Chapter

Introductory Chapter: Pharmacogenetics

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1. Introduction

Pharmacogenetics is the study of how individual genetics affect drug responses. Many studies investigated the impact of gene variation on the pharmacokinetic and pharmacodynamic of different drugs. This chapter gives an overview of the current state of the pharmacological genetic aspects of these treatments. Drugs with genetic information to support product labeling, clinical guidelines, or significant mechanical effects are discussed. At this point, clinically relevant genetic variation in drug-metabolizing enzymes may reveal the dosage of certain drugs metabolized in the liver. In addition, genetic variation in immune genes can be tested to assess the risk of serious hypersensitivity reactions to certain drugs.

2. Pharmacogenetics and pharmacokinetics

Pharmacogenetic studies mainly focus on the difference in pharmacokinetic parameters after drug administration. These involve clinical investigation of different genes and their effect on biotransformation of drugs to metabolites; for example, tricyclic antidepressants were metabolized in different rates in different populations [1]. Most drugs used to treat neurological and psychiatric diseases are metabolized by the liver. Many genes encoding phase 1 (oxidation) and phase 2 (combined) drug-metabolizing enzymes contain genetic polymorphisms, which are known to affect their metabolic activity. In addition, the pharmacokinetic profile of certain drugs is highly affected by transport proteins that allow the absorption and distribution. These proteins are mainly expressed in hepatic tissue and in blood–brain barrier. The most common biotransformation enzymes are cytochrome P450 (Phase 1), glucuronidase, and catechol/thiopurine methyltransferase (Phase 2). Furthermore, different neurological drugs are affected by transporters, such as P-glycoprotein.

Genetic variation in drug metabolism can alter the biotransformation of a particular drug and can occur due to a combination of inherited alleles from each parent. The results of the functioning of various combinations of drug-metabolizing enzyme alleles may vary slightly depending on the characteristics of the mutation (e.g., fully inactivated enzyme, altered enzyme expression), but are generally maximal. Five categories are considered clinically relevant: (1) low- or no-enzyme activity, (2) medium-enzyme activity (reduced enzyme activity between normal and poor enzyme), (3) normal-enzyme activity (genetically unchanged enzyme activity), (4) fast-enzyme activity (with less increased enzyme activity compared to normal one), and (5) highly fast-enzyme activity (compared to fast-enzyme activity) [2].

3. Pharmacogenetics and pharmacodynamics

Genetic polymorphisms occurring in drug receptors or other biological targets are thought to be responsible for some of the observed variances in response and tolerance to treatment. For neurological and psychiatric conditions, this may include variations affecting the expression of the target receptor, the structure of the receptor, the arrangement of substance neurotransmitters, and second messenger pathways. Beside the pharmacokinetic variation due to biotransformation, the pharmacodynamics of few drugs are mainly affected by genetic markers that are mentioned in the clinical guidelines. Three famous examples showing the effect of pharmacodynamic-related genes are hypersensitivity risks related to immunological genes, inborn metabolism variations due to gene variants, and antiepileptic drugs associated with life-threatening consequences. In addition, numerous studies have been performed to identify and characterize genetic variants related to pharmacodynamics. In many cases, these signs may also be related to the risk of an underlying disease or illness. A simple example is the biopharmaceutical aspects of hypersensitivity reactions [3].

4. Personalizing medicine

Personalized medicine was recognized in the early nineteenth century by Sir William Osler who studied the variation in drug responses among individuals. This concept evolved over years genomic information have been incorporated into patient's clinical diagnosis and treatment. The major areas of applied research in this field involve identifying the genetic basis of common diseases, studying how genes and the environment interact to cause human disease, and using pharmacogenetic biomarkers to facilitate more effective drug therapy. Pharmacogenetics has become one of the leading and potentially most actionable areas of the personalized medicine paradigm, as evidenced by the increased availability of clinical pharmacogenetic testing among Clinical Laboratory Improvement Amendments-approved

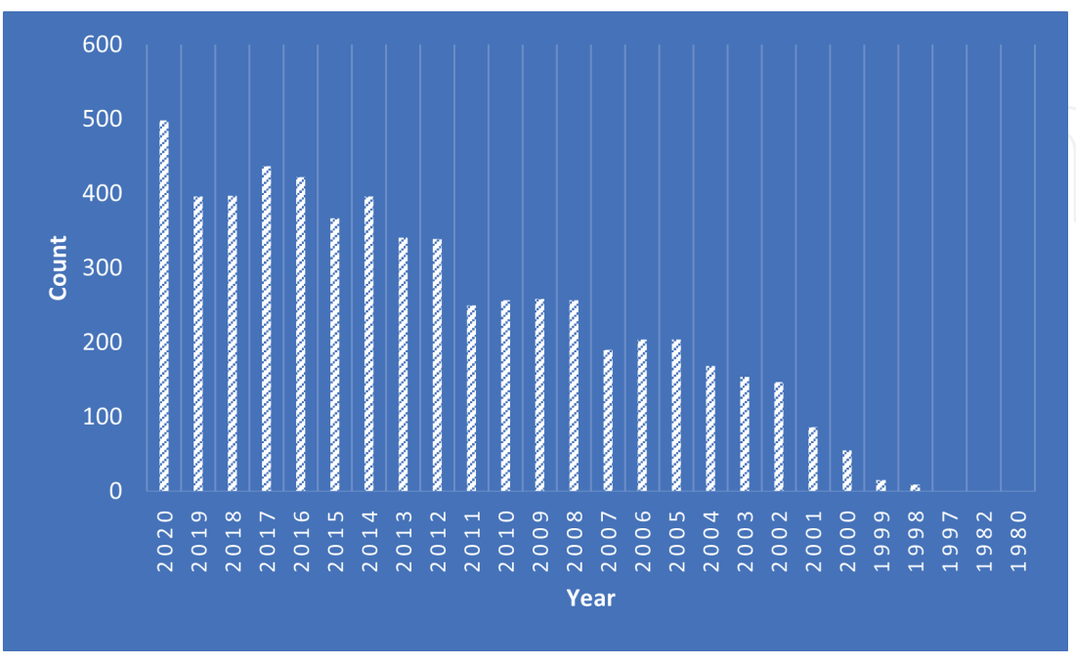

Figure 1.
Number of publications—PubMed citations (http://www.ncbi.nlm.nih.gov/pubmed) by date using the keyword "pharmacogenetics," "pharmacogenomics," or "clinical pharmacogenetics."

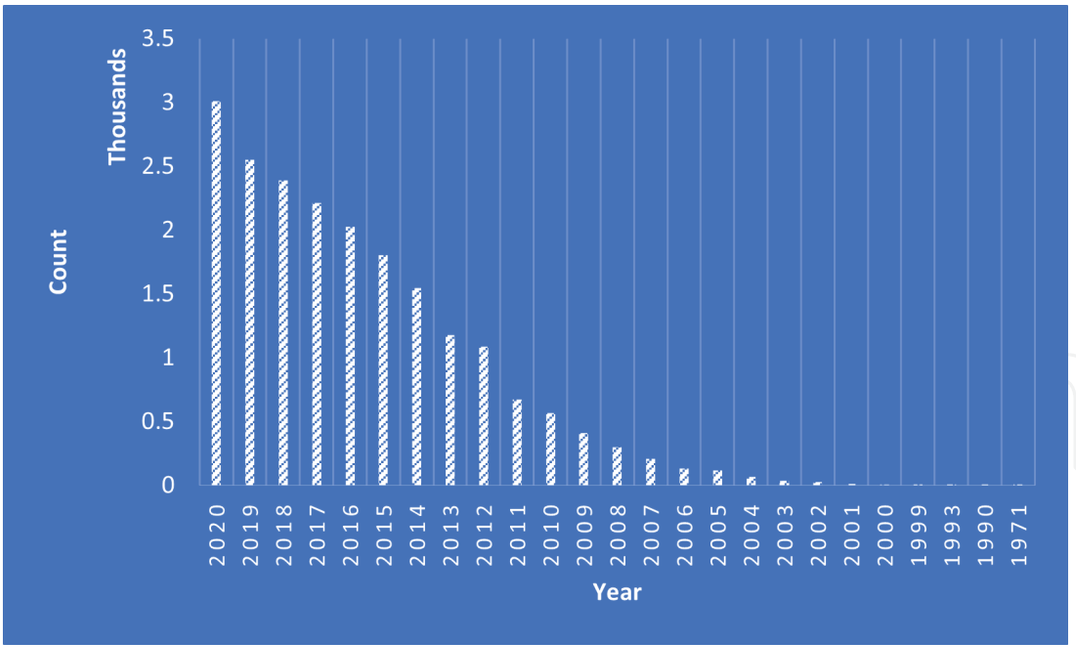

Figure 2.
Number of publications—PubMed citations (http://www.ncbi.nlm.nih.gov/pubmed) by date using the keyword "personalized medicine."

laboratories over the past few years. Moreover, the literature in pharmacogenetic studies over the past decade (**Figure 1**) has proved exponential growth beside FDA acknowledgement. A significant increase was observed starting from 2000 with 55 publications till 2020 with 498 publications. Furthermore, the term personalized medicine (**Figure 1**) was also used from 2000 with 7 publications till 2020 with 3009 publications (**Figure 2**) [4].

In conclusion, pharmacogenetics and personalized medicine showed a rapid growth over years with a great intention to apply the knowledge gained in clinical practice. Important genetic associations have been identified between variant genotypes and drug response phenotypes that encouraged the FDA to revise drug labels to include relevant pharmacological genetic information and recommendations for some certain drugs. However, despite the availability of pharmacological genetic tests from Clinical Laboratory Improvement Amendments-approved laboratories, physician implementation of pharmacological genetic investigation has been unsatisfactory, maybe due to lack of awareness or inadequate professional guidance and limited coverage of testing coverage. Therefore, selected pharmacogenetic examples have been accepted into clinical practice and several others are currently being evaluated in randomized controlled trials.

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