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Pharmacogenomics

Introduction

Pharmacogenomics is defined as the study of influence of genetic variations on individual differences in response to pharmacological agents.[1] Pharmacogenetics is a subset of pharmacogenomics and is the study of the influence of variation in DNA sequence on differential drug responses.[1] Apart from variation in the DNA sequence, pharmacogenomics also includes epigenetics or transcriptomic changes. Variations in genetic makeup at any of the below-mentioned steps within a population may lead to unpredictable clinical responses and toxicity profiles. Identification of these genetic factors will help in the optimization of therapy, predicting response or adverse events and individualize therapy.

1. Pharmacokinetics – drug absorption, activation, metabolism, or excretion
2. Pharmacodynamics – genetic variations that reduce the binding affinity of the drug to its receptor or resistance mechanisms to circumvent or block the drugs action
3. Disease pathogenesis and response to specific therapies: genomic studies helped to identify targetable driver mutations, which lead to a paradigm change in oncology care
4. Idiosyncratic reactions such as susceptibility to a hypersensitivity reaction to a certain drug.

Goals

- To improve the efficacy of drugs
- To avoid serious adverse reactions of drugs
- To select patient who might benefit the most from the drug
- To reduce cost by avoiding ineffective treatments/ adverse reactions.

Applications with Examples

To minimize toxicities of cancer treatments

a. Thiopurines and polymorphisms in thiopurine-S-methyltransferase (TPMT). Polymorphisms in the TPMT gene lead to the decreased or absent activity of the enzyme and an increased risk of treatment-related adverse events. TPMT allele variants *2 and *3 account for more than 95% of defective TPMT activity in patients. One in 10 people is heterozygous for these variants with reduced TPMT activity, and starting dose of 6 MP dose should be around 50%. Less than 0.5% of population are homozygous with absent TPMT activity. In these people, the initial dose should be 1/10th of normal dose of 6 MP and gradually titrated based on myelosuppression[2]

b. Polymorphisms in the solute carrier organic anion transporter 1B1 gene are responsible for interindividual variation in methotrexate levels and toxicity following administration of high-dose methotrexate

c. Dihydropyrimidine dehydrogenase (DPD) polymorphisms and 5-fluorouracil (5FU) metabolism. DPD deficiency increases incidence and severity of 5 FU-related toxicities such as mucositis, diarrhea, and myelosuppression. Dose modifications are required in heterozygous individuals and drug should be avoided in homozygous individuals.[3] The dose of oral capecitabine also should be modified according to the DPD status

d. UGT1A1 polymorphisms and Irinotecan metabolism. This enzyme is involved in glucuronidation of various drugs including irinotecan. Polymorphisms leading to reduced UGT1A1 activity are associated with severe mucositis and myelosuppression following irinotecan administration.[4]

Pathogenesis and therapeutics

Example – Ovarian cancers with BRCA mutations are usually high-grade serous epithelial cancers and show increased sensitivity to platinum compounds and poly ADP ribose polymerase inhibitors.

Biomarkers for drug resistance

Example – in colonic cancer, in patients with RAS (K-RAS/ N-RAS) mutations, the use of epidermal growth factor receptor (EGFR)-targeted therapies such as cetuximab and panitumumab can be counterproductive, whereas they are beneficial in patients with RAS wild-type tumors.

Applications to individual cancers

Genomics also changed the landscape of cancer therapeutics by the identification of somatic or germ line mutations in the pathogenesis of different malignancies. These mutations can be targeted with either monoclonal antibodies or small-molecule inhibitors.

Examples:

a. Nonsmall-cell lung cancer (NSCLC)-anaplastic lymphoma kinase (ALK)-positive NSCLC and ALK inhibitors (Crizotinib). EGFR-mutated NSCLC and EGFR tyrosine kinase inhibitors (gefitinib and erlotinib)

b. Breast Cancer – Her 2 neu amplification and Her 2 neu-targeted therapy – trastuzumab

c. Melanoma – BRAF V600E mutation – vemurafenib, dabrafenib, and trametinib

d. Use of immune checkpoint inhibitor therapy in tumors with microsatellite instability-H.

Limitations

- A lack of education on the benefits of pharmacogenetic testing
- Potential for the delay in therapy while awaiting results of genotyping

- Differing opinion regarding the threshold of evidence required for implementation in clinics
- Polygenic influence on drug metabolism dwarfs the impact of single gene and adds financial toxicity to evaluate multiple genes
- Lack of cost-effectiveness analyses.

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Conflicts of interest

There are no conflicts of interest.

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