Medical Committee
The University of Jordan

PHARMACOLOGY

Slide # : 7

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SHEET

SLIDES

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Introduction pharmacology

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PhD of Molecular Pharmacology

GENE

- **A code made up of pairs of bases carried on the DNA molecule.**
- **Each DNA molecule contains many genes.**
- **The basic physical and functional units of heredity**
- **Genes vary in size and exon content**
- **has regulatory sequences such as promoters and enhancers, which control the transcription of the open reading frame.**

GENE

- **Each chromosome carries a couple of thousand genes**
- **Many of these are common to all human beings.**

  99.9% of your DNA is identical to everyone else's.

- **The remaining 0.1% influences the differences between us**
  - **height, hair color and susceptibility to a particular disease**
  - **And so on**

What drugs

1. Drug with narrow therapeutic range
eg; theophyline

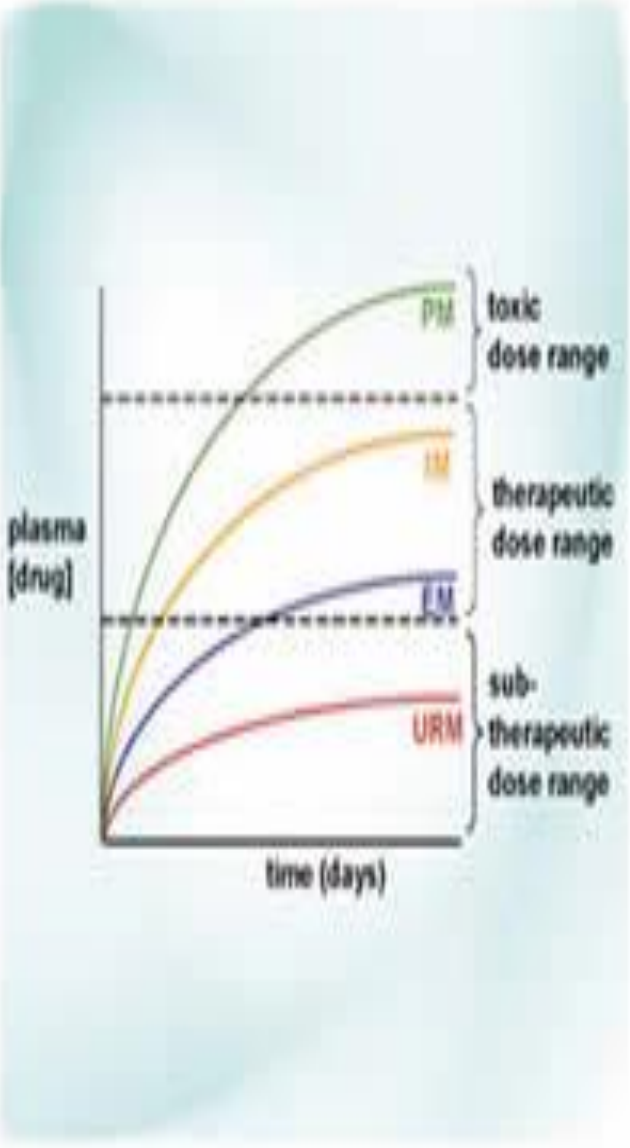
2. Drug with life-threatening adverse effects
eg; warfarin

3. Drug therapies of which individual response can badly be predicted
eg; antidepressant drugs

4. Drug therapies of which quick response is required
eg; analgesic drugs

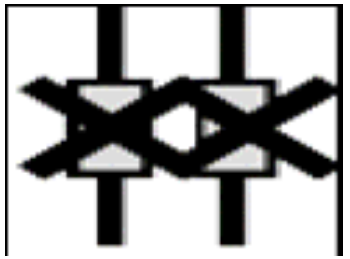
Classification of Drug Metabolism

- Drug metabolism is arbitrarily classified into 3 or 4 classes, depending on the enzyme involved
- These classifications may represent genetic polymorphism or groups of polymorphism
- The classes include:
  - PM = poor metabolizers
  - IM= intermediate metabolizer
  - EM = extensive metabolizers
  - URM = ultrarapid metabolizers

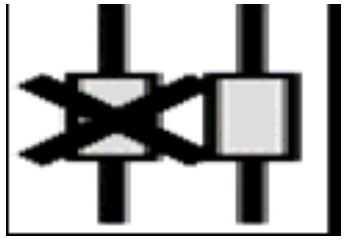


Phenotypes of CYP450

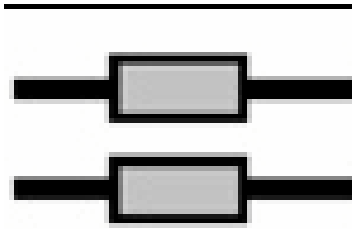
1. Poor metabolizer (PM)
- has low metabolic capacity
- has two mutant alleles



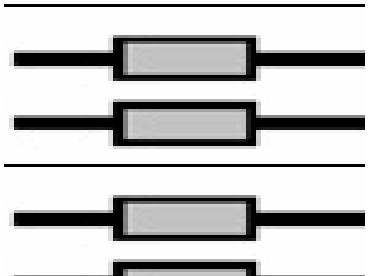
2. Intermediate metabolizer (IM)
- has metabolic capacity between PM and EM
-has one reduced activity allele and one null



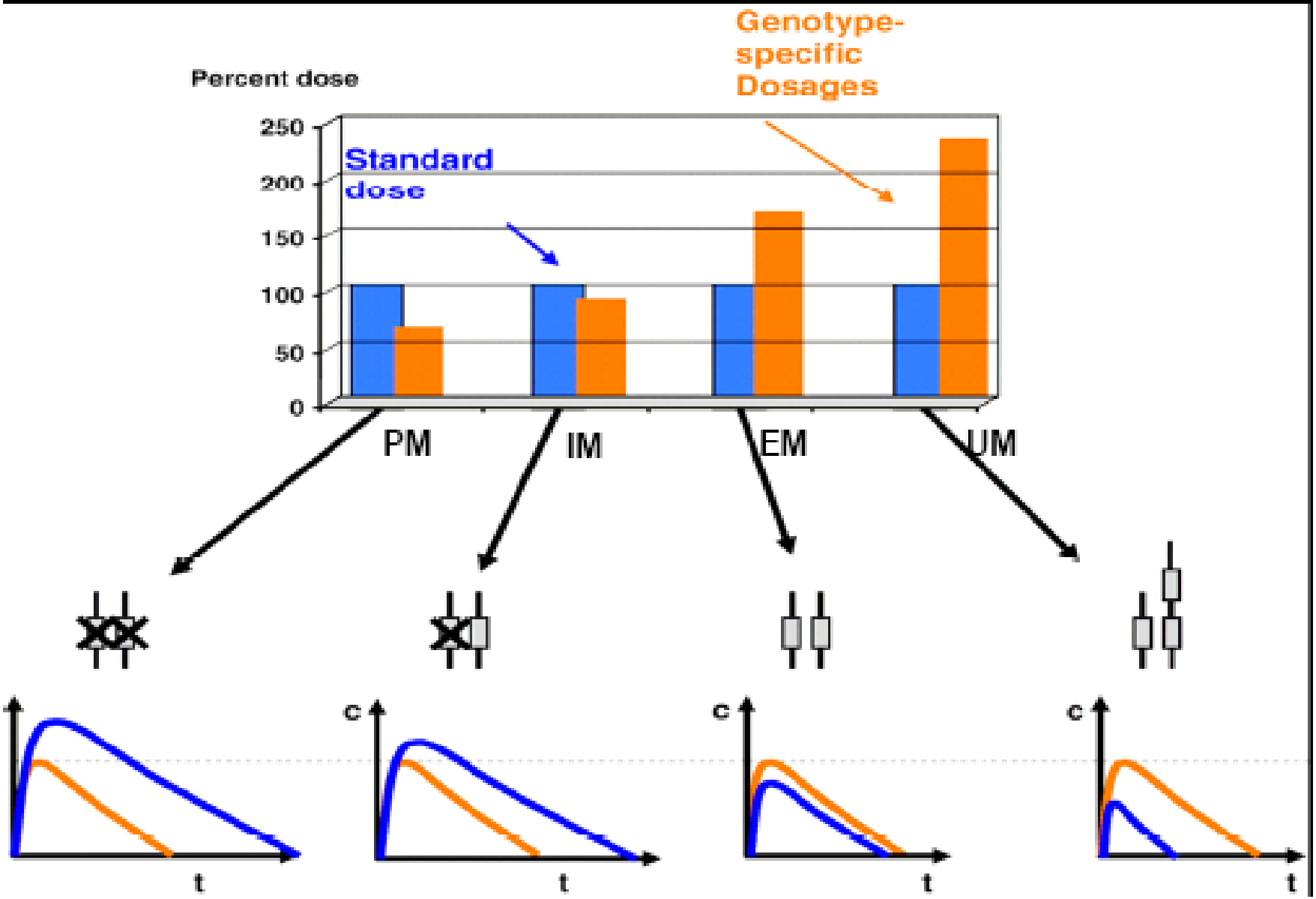
3. Extensive metabolizer (EM)
- has regular metabolic capacity
- has at least one and no more than two normal functioning alleles



4. Ultrarapid metabolizer (UM)
- has higher metabolic capacity than EM
- has multiple copies of functional alleles



Dose Adjustment Based on Genotypic Differences



Phenotype	Active Drug (requires metabolism for detoxification such as CYP2C19 mediated metabolism of omeprazole)	Prodrug (requires metabolism for activity such as CYP2D6 mediated metabolism of codeine to morphine)
Poor	•Accumulation of drug may lead to adverse reactions •May require lower dose	•Poor efficacy •Accumulation of prodrug
Extensive and or Ultrarapid	•Poor efficacy •May require higher dose or more frequent dosing	•Good efficacy •May require lower dose

Table 1. Pharmacogenetics of Phase I Drug Metabolism.*

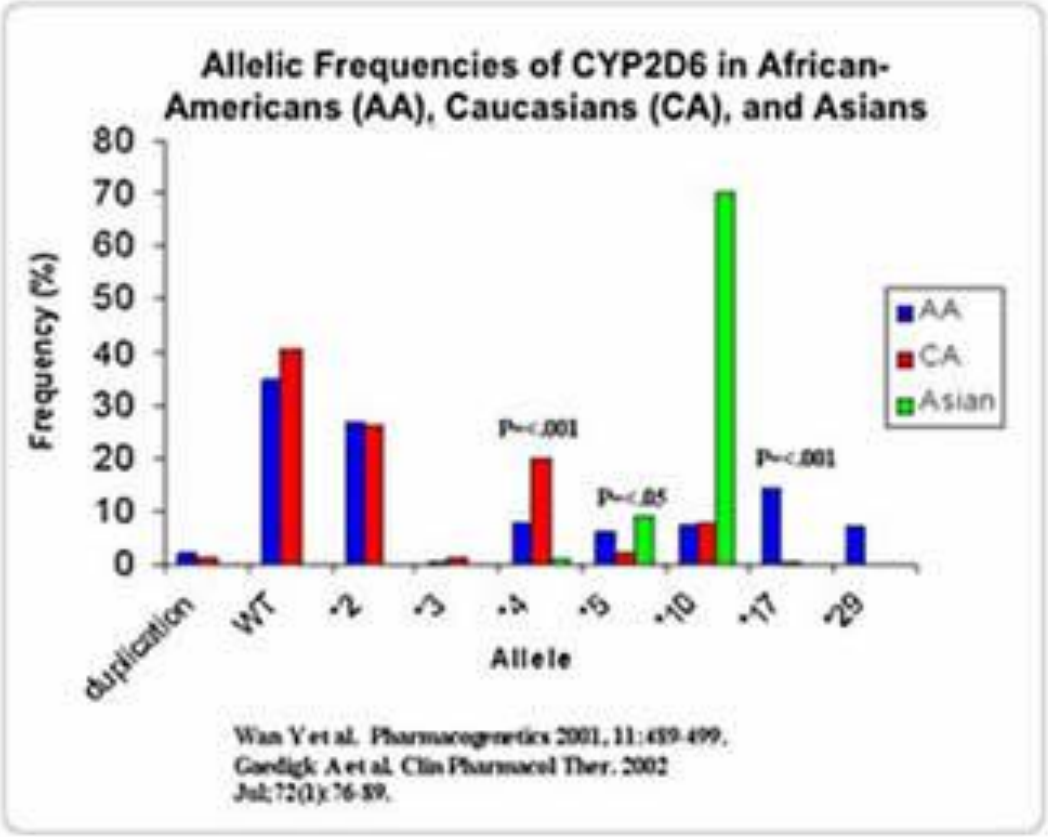
Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	6.8% in Sweden 1% in China[17]	Debrisoquin[15] Sparteine[16] Nortriptyline[23] Codeine[27,28]	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England[29] (those homozygous for the *2 and *3 alleles)	Warfarin[29,30] Phenytoin[31,32]	Enhanced drug effect[29-32]
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans[33] 3.3% in Sweden 14.6% in China[17] 18% in Japan[33]	Omeprazole[34,35]	Enhanced drug effect[36,37]
Dihydropyrimidine dehydrogenase	Approximately 1% of population is heterozygous[38]	Fluorouracil[39,40]	Enhanced drug effect[39,40]
Butyrylcholinesterase (pseudocholinesterase)	Approximately 1 in 3500 Europeans[41]	Succinylcholine[9,41]	Enhanced drug effect[9,41]

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

CYP2D6

- Discovered in the 1970s, one of the most widely studied polymorphisms in drug metabolism
- 2% of total liver CYP content
- Distribuiton of PM: 7% of Caucasians, 1% of Asians
- Involved in metabolism of several drugs
  - Psychotropic medications: tricyclic antidepressants, SSRIs, classical and atypical antipsychotics
  - Cardiovascular drugs
  - β-receptor antagonists: metoprolol, propranolol, timolol
  - Phenacetine
  - Codeine
  - Abused drugs

Ethnicity and distribution of CYP2D6 genotypes

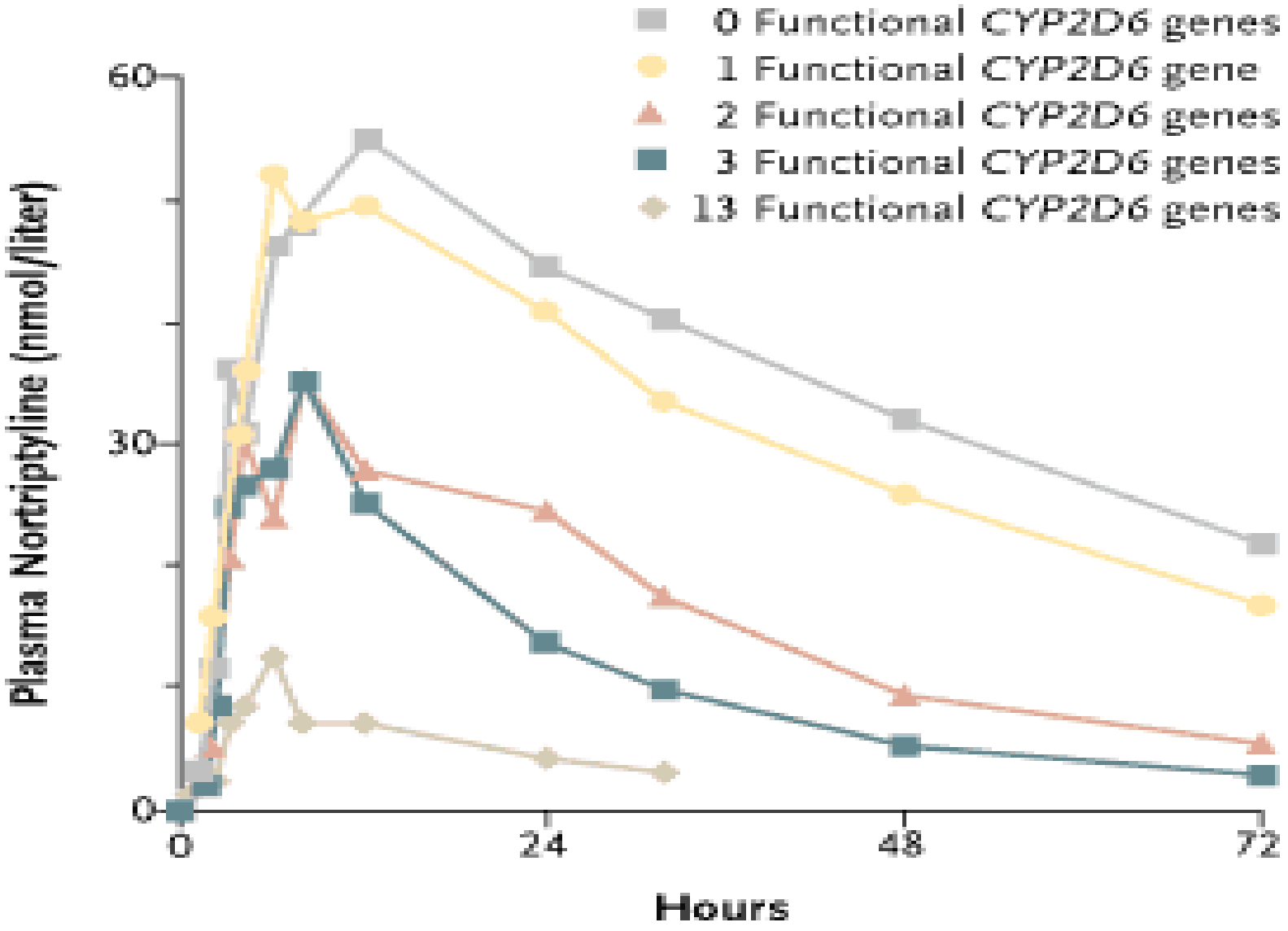


CYP2D6

- More than 50 alleles, encoding enzymes with inactive / decreased / increased / normal catalytic function.

- Poor metabolisers
  - are at risk of drug toxicity even at standard doses, resulting in poor compliance
  - may also present with treatment resistance to prodrugs that require activation (codeine)

- Ultrarapid metabolisers:
  - delayed therapeutic response or treatment resistance (29% of Ethiopians carry multiplicated functional CYP2D6 alleles)


0 Functional CYP2D6 genes
1 Functional CYP2D6 gene
2 Functional CYP2D6 genes
3 Functional CYP2D6 genes
13 Functional CYP2D6 genes
Plasma Nortriptyline (nmol/liter)
60
30
0
0
24
48
72
Hours


5-10% PMs
1-2% UMs
3.6% UMs
7-10% UM
10% UMs
20% UMs
1-2% PMs
29% UMs
ALGERIA
LIBYA
EGYPT
SUDAN
IRAN
SOUTH ATLANTIC OCEAN


5-10% PMs
1-2% UMs
3.6% UMs
7-10% UM
10% UMs
13 % UMs
20% UMs
1-2% PMs
29% UMs
ALGERIA
LIBYA
EGYPT
SUDAN
Springer

Information for Healthcare Professionals: Use of Codeine Products in Nursing Mothers

Update: The issues described in this communication have been addressed in product labeling (see Drugs@FDA)

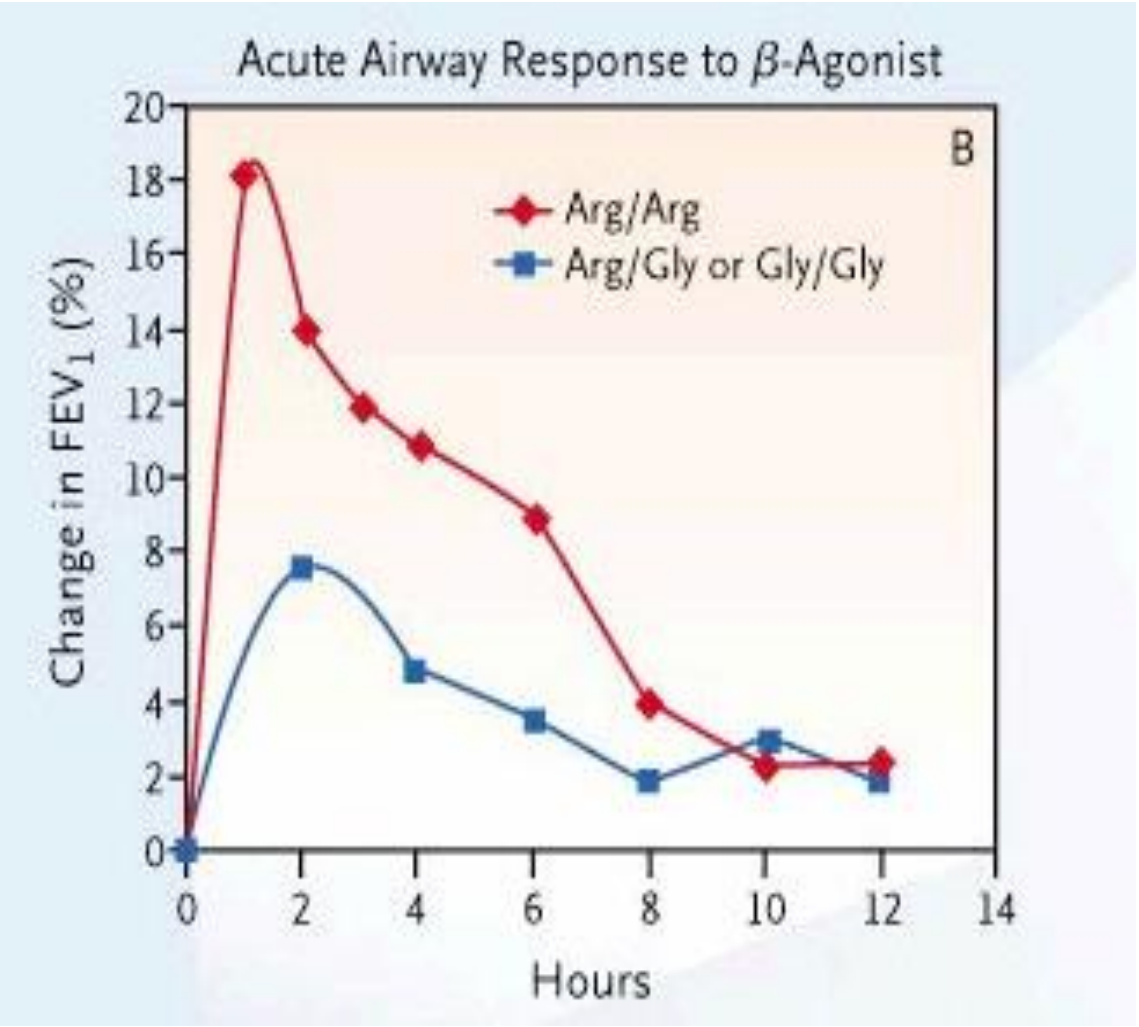
FDA Alert: [8/17/2007] FDA has important new information about a very rare, but serious, side effect in nursing infants whose mothers are taking codeine and are ultra-rapid metabolizers of codeine. These babies may be at increased risk for morphine overdose.

Pharmacogenomics
Drug Targets

- Direct protein target of drug
  - Receptor
  - Enzyme

- Proteins involved in pharmacologic response
  - Signal transduction proteins or downstream proteins

Beta-2 Polymorphisms and Response to Albuterol

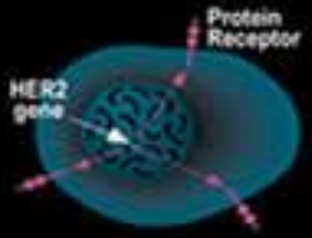


- **Single 8 mg albuterol dose**
- **Albuterol-evoked increases in FEV_1 were higher and more rapid in Arg16 homozyotes compared with Gly carriers**
- **Codon 16 polymorphism is a determinant of bronchodilator response to albuterol**

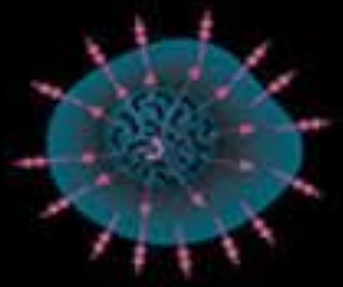
Lima JJ et al. Clin Pharmacol Ther 1999; 65: 519-25

Lima JJ. Clin Pharmacol Ther 1999; 65:519-25

Trastuzumab (Herceptin®)



In a normal breast tissue cell, the Her-2 gene is expressing cell surface receptor required for normal cell growth.



In certain types of breast cancers, the Her-2 gene is over-expressing this cell surface receptor, contributing to cancerous cell growth.
This is the case in ~30% of breast cancers.

Herceptin (trastuzumab) is an antibody that blocks the cell surface receptor and thereby prevents further growth. As a result, disease progression is slowed down.