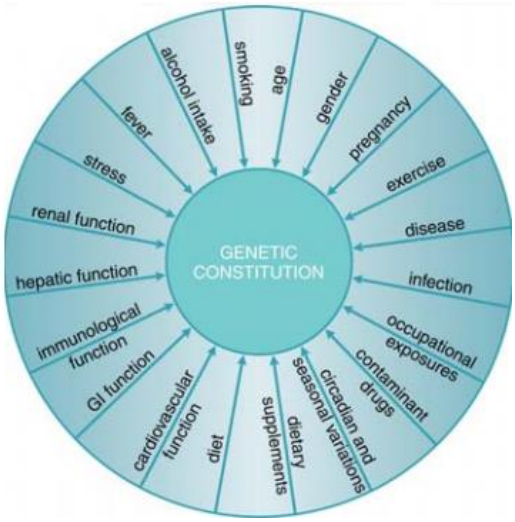
Human pharmacology

Human pharmacology I – Pharmacogenetics

Individual variation in drug response

- Variability can cause: **lack of efficacy** or **unexpected side-effects**.



  - Types of variability include: **pharmacokinetic** (enzymes), **pharmacodynamic** (receptors), or **idiosyncratic**.
  - Main **causes of variability**:
    - Age
    - Genetic factors
    - Physiological states (e.g. *pregnancy*)
    - Pathological states (e.g. *kidney/liver disease*)
    - Drug interactions

Importance of genetics in drug metabolism

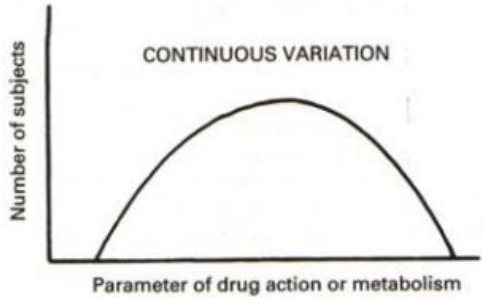
- Drug half-lives shown to be:
  - **Very similar in identical twins**
  - Markedly ***different*** in fraternal twins.
  - Markedly ***different*** in unrelated individuals.
  - Therefore, **genetic control** of metabolism **is a dominant factor**.
    - **Environmental control** of drug metabolism if a factor of **SECONDARY IMPORTANCE!**
      - **Note:** environmental factors may contribute to *population variability* – while not through a genetic mechanism, they may act at a ***transcriptional level***.

Molecular mechanisms of genetic polymorphism

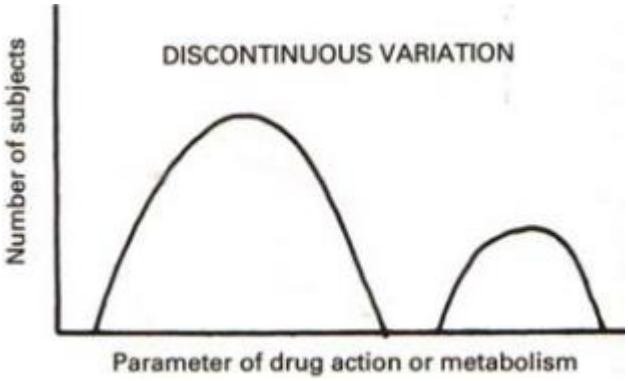
- **Single Nucleotide Polymorphisms** (SNPs)
  - Coding, **nonsynonymous** e.g. *TPMT*3A*
    - Single nucleotide change cause **change in amino acid sequence**, e.g. CCG → CAG changes **Pro → Gln**
  - Coding, **synonymous** e.g. *ABCB1 C3435T*
    - Single nucleotide change that codes for the **same amino acid**, e.g. CCG → CCA changes **Pro → Pro**
  - **Noncoding** (**promoter, intronic**) e.g. *CYP3A5*3*
    - May alter **rate of transcription**.
- **Indels**
  - Insertions/deletions, involve insertion or deletions of base-pair sequences.
- **Copy Number Variations** (CNVs)
  - Involve **gene duplications**

        - e.g. ***CYP2D6***, can have up to **13 copies**
    - Or **large deletions**
        - E.g. entire *GSTT1* and *GSTM1*

Variation in response – genetic



- **Continuous variation** in response to a drug implies that the genes involved are **essential genes that are least likely to be polymorphic** → i.e., highly ***conserved***



- **Discontinuous variation** in response to a drug implies that involves **polymorphic genes**.

The concept of polymorphism

- Polymorphism is defined as *the occurrence together of two or more discontinuous forms in a species in such proportions that the **rarest of them** cannot be **maintained** merely by recurrent mutation*.
    - i.e., the polymorphism is maintained due to being advantageous in particular conditions.
- Genetic variation exists in populations so that a **swift response** can be made to changes in the environment. Once phenotype will **better survive** the direction of the change in the environment.

Inter-ethnic variability in drug response

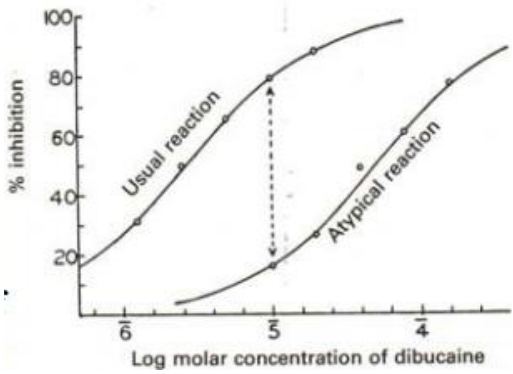
- Different ethnic groups **respond differently** to ***some*** drugs
- Most examples of such response variation are due to **genetic polymorphisms in *drug metabolising enzymes*** e.g. N-acetyltransferases (phase 2 metabolism); CYP450's (phase 1 metabolism)
- Enzyme activity then **modulates drug concentration** and hence **response** (**PHARMACOKINETIC**)
- Genetic differences in **receptor function** also occur (**PHARMACODYNAMIC**)

Enzyme polymorphism: human cholinesterase

- Drug: **succinylcholine** (*suxamethonium*) acts by **blocking neuromuscular junction**
- Enzyme: **pseudocholinesterase** in plasma hydrolyses succinylcholine
- Metabolites: **succinic acid** + **choline** (***no pharmacological actions***)

- Polymorphism: hydrolysis of succinylcholine by butyrlcholinesterase (pseudocholinesterase) is impaired in **1:3500** **'white' subjects**; leads to **prolonged muscle paralysis** and **apnea**.

Enzyme polymorphism: inhibiting cholinesterase



- **Dibucaine** inhibits pseudocholinesterase.
- Extent of inhibition is dependent on the **enzyme phenotype** or **genotype**.
  - Classifies **cholinesterase phenotypes** & **assess risk**.
- Polymorphism is caused by **MANY POINT MUTATIONS** – major one at **NUCLEOTIDE 29** causes **G → A** change in enzyme and reduces activity. Others **increase activity**.

Enzyme polymorphism: *N-Acetyltransferases*

- **First** example of **genetic control of drug disposition**
- Found that humans could be classified as "***rapid***" or "***slow***" with regard to their ability to metabolise the drug **ISONIAZID** (**antituberculosis agent**, isoniazid converted to *acetylisoniazid*, which is inactive).
- Individuals with 1 or 2 **wild-type alleles** classified as **rapid**; those with **2 mutated** alleles as **slow**.
  - Other relevant drugs: **procainamide** (anti-arrhythmic drug); **hydralazine** (anti-hypertensive agent)

Isoniazid – *NAT2* phenotype

Ethnic grouping of **slow acetylators**:

Orientals	**% slow**	**Caucasians**	**% slow**
Japanese	7-12	**UK**	53-62
Korean	11	**Canadian**	59-70
Philipino	28	**Finns**	61-64
Chinese	13-22	**German**	57
Thai	18	**Italian**	49
Ainu	13	**Australian (?)**	54

Therefore the *NAT2* genotype with **2 mutated alleles** is more common in Caucasians (***slow*** acetylators.)

NAT2 genotype with **1 or 2 *wild type*** alleles is more common in orientals (***rapid*** acetylators).

NAT2 phenotype & colorectal cancer

- When compared with **age and gender-matched controls**, data suggests that there is an ***excess of rapid acetylators*** with among patients with **colorectal cancer**.

Colorectal cancer – possible mechanisms

- Metabolism of **dietary** & **environmental amines** occurs by **CYP1A2** in the liver
  - Produces **N-hydroxy metabolite**
  - NAT2 enzyme mediates **acetylation** of the N-hydroxy metabolite
  - Forms **reactive metabolite** that can form **covalent conjugates with DNA**
  - NAT2 activity is present in **greater concentrations** in the colon epithelium of **rapid acetylators** than of slow acetylators, **increasing the exposure of their colons to reactive N-acetyl metabolites**

Pharmacogenetics of phase 1 metabolism

CYP450 enzymes

- One member – CYP**2D6** – represents one of the most intensively studied examples of pharmacogenetic variation.
  - Approximately 5—10% of **white** subjects found to have a relative **deficiency** in their ability to **oxidise the anti-hypertensive drug debrisoquine**.
- Genetic variants responsible for **low levels of CYP2D6** range from:
  - **SNPs** that alter amino acid sequence of the encoded protein (***non-synonymous***)
  - **SNP**s that alter **RNA splicing** (***non-coding***)
  - **Deletions** of the CYP2D6 gene
- Genetic variants that are responsible for **ultra-rapid metabolism** are due to ***multiple copies*** (duplications) of the CYP2D6 gene (***copy number variation***)
- Overall >75 CYP2D6 variations have been described.
  - Among **northern Europeans**, multiple copies of CYP2D6 gene is relatively **infrequent**. However in ***some*** **East African** populations, frequency can be as high as **29%**.

Drug effects of CYP2D6 polymorphism

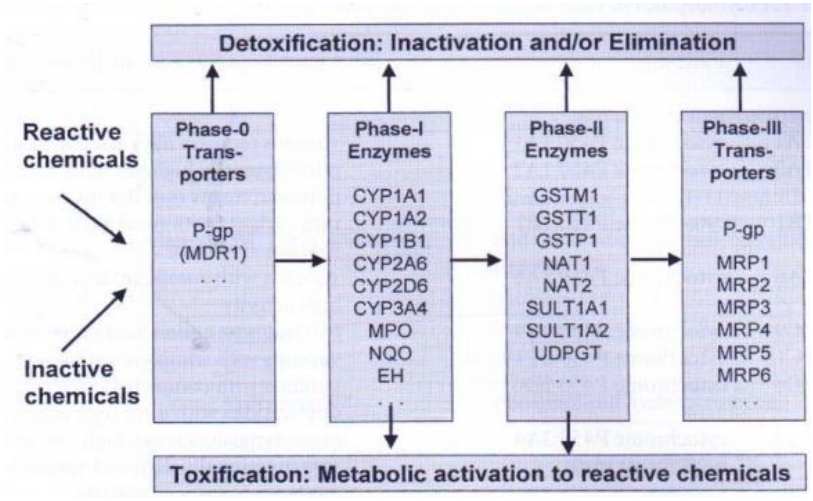
1. Nortriptyline

- Nortriptyline used to treat **hypertension**
  - No/low CYP2D6 → huge increase in plasma drug concentration → increase in clinical response (massive blood pressure drop)
    - 65—80% of Caucasians are **extensive metabolisers**, requiring much higher doses
    - Same applies for **sparteine**, **debrisoquin**.

2. Codeine

- Codeine metabolised by CYP2D6 into active metabolites **morphine**
  - Rapid metabolisers would **produce more morphine** than normal, possibly leading to morphine overdose at lower doses
  - Poor metabolisers would produce **less morphine**, & more of the drug would be cleared unchanged → don't get analgesic effects of the drug.

Polymorphisms in drug transporters & metabolism – link to cancer susceptibility



- Polymorphism in Phase-0 transporters can lead to reduction in reactive chemicals being detoxified
- Polymorphism in Phase-3 transporter can lead to reduction in metabolites being detoxified, leading to increased chance of toxification