Lecture 5. Pharmacogenomics.

Learning outcomes:
1. Explain the difference between the terms “pharmacogenetics” and “pharmacogenomics”.
2. Characterize the mechanisms of genetically based human reactions to the medical drugs, give the specific examples.
3. Describe the methods of pharmacogenomics.

Pharmacogenomics is the study of the role of the genome in drug response. Its name (pharmaco- + genomics) reflects the combining of pharmacology and genomics. Pharmacogenomics analyzes how the genetic makeup of an individual affects his/her response to drugs. It deals with the influence of acquired and inherited genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with **pharmacokinetics** (drug absorption, distribution, metabolism, and elimination) and **pharmacodynamics** (effects mediated through a drug's biological targets). The term pharmacogenomics is often used interchangeably with **pharmacogenetics**. Although both terms relate to drug response based on genetic influences, **pharmacogenetics** focuses on **single drug-gene interactions**, while pharmacogenomics encompasses a more genome-wide association approach, incorporating genomics and epigenetics while dealing with the effects of multiple genes on drug response.
The most prevalent **drug-metabolizing enzymes** (DME) are the **Cytochrome P450** (CYP) enzymes. These enzymes introduce reactive or polar groups into xenobiotics such as drugs. The term Cytochrome P450 was coined by Omura and Sato in 1962 to describe the membrane-bound, heme-containing protein characterized by 450 nm spectral peak when complexed with carbon monoxide. The human CYP family consists of 57 genes, with 18 families and 44 subfamilies.
The **vitamin K epoxide reductase complex subunit 1** (**VKORC1**) is responsible for the pharmacodynamics of warfarin. VKORC1 along with CYP2C9 are useful for identifying the risk of bleeding during **warfarin** administration. Warfarin works by inhibiting VKOR, which is encoded by the VKORC1 gene. Individuals with polymorphism in this have an affected response to warfarin treatment.
Thiopurine methyltransferase (TPMT) catalyzes the S-methylation of thiopurines, thereby regulating the balance between cytotoxic thioguanine nucleotide and inactive metabolites in hematopoietic cells. TPMT is highly involved in 6-MP metabolism and TMPT activity and TPMT genotype is known to affect the risk of toxicity. Excessive levels of 6-MP can cause myelosuppression and myelotoxicity. **Codeine, clopidogrel, tamoxifen, and warfarin** a few examples of medications that follow the above metabolic pathways.
Pharmacogenomics uses the research methods of molecular biology, biochemistry and biotechnology such as **polymerase chain reaction (PCR**), different types of **genome sequencing** (DNA sequencing), different methods of **genotyping (RFLP, AFLP, DNA microarray**), **bioinformatical methods, proteomic methods** and etc.

The questions for self - control:
1. What are the “pharmacogenetics” and “pharmacogenomics”?
2. Which drug metabolizing enzymes do you know and what are their functions?
3. Give some specific examples of poisoning by the medical drugs and explain its mechanisms.
4. What are the research and diagnostic methods of pharmacogenomics? What is the base of each method?

Recommended readings:
1. Ermak, Gennady (2015). Emerging Medical Technologies. World Scientific. ISBN 978-981-4675-80-2.

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3. "Center for Pharmacogenomics and Individualized Therapy". Retrieved 2014-06-25.
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5. Sheffield LJ, Phillimore HE (2009). "Clinical use of pharmacogenomic tests in 2009". Clin Biochem Rev. 30 (2): 55–65. PMC 2702214. PMID 19565025.
6. Shin J, Kayser SR, Langaee TY (April 2009). "Pharmacogenetics: from discovery to patient care". Am J Health Syst Pharm. 66 (7): 625–37. doi:10.2146/ajhp080170. PMID 19299369.
7. "Center for Genetics Education".
8. Nebert DW, Russell DW (October 12, 2002). "Clinical importance of the cytochromes P450". Lancet. 360 (9340): 1155–62. doi:10.1016/s0140-6736(02)11203-7. PMID 12387968. S2CID 13577054.
9. Hart SN, Wang S, Nakamoto K, Wesselman C, Li Y, Zhong XB (January 2008). "Genetic polymorphisms in cytochrome P450 oxidoreductase influence microsomal P450-catalyzed drug metabolism". Pharmacogenet Genomics. 18 (1): 11–24. doi:10.1097/FPC.0b013e3282f2f121. PMID 18216718. S2CID 38880360.
10. Crews KR, Hicks JK, Pui CH, Relling MV, Evans WE (October 2012). "Pharmacogenomics and individualized medicine: translating science into practice". Clin Pharmacol Ther. 92 (4): 467–75. doi:10.1038/clpt.2012.120. PMC 3589526. PMID 22948889.
11. Sim SC, Kacevska M, Ingelman-Sundberg M (February 2013). "Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects". Pharmacogenomics. 13 (1): 1–11. doi:10.1038/tpj.2012.45. PMID 23089672.
12. Yu Liu. OMICS in Clinical Practice / 2014 by Apple Academic Press, Inc. – 456 p.