Pharmacogenetics

PHC 721

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Pharmacogenetics vs. Pharmacogenomics

Pharmacogenetics:

The study of the genetic basis for differences in drug responsiveness among humans.

Pharmacogenomics:

The study of variations in DNA and RNA characteristics as related to drug response.

The terms Pharmacogenetics & Pharmacogenomics are sometimes used interchangeably.

TOPICS:

- Personalized Medicine
- Genetic Influences on Drug Metabolism
- Genetic Influences on Drug Action
- Inherited Diseases that Predispose to Drug Toxicity

Personalized Medicine

Variability in drug response among individuals is due to Genetic and Environmental Effects on drug Pharmacokinetics (ADME) and Pharmacodynamics (receptors or downstream signaling).

Mutation $\Rightarrow$ a change in the nucleotide sequence of DNA.
Single nucleotide polymorphisms (SNPs) are very common and may change the function or level of expression of the corresponding protein (e.g., drug metabolic enzymes, drug transporters, etc.).

EXAMPLE: Idiosyncratic adverse drug reactions as a genetically-determined variation in the activity of metabolic enzymes or target proteins.

Balanced Polymorphisms
$\Downarrow$
a substantial fraction of a population differs from the remainder over many generations due to heterozygotes experiencing selective advantage
(e.g., **functionally defective CYP2D6** – 7-10% Caucasians, 30% Chinese;
CYP2D6 duplication – ultra-rapid metabolism – 30% Egyptians;
Polymorphism in ryanodine receptors (RyR1) – Malignant Hyperthermia – **Isoflurane** – 1:20,000;
Low levels of Aldehyde Dehydrogenase activity – Ethanol Sensitivity – Orientals).

By defining patient's DNA sequence from a blood sample, providers will be able to select the safest and most effective drug and its dose 'personalized' for this patient.

Genetic Influences on Drug Metabolism

Three Drug Oxidation Polymorphisms receiving Most Clinical Attention, including Dentistry:

CYP**2D6,** CYP**2C9 and** CYP**2C19**

CYP2D6

(affects 25 % of all currently used drugs)

Poor Metabolizer CYP2D6 Phenotype:

1) gene deletion ⇒ absence of protein,
2) defective splicing ⇒ inactive enzyme,
3) missense SNPs ⇒ ↓ enzyme stability or ↓ substrate affinity

Higher concentrations of parent drug following administration ⇒ Greater adverse effects
Therapeutic failure of [prodrugs]/[less active forms] requiring CYP2D6 for activation
(e.g., Codeine → Morphine)

Ultrarapid CYP2D6 Phenotype:

gene duplication ⇒ ↑ active enzyme

Ultrarapid conversion to more active drug forms ⇒ ↑ risk of life-threatening drug effects
(e.g., Codeine → Morphine)

CYP2C9

Catalyzes the oxidation of Warfarin (anticoagulant; Vitamin K antagonist)

Allelic variants of *CYP2C9* encode enzymes with reduced or altered affinities ⇒
up to 90% reduction in Warfarin clearance ⇒ Bleeding complications

CYP2C19

Catalyzes the oxidation of Clopidogrel (antiplatelet)

Patients with Poor or Intermediate CYP2C19 Phenotypes ⇒ Inadequate therapeutic effects

Genetic Influences on Drug Action

Genetic Polymorphisms exist in most, if not all, proteins, including drug receptors.

β-Adrenergic Receptor Polymorphisms

(critical sympathetic responses in the cardiovascular, respiratory and gastrointestinal systems)

β_2-Adrenergic Receptor Genotype Variation

Affects therapeutic response to selective β_2-Adrenergic Agonists (e.g., Albuterol)

Polymorphisms of β-Adrenergic Receptors & Treatment of Cardiovascular Diseases

1) Alteration of agonist or antagonist efficacy (a variant β_1 or β_2 receptor)
2) Alteration of drug efficacy secondary to an effect of the polymorphism on cardiovascular function

(e.g., a patient with β_2 receptor variant that results in lower systemic vascular resistance $\Rightarrow$ altered sensitivity to vasodilation via another mechanism, secondary to the altered vascular tone)

Genetic Polymorphisms in Dopaminergic and Antipsychotic Drug Receptor Targets

- Drug abuse liability, the reinforcing effects of alcohol, cocaine and nicotine
- Incidence of tardive dyskinesias following long-term treatment of Schizophrenia
- Lack of effectiveness of antipsychotic drugs in some patients with Schizophrenia

(dopaminergic, adrenergic, serotonergic and/or histaminergic receptor polymorphisms)

Inherited Diseases that Predispose to Drug Toxicity Relevant to Dentistry

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Catalyzes the formation of reduced NADPH, which maintains glutathione in its reduced form.

Located on X-chromosome ($\Rightarrow$ sex-linked)

G6PD deficiency is common (Mediterranean peoples, African and Indian descent, in East Asia)

Methemoglobinemia and Hemolysis

DRUGS: Analgesics (Aspirin), Antibacterials (Ciprofloxacin)

Ryanodine R1 Receptor (Ry1R) Variant

Controls intracellular calcium flux from the sarcolemma.

Malignant Hyperthermia (potentially fatal) and Muscle Spasm

DRUGS: General Anesthetics – Inhalational Anesthetics (Isoflurane)