug detoxification or transport. However, idiosyncratic toxicities have been reported which also are examples of pharmacogenetics. Drug-induced liver disease has been associated with occurrence of HPA-B*5701 allele. This allele has also been incriminated in abacavir-induced hypersensitivity reactions; genetic testing is recommended prior to initiation of abacavir as an antiviral agent [6]. Severe cutaneous reactions with carbamazepine including Stevens-Johnson syndrome have been associated with HLA-B*1502 allele in Asians, with variation in incidence depending upon place of ancestry from Asia. As a result, in 2007 the FDA recommended all patients of Asian descent be screened for this allele prior to initiation of therapy [5].

Increased risk of thromboembolic disease during oral contraception use is well documented, particularly when variation in genes for factor V Leiden or prothrombin gene variations are present. Genetic predisposition may also be incriminated in risk of QT-interval prolongation and risk of torsades de pointes due to genetic mutations in channel proteins affecting potassium and sodium transport [4].

Specific Cardiovascular Agents of Interest

The following are brief summaries of documented relationships of cardiovascular pharmacogenomics for target drugs, with more extensive published reviews available [9–16].

Warfarin

Wide interindividual variations in drug dosing and response for warfarin exemplify the potential impact of pharmacogenetics in clinical practice [4, 9, 12, 15, 16]. Multiple genetic variations in warfarin biotransformation pathways have been documented.

This anticoagulant undergoes complex biotransformation, as it is a racemic mixture of the S isomer (metabolized through CYP2C9) and less active R isomer (metabolized through CYP3A4, CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C18, and CYP2C19). As the S isomer accounts for the majority of anticoagulant activity with highest inhibition of the VKORC1 enzyme in vitamin K-dependent clotting, variants in CYP2C9 increase risk of bleeding or delayed onset of drug effects. Although variants are rare in Asians and African-Americans, Caucasians may demonstrate alterations in CYP2C9*2 (8–20 %) or CYP2C9*3 (6–10 %) activity, with

altered drug pharmacokinetics and increased risk of elevated INR and bleeding. Importantly, there may be delay in time to optimal INR due to delayed clearance [15].

Additionally, multiple polymorphisms in the target VKORC1 gene coding vitamin K epoxide reductase activity have been documented, altering pharmacodynamic responses for warfarin independent of CYP2C9 activity. Depending upon the individual's genotype pattern, warfarin doses may be widely variable. VKORC1 polymorphism vary by race and may explain why, for example, Asian patients require lower daily drug doses when compared to doses for those of European or African ancestry [15].

The changes in VKORC1 and CYP2C9 activity account for approximately 40 % of variation. Polymorphisms in CYP4F2 (vitamin K_1 oxidase, responsible for epoxide form metabolism) may also affect dose requirements. Genotyping of VKORC1 and CYP2C9 may assist in drug dosing and has been the basis for over 40 pharmacogenetically based dosing algorithms. Warfarin labeling includes a table of starting doses based upon patient VKORC1 and CYP2C9 genotyping. Warfarin pharmacogenomic testing is available, although expensive and with limitations in profile of polymorphisms detected. At this time, there is no consensus as to who should be tested, when it should occur, and the predictive nature of dosing tables. Clinical utility of testing remains to be validated, with extensive studies currently underway.

Clopidogrel

Clopidogrel, as an antiplatelet agent, demonstrates reduced drug responsiveness in up to 30 % of patients [4, 9–13, 15]. It is a prodrug requiring a two-step activation by multiple CYP450 isoenzymes including CYP2C19 pathways to generate the active metabolite, with reduced rates of metabolism, decreased platelet activation, and higher risk of cardiovascular event compared to those with normal CYP2C19 activity [10]. Carriers of CYP2C19*2 and CYP2C19*3 are "poor metabolizers," with nonfunctional enzymes, while carriers of CYP2C19*17 demonstrate increased activity ("ultrarapid metabolizers"). CYP2C19*2 polymorphism is found in approximately 15 % Caucasians and Africans and 30 % Asians [12].

In 2010, a black box label was added for clopidogrel (Plavix) to highlight the role of *CYP2C19* gene variants in drug response, specifically "slow metabolizers." However, as reviewed by Goswami et al., studies of CYP2C19 polymorphism and drug efficacy have yielded variable results, suggesting that this polymorphism may account for only 12 % of response variability [11].

CYP2C19 genotyping is available for diagnostic testing. Complete genotyping profiles are not available and the testing is expensive. The Clinical Pharmacogenetics Implementation Consortium has provided an algorithm for antiplatelet agents using genetic testing [13]. However, routine genetic testing is not yet supported and the clinical utility of such testing has not been demonstrated [15].

Beta-Blockers

Response to beta-blockers may also be influenced by genetic polymorphism [4, 12, 14]. Polymorphisms in CYP2D6 may determine pharmacokinetic variation for selected beta-blockers such as metoprolol and carvedilol, as highlighted in drug labeling. Other SNP variations in beta-1 and beta-2 receptor genes as well as polymorphisms in alpha-receptors may also influence drug response, although data has been inconsistent.

Statins

HMGCR inhibitors also provide examples of pharmacogenetic linkage to observations of drug dosing, efficacy, and toxicity [4, 12]. Pharmacokinetic variations with altered dose requirements may result from polymorphisms of CYP3A4 enzymes. The presence of H7 haplotypes of HMGCR and L5 haplotype of LDLR

may reduce state responsiveness. Genotyping may also be helpful in prediction of risk of myalgias and other muscle toxicity. The SLC01B1*5 allele mediating hepatic uptake has been associated with higher statin concentrations and may dramatically increase risk of myopathy or myalgias [4, 12].

Pharmacogenomic Testing and Utilization

In 2011, over 70 medications contained pharmacogenomic information in FDA-approved drug labeling. FDA-required labeling revisions have been made for dozens of drugs including warfarin, carbamazepine, imatinib, warfarin, irinotecan, and mercaptopurine [17–21]. Pharmacogenetic testing is available for many commonly used medications ranging from anti-infective agents, chemotherapeutic agents, immunosuppressants, antiepileptic agents, cardiovascular agents, to warfarin, although there are relatively few FDA-approved pharmacogenetic test methods available [11]. Stanek et al. reported only 10.3 % of surveyed physicians had ordered such testing in the preceding 6-month interval, while 26.4 % anticipated ordering testing in the next 6-month period. Although 97.6 % of physicians agreed that pharmacogenetics may affect drug response, less than 30 % had received relevant education in the area [18]. In a random telephone survey, most US adults favored testing to evaluate side effect risk and to improve dosing or drug selection. However, those surveyed were unlikely to authorize testing if there was a chance of DNA sharing and loss of confidentiality [19].

Pharmacogenetic testing generally occurs for an individual patient for a target drug. However, a more prospective use of pharmacogenetics has been proposed using data embedded in electronic medical records so as to prospectively aid drug prescribing. Initial work by Schildcrout et al. has demonstrated that approximately 65 % of over 50,000 patients were exposed to at least one pharmacogenetic target drug and that 383 toxicity events could have been prevented with preemptive genotyping programs [17]. Johnson et al. described a customized system for generating patient-specific genotyping for a wide array of SNPs with relatively low cost and rapid turnaround, with capability of placement in a patient medical record [20]. O'Donnell et al. also reported a medical model for implementing preemptive genotyping which could be the basis for further study of genetic utility [21].

The universal use of pharmacogenetic testing remains controversial, even for drugs with known genetic variations that may significantly affect toxicity risks or efficacy. Variable reimbursement practices, especially for private insurers, high test cost, and significant lag time to results provide logistical impediments. The greater question is the utility of testing and impact on outcomes of therapy, which remain active areas of research for major drugs at this time.

Conclusion

Drug response is the result of the complex interplay of environmental and genetic factors. Drug biotransformation and interaction with target receptors or enzymes is determined by genotype and is significantly a product of patient heredity. "Personalized medicine" using preemptive pharmacogenetic information linked to medical records for use at time of initial prescribing may reduce patient risk and enhance outcomes. As rapid scientific and technologic advances are enabling these advancements, the next critical research questions must examine the utility of pharmacogenetic testing in patient care.

References

1. Crews KR, Hicks J, Pui CH, Relling MV, Evans WE (2012) Pharmacogenomics and individualized medicine: translating science into practice. Clin Pharmacol Ther 92:467–475
2. Brazeau DA, Brazeau GA (2011) Principles of the human genome and pharmacogenomics. American Pharmacists Association, Washington, DC
3. Zineh I, Pacanowski MA (2011) Pharmacogenomics in the assessment of therapeutic risks versus benefits: inside the United States Food and Drug Administration. Pharmacotherapy 31:729–735

4. Cavallari LH, Yam YW (2011) Pharmacogenetics. In: Talbert RL, DiPiro JT, Matzke GR, Posey LM, Wells BG, Yee GC (eds) Pharmacotherapy: a pathophysiologic approach, 8th edn. McGraw-Hill, New York
5. Ma JD, Lee KC, Kuo GM (2012) Clinical application of pharmacogenomics. J Pharm Pract 25:417–427
6. Daly AK (2010) Pharmacogenetics and human genetic polymorphisms. Biochem J 429:435–449
7. Belle DJ, Singh H (2008) Genetic factors in drug metabolism. Am Fam Physician 77:1553–1560
8. Lanfear DE, McLeod HL (2007) Pharmacogenetics: using DNA to optimize drug therapy. Am Fam Physician 76:1179–1182
9. Aquilante CL, Beitelshees AL, Cavallari LH, Lee CR, Maciejewski S, Momary KM et al (2009) Key articles relative to cardiovascular pharmacogenomics. Pharmacotherapy 29:1110–1151
10. Pare G, Mehta SR, Yusuf S et al (2010) Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. N Eng J Med 363:1704–1714
11. Gotswami S, Cheng-Lai A, Nawarskas J (2012) Clopidogrel and genetic testing: is it necessary for everyone? Cardiol Rev 20:96–100
12. Wells QS, Delaney JT, Roden DM (2012) Genetic determinants of response to cardiovascular drugs. Curr Opin Cardiol 27:252–261
13. Scott SA, Sangkuhl K, Gardner EE et al (2011) Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450-2C19 genotype and clopidogrel therapy. Clin Pharmacol Ther 90:328–332
14. Johnson JA (2012) Advancing management of hypertension through pharmacogenomics. Ann Med 44(Suppl 1):S17–S22
15. Shin J (2012) Clinical pharmacogenomics of warfarin and clopidogrel. J Pharm Pract 25:428–438
16. Gulseth MP, Grice GR, Dager WE (2009) Pharmacogenomics of warfarin: uncovering a piece of the warfarin mystery. Am J Heath Syst Pharm 66:123–133
17. Schildcrout JS, Denny JC, Bowton E, Gregg W, Pulley JM, Basford MA et al (2012) Optimizing drug outcomes through pharmacogenetics: a case for preemptive genotyping. Clin Pharmacol Ther 92:235–242
18. Stanek EJ, Johnson SCL, Taber KA, Khalid M, Patel A, Verbrugge RR et al (2012) Adoption of pharmacogenetic testing by US physicians: result of a nationwide survey. Clin Pharmacol Ther 91:450–458
19. Haga SB, O'Daniel JM, Tindall GM, Lipkus IR, Agans R (2012) Survey of US public attitudes toward pharmacogenetic testing. Pharmacogenet J 12:197–204
20. Johnson JA, Burkley BM, Langaee TY, Clare-Salzler MJ, Klein TE, Altman RB (2012) Implementing personalized medicine: development of a cost-effective customized pharmacogenetics genotyping assay. Clin Pharmacol Ther 92:437–439
21. O'Donnell PH, Bush A, Spitz J, Danahey K, Saner D, Das S et al (2012) The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. Clin Pharmacol Ther 92:446–449