Pharmacogenetics

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Pharmacogenetics

A branch of science focused on the effect of genetic diversity on response to drug

Genetic diversity can influence pharmacological effect

- Absorption (e.g. ABCB1 -> glycoproteinP)
- Metabolism (e.g. cytochrome P450)
- Mechanism (receptors, ion channels)

Clopidogrel

- Absorption (glycoprotein P, encoded by ABCB1)
- Bioactivation (CYP3A4, CYP3A5, CYP2C19)
- Active metabolite binds to platelet's ADP receptor (encoded by P2RY12), inactivating fibrinogen receptor (encoded by ITGB3).

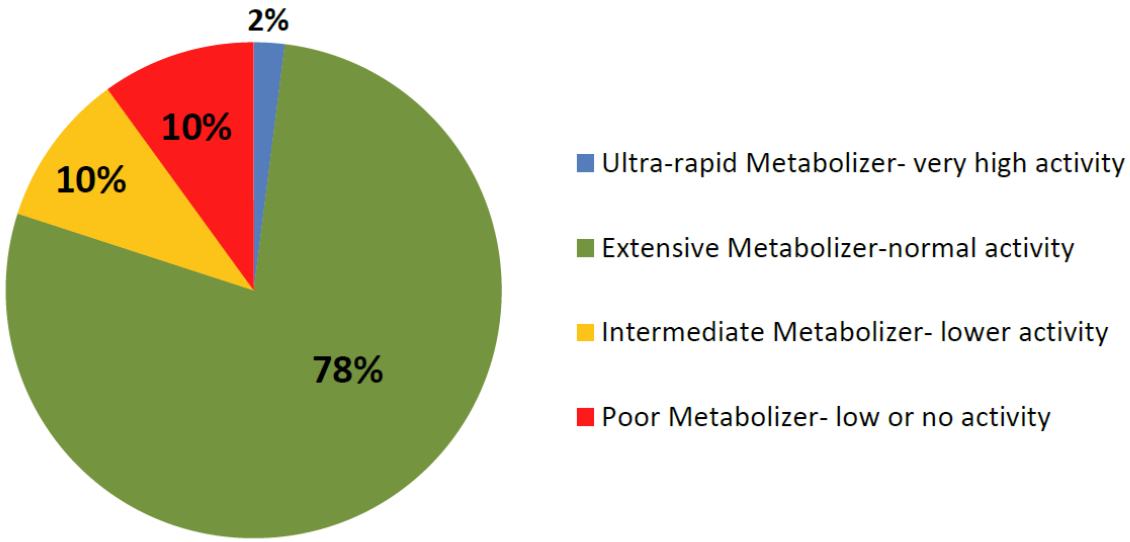
Pharmacogenetic diversity – differences in oxidation speed

- **Phenotypes of oxidation:**
  - EM (extensive metabolizers) – neutral phenotype; fast rate of oxidation
  - PM (poor metabolizers) – slow oxidation rate
  - IM (intermediate metabolizers) – slower than EM, faster than PM
  - UM (ultrarapid metabolizers) – much faster than EM
- **Poor metabolizers (PM):**
- **Drug**:
  - normal dose = increased blood concentration, can cause adverse effects (solution: **lower dose**)
- **Pro-drug**:
  - normal dose doesn't reach therapeutic level (solution: **higher dose** or switch to drug **not metabolized by this enzyme**)
- **Ultrarapid metabolizers(UM):**
- **Drug**:
  - normal dose doesn't reach therapeutic level (solution: **higher dose** or switch to drug **not metabolized by this enzyme**)
- **Pro-drug**:
  - normal dose = increased blood concentration, can cause adverse effects (solution: **lower dose**)

Cytochrome P-450 – genetic cause for different oxidation phenotypes

- The most important oxidative enzymatic system involved in drug metabolism
- More than 40 isoenzymes that show variable catalytic activity and uniform action
- Responsible for biotransformation of different classes of drugs (above 80% of the drugs).
- CYP2D6 was intesively studied
  - >100 allelic variants (high diversity)
  - Metabolizes 25% of all known drugs

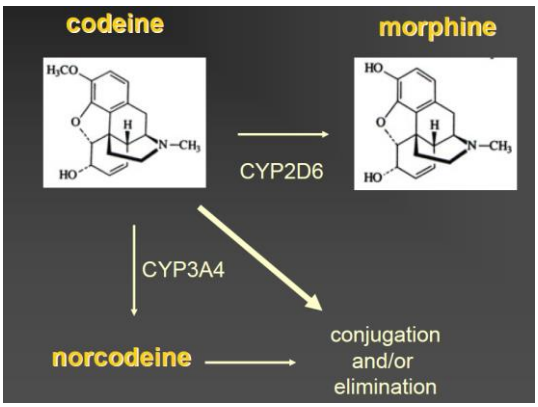
Proportions of oxidation phenotypes in Caucasians



Imipramine, Paroxetine

- Metabolized by CYP2D6
- Drugs, so PM may lead to increased toxicity while UM – inefective treatment

Codeine



- Prodrug

Warfarin

Pharmacokinetics: CYP2C9*2 and CYP2C9*3:

- Decreased enzyme activity
- Longer half-time, lower dose effective

Pharmacodynamics: VKORC1:

- Warfarin is an inhibitor of VKORC1 (pharmacodynamics)
- SNP1639G/A
    - Allele A: decreased enzyme expression➔ lower dose effective
    - Allele G: decreased enzyme expression

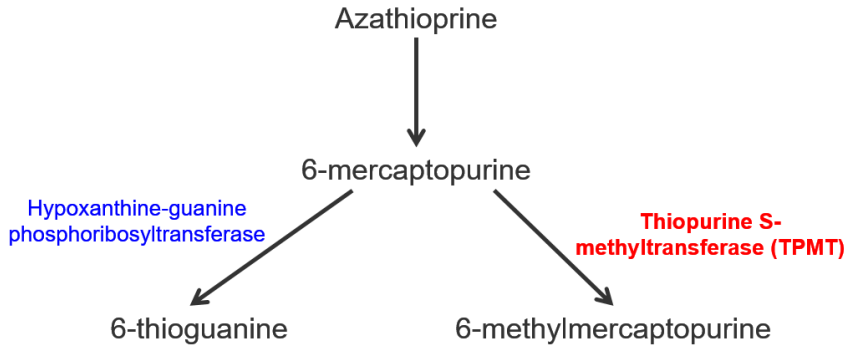
		CYP2C9					
		*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
VKORC1	GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
	AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
	AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Azathioprine

Immunosupressant with severe adverse effects (associated with thiopurine toxicity)

Myelosuppression resulting from thioguanine accumulation

Gene-candidate approach: genotyping enzymes metabolizing azathioprine



- In patients with low TPMT activity (PM) treated with azathioprine, toxic metabolites (thioguanine nucleotides) are accumulated in the cells, inhibiting the activity of the bone marrow.
- 0.3% (1 in 300) individuals inherit two non-functional TPMT allelles (homozygous) & have little or no TPMT activity.
- Approximately 10% of Caucasians & African Americans inherit one non-functional TPMT allele (heterozygous) that confers intermediate TPMT activity.
- USA: mandatory genotyping TPMT **before** treatement with azathioprine

Abacavir

Abacavir – Reverse transcriptase inhibitor used to treat infections with human immunodeficiency virus (HIV)

4.3% of patients exposed to the drug develop a hypersensitivity reaction which can ultimately result in death

Genetic studies focused on HLA region revealed a clinical marker of this hypersensitivity - HLA-B*5701 allele

Malignant hyperthermia

- Life threatening condition caused in some patients by drugs used for general anesthesia
- Extremely fast increase in body temperature, significant increase in muscle oxygen metabolism
    - Accumulation of CO_2 in the body
    - Increase in body temperature up to 43-44°C!
- RYR1 rianodine receptor mutation
    - Autosomal dominant tract
    - Frequency: 1/5000 cases of anesthesia
    - Incorrect uncontrolled release of calcium ions from the sarcoplasmic reticulum; active Ca removal requires large amounts of energy => heat generation
- Dantrolen: inhibits the release of calcium ions stored in the sarcoplasmic reticulum
    - intravenously, prophylactically before the procedure 1 mg / kg, therapeutically 2.5 mg / kg body weight

5-fluorouracil

- Dihydropirymidyne dehydrogenase (DPD) has more than 20 alleles; allele *DPD*2A* has the greatest clinical importance as it causes big decrease in enzyme activity.
- The frequency of allele *DPD*2A* in Caucasians - 1/135 individuals.
- Even in heterozygote *(wt/ DPD*2A)* the enzyme activity becomes decreased, increasing the risk of 5FU toxicity (neurotoxicity and bone marrow suppression)

- As a result - the carriers of DPD*2A allele have *4 x higher risk of death after standard dose of FU*

Guidelines and pharmacogenetics calculators

https://www.pharmgkb.org/guidelineAnnotations