SIGNIFICANCE OF PHARMACOGENETICS IN MODERN MEDICINE AND PHARMACY

Nikola Stefanović

University of Niš - Faculty of Medicine, Department of Pharmacy, Niš, Serbia

Most drugs have been developed and approved based on pharmacokinetic and pharmacodynamics (PK/PD) studies in larger subject population. However, interindividual differences in the PK/PD of concrete drugs may cause different therapeutic response or presence of side effects within standard treatment protocol. Modern medicine and pharmacy strive for personalized solutions in order to achieve optimal therapeutic outcomes for each individual patient. This approach includes identification of factors of variability in drug response and theirs implementation in therapeutic algorithms. In accordance, it has been shown that genetic factors significantly contribute to variability in drug disposition and effects (1). The development and availability of biotechnology and information technologies have led to new discoveries. In the last 15 years, after complete sequencing and mapping of the human genome (2003), accelerated development and research in pharmacogenetics has started. The pharmacogenetics is a scientific discipline whose task is to study the association between individual genes and the PK/PD characteristics of drugs. Single nucleotide polymorphisms in a DNA molecule, present in the genes of metabolic enzymes, transporters and target proteins, are responsible for their different individual activity and function. Also, an association between drug side effects and certain human leukocyte antigen (HLA) gene polymorphisms has been established. Studies have shown an association between variability in certain genes and pharmacokinetic parameters and/or clinical effects of drugs, such as cytochrome P450 (CYP) 2C9 and VKORC1 genes and warfarin, CYP2C19 gene and clopidogrel, HLA-B genes and allopurinol, abacavir, carbamazepine, CYP2C19 and CYP2D6 genes and antidepressants, SLCO1B1 genes and simvastatin, DYPD genes and fluoropyrimidines, CYP3A5 genes and tacrolimus, but also other gene-drug pairs. CYP3A4/5 metabolizes the largest number of drugs (about 30%), but CYP2D6 and CYP2C19 have been pharmacogenetically more significant. It was shown that the distribution of certain gene polymorphisms (eg. HLA-B) differs in relation to race/ethnicity. This is of a particular importance due to selection of a drug/dosage regimen in different patient populations or in multiethnic societies (2,3). The introduction of pharmacogenetic tests into routine clinical practice may contribute to the development of personalized therapy, where each drug or combination of drugs is optimized to the individual genetic makeup.

References

1. Textbook of Personalized Medicine. Jank KK, editor. 3rd ed. Humana Press (Springer): New York, 2021.
2. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013; 138: 103-141.
3. Osanlou O, Pirmohamed M, Daly AK. Pharmacogenetics of Adverse Drug Reactions. Adv Pharmacol. 2018; 83:155-190.

ZNAČAJ FARMAKOGENETIKE U SAVREMENOJ MEDICINI I FARMACIJI

Nikola Stefanović

Univerzitet u Nišu - Medicinski fakultet, Katedra za farmaciju, Niš, Srbija

Većina lekova je razvijena i odobrena na osnovu farmakokinetičkih i farmakodinamičkih (FK/FD) ispitivanja u većim populacijama ispitanika. Međutim, interindividualne razlike u FK/FD pojedinih lekova mogu usloviti različit terapijski odgovor ili ispoljavanje neželjenih efekata pri standardnom terapijskom protokolu. Savremena medicina i farmacija teže personalizovanim rešenjima u cilju ostvarivanja optimalnih terapijskih ishoda za svakog pojedinačnog pacijenta. Ovaj pristup podrazumeva identifikovanje faktora varijabilnosti u odgovoru na lek i njihovo sagledavanje u okviru terapijskih algoritama. U skladu s tim, pokazano je da genetski faktori značajno doprinose varijabilnosti u dispoziciji i efektima lekova (1). Razvoj i dostupnost biotehnologije i informacionih tehnologija dovele su do novih otkrića. U poslednjih 15 godina, nakon kompletnog sekvenciranja i mapiranja humanog genoma (2003.), započet je ubrzani razvoj i istraživanja u farmakogenetici, naučnoj disciplini čiji je zadatak proučavanje povezanosti pojedinačnih gena sa FK/FD karakteristikama lekova. Polimorfizmi jednog nukleotida u molekulu DNK, koji su prisutni u genima metaboličkih enzima, transportera i ciljnih proteina delovanja lekova, odgovorni su za njihovu različitu individualnu aktivnost i funkciju. Takođe, utvrđena je povezanost neželjenih efekata lekova i određenih genskih polimorfizama humanog leukocitnog antigena (HLA). Studije su pokazale povezanost između varijabilnosti određenih gena i farmakokinetičkih parametara, odnosno kliničkih efekata lekova, poput citohrom P450 (CYP) 2C9 i VKORC1 gena i varfarina, CYP2C19 gena i klopidogrela, HLA–B gena i alopurinola, abakavira, karbamazepina, CYP2C19 i CYP2D6 gena i antidepresiva, SLCO1B1 gena i simvastatina, DYPD gena i fluoropirimidinskih antineoplastika, CYP3A5 gena i takrolimusa, ali i druge parove gen-lek. CYP3A4/5 metaboliše najveći broj lekova (oko 30%), dok CYP2D6 i CYP2C19 imaju najveći farmakogenetski značaj. Takođe, pokazana je razlika u distrubuciji određenih polimorfizama gena (npr. HLA-B) u odnosu na rasu/etnicitet. Ovo je od posebne važnosti kod izbora leka ili doznog režima kod različitih populacija ljudi ili u multietničkim sredinama (2,3). Uvođenje farmakogenetskih testova u rutinsku kliničku praksu može doprineti razvoju personalizovane terapije, gde je lek ili kombinacija lekova prilagođena genetici pojedinca.

Literatura

1. Textbook of Personalized Medicine. Jank KK, editor. 3rd ed. Humana Press (Springer): New York, 2021.
2. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013; 138: 103-141.
3. Osanlou O, Pirmohamed M, Daly AK. Pharmacogenetics of Adverse Drug Reactions. Adv Pharmacol. 2018; 83:155-190.