Pharmacogenomic Applications in Psychiatry

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Financial Disclosures

- Medical Director, Brain Health
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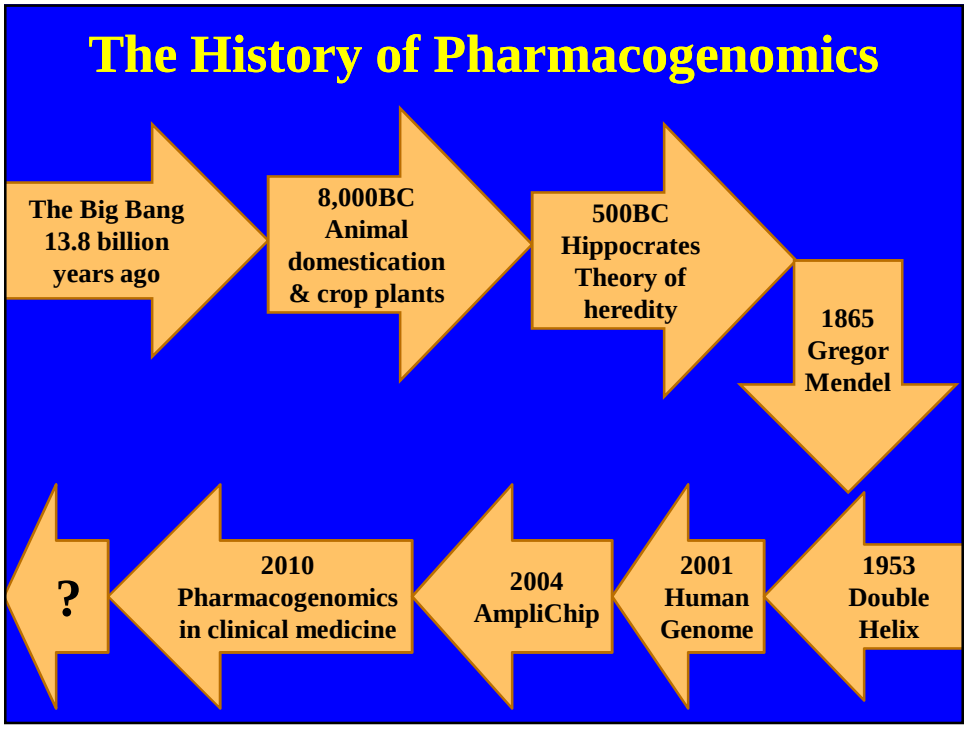
- Consulting Psychiatrist, Exeter Hospital, Exeter, NH
- Volunteer consultant to the Insight Meditation Society Barre, MA
- Speaker/consultant for Millennium Health
- Speaker/consultant for AstraZeneca
- Speaker/consultant for Sunovion
- Speaker for Forest (Actavis/Allergan)
- Speaker/consultant for Takeda/Lundbeck
- Speaker/consultant for Otsuka/Lundbeck

The handout for this presentation is available in full color, two slides per page for easy viewing, and downloadable at my website's homepage:

www.brain-health.co/

Objectives

- **Appreciate the sequence of scientific advancements that allowed for the current clinical applications of pharmacogenomics in daily psychiatric clinical practice.**
- **Develop a familiarity of the pharmacogenetic tests that are currently available to the clinical practitioner relevant to psychiatry.**
- **Understanding a Paradigm Shift: Pharmacogenomic testing setting a new "standard of care".**



The Founder of Modern Genetics

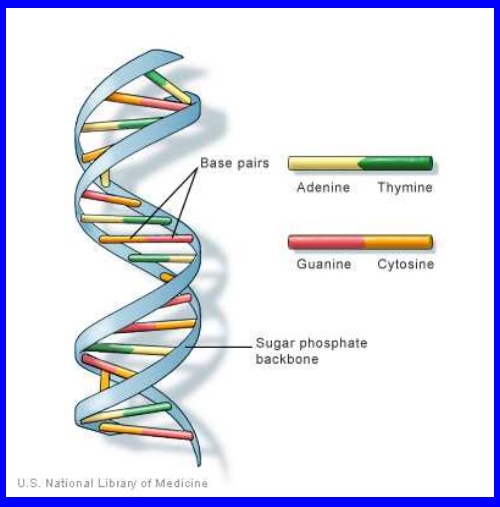
Gregor Mendel, Abbot
Augustinian Monastery
1865 published
"Experiments on Plant Hybrids"
at the Brno Society of Natural Science

1953

The proposal of DNA as a ***Double Helix***

James Watson
and
Francis Crick

The Structure of DNA



http://ghr.nlm.nih.gov/handbook/basics/dna

The Story of DNA - 1954

(deoxyribonucleic acid)

"In recent years suspicion has been growing that the key to the specificity of the chromosome lies not in their protein, but in their DNA. DNA is found in all chromosomes – and only in chromosomes (with minor exceptions) . . . . Then there is suggestive evidence in two cases that DNA alone, free of protein, may be able to carry genetic information . . . . we suspect that the order of the bases is what confers specificity on a given DNA."

Crick FHC. The Structure of the Hereditary Material. *Scientific American*; October 1954.

1966 – 12 years later

"Two major classes of chainlike molecules underlie the functioning of living organisms: the nucleic acids and the proteins.

The former include DNA, which embodies the hereditary message of each organism, and RNA, which helps to translate that message into the thousands of different proteins that activate the living cell.

In the past dozen years biochemists have established the complete sequence of amino acid subunits in a number of different proteins. Much less is known about the nucleic acids."

Holley RW. The Nucleotide Sequence of a Nucleic Acid. *Scientific American*; February 1966.

The Genetic Code

"By ingenious experiments with bacterial viruses (Francis Crick) established that the "letters" in the code are read off in simple sequence and that "words" in the code most probably consist of groups of three letters. The code letters in the DNA molecule are the four bases, or chemical subunits, adenine, guanine, cytosine and thymine, respectively denoted A, G, C and T."

(continued)

Nirenberg MW. The Genetic Code: II. *Scientific American*; March 1963.

The Genetic Code

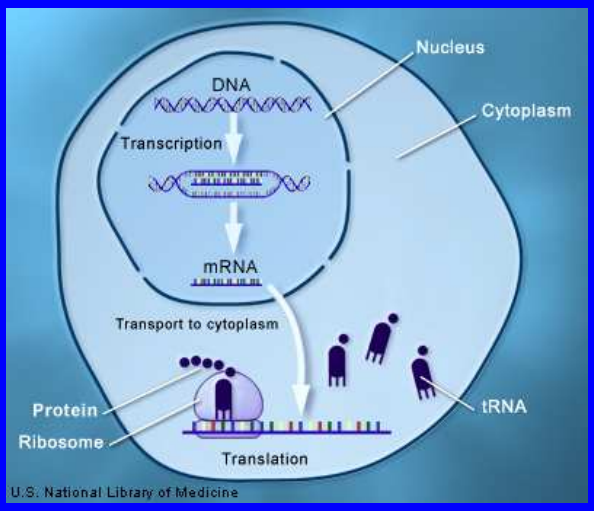
(continued)

"This article describes how various combinations of these bases, or code letters, provide the specific biochemical information used by the cell in the construction of proteins: giant molecules assembled from 20 common kinds of amino acids. Each amino acid subunit is directed to its proper site in the protein chain by a sequence of code letters in the DNA molecule that each organism inherits from its ancestors."

(continued)

Nirenberg MW. The Genetic Code: II. *Scientific American*; March 1963.

From DNA to a Protein



http://ghr.nlm.nih.gov/handbook/howgeneswork/makingprotein

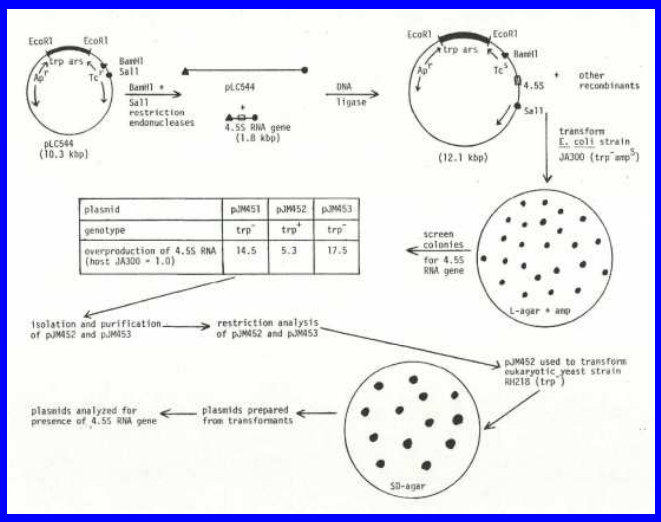
The Genetic Code

(continued)

"It is this DNA that is shaped by evolution. Organisms compete with each other for survival; occasional random changes in their information content, carried by DNA, are sometimes advantageous in this competition. In this way organisms slowly become enriched with instructions facilitating their survival."

Nirenberg MW. The Genetic Code: II. *Scientific American*; March 1963.

1981



Miller J: An Analysis of the Fate of the Escherichia coli 4.5S RNA Gene in Yeast Using a Recombinant Plasmid; Senior Honors Thesis; University of MA, Amherst; 1981.

Late 1980s
DNA sequencing tools rapidly improving

James Watson organized a government science program:

The Human Genome Project

Directed by the US National Institute of Health, with collaborative research by contributors including universities across the United States, and international partners in the United Kingdom, France, Germany, Japan, and China. Target date to sequence all 3 billion base pairs in the human genome was 2005.

The Human Genome Project formally began in 1990 and was completed in 2003, 2 years ahead of its original schedule. Francis Collins became the Chief researcher for the NIH. It remains the world's largest collaborative biological project.

May 1998 – a surprising announcement

A parallel project was conducted outside of government by the Celera Corporation, or Celera Genomics, which was formally launched in 1998.

Biochemist and business entrepreneur J. Craig Venter announced that his company had joined the race to complete the sequencing of the entire human genome, and that their target date was 2001 – five years before the world scientific community's Human Genome Project.

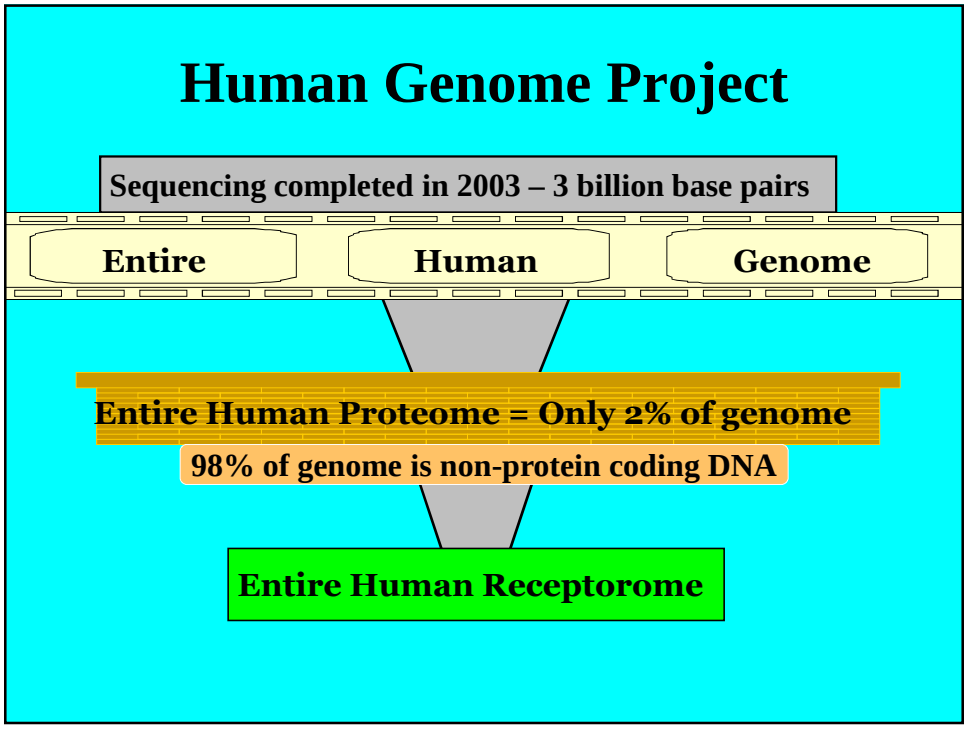
Needless to say, Dr. Venter pissed off a lot of people!!!!

June 26, 2000

President Bill Clinton held a press conference in the East Room of the White House, with Francis Collins and Craig Venter on either side of him, and announced to the world that:

"We are here to celebrate the completion of the first survey of the entire human genome. Without a doubt, this is the most important, most wondrous map ever produced by mankind."

Shreeve J. *The Genome War*. New York. Ballantine Books; 2004.



December 24, 2004
FDA approved the AmpliChip CYP450 Test

First FDA approved pharmacogenetic test.

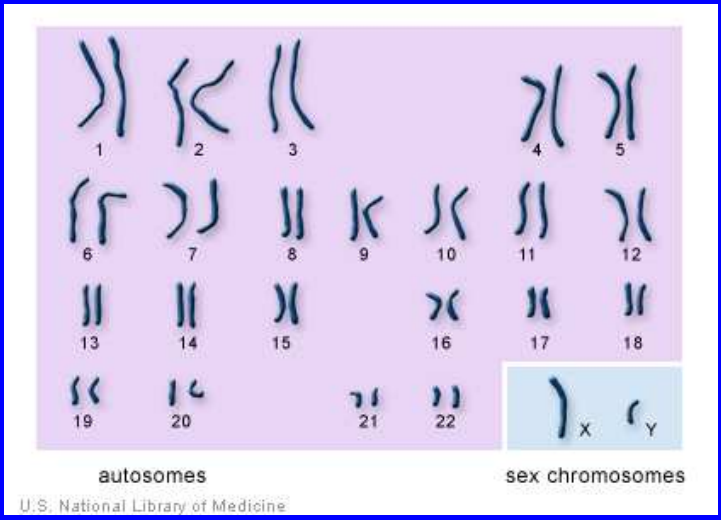
Manufactured by Roche.

Uses micro array technology from Affymetrix (GeneChip) to determine the phenotype of a patient at the two most genetically diverse cytochrome P450 enzymes: 2D6 and 2C19.

AmpliChip is limited because it:

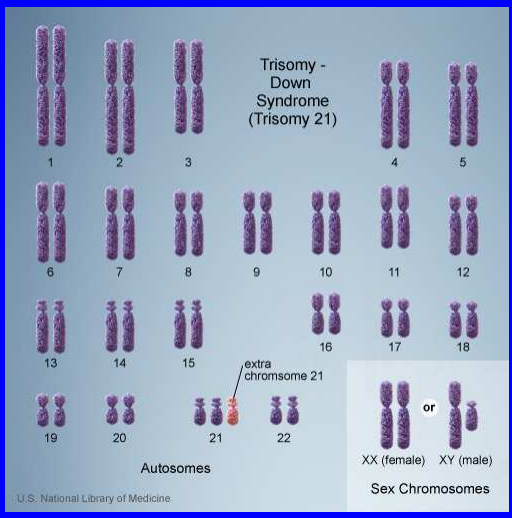
1) is not able to determine multiple copies of one gene
2) does not identify the larger array of genotypes discovered since it was developed

Human Genome: 23 chromosomes



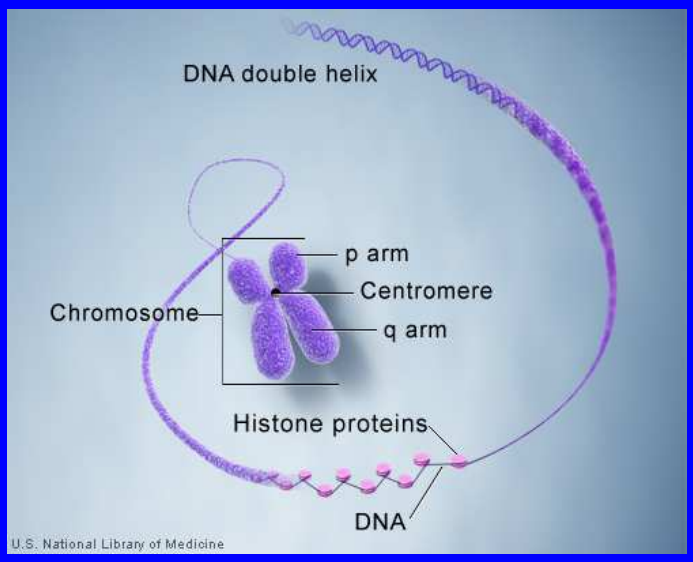
http://ghr.nlm.nih.gov/handbook/basics/howmanychromosomes

Trisomy 21 = Down Syndrome



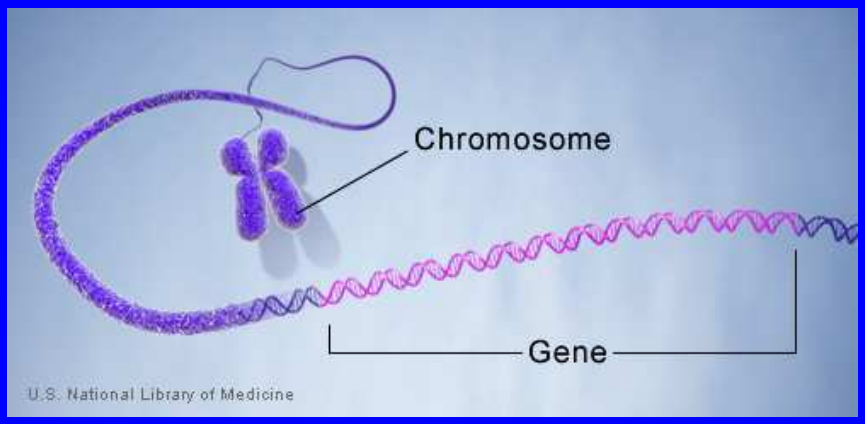
http://ghr.nlm.nih.gov/handbook/illustrations/numericalchanges?show=trisomy

Structure of a chromosome



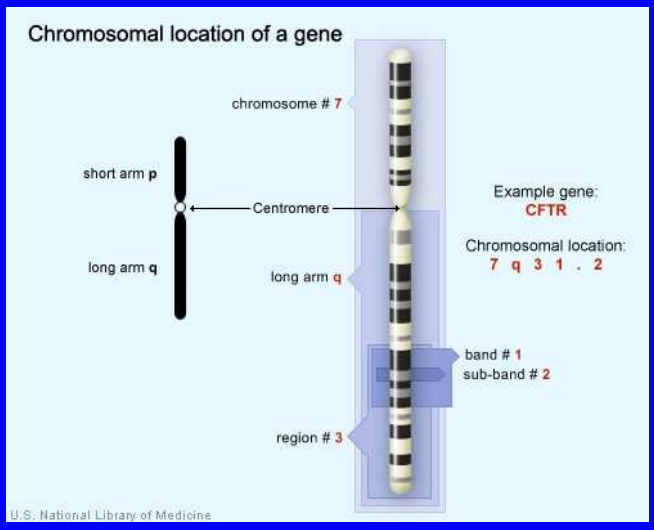
http://ghr.nlm.nih.gov/handbook/basics/chromosome

Structure of a gene



http://ghr.nlm.nih.gov/handbook/basics/gene

Defining a gene's location in the genome



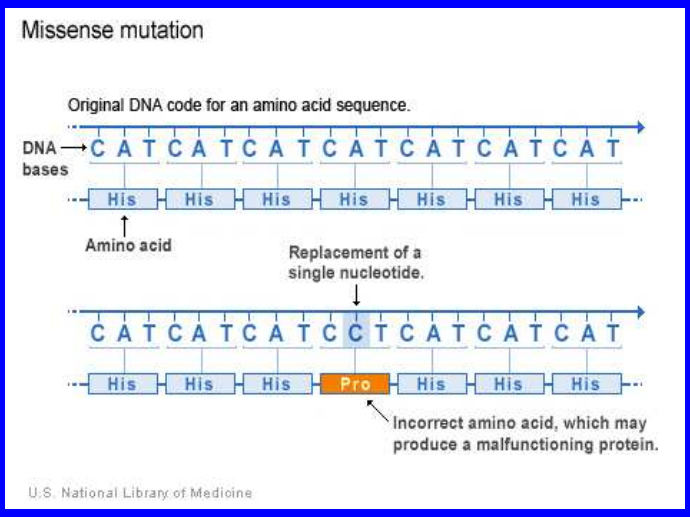
http://ghr.nlm.nih.gov/handbook/howgeneswork/genelocation

Types of genetic mutations creating polymorphic phenotypes

- **Missense**
- **Nonsense**
- **Insertion**
- **Deletion**
- **Duplication**
- **Frame shift**
- **Repeat expansion**

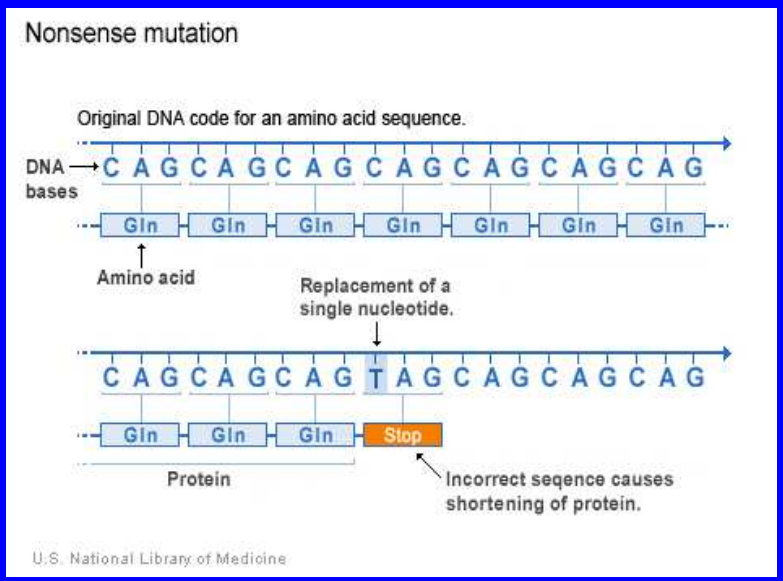
Missense mutation

"single nucleotide polymorphism" = SNP



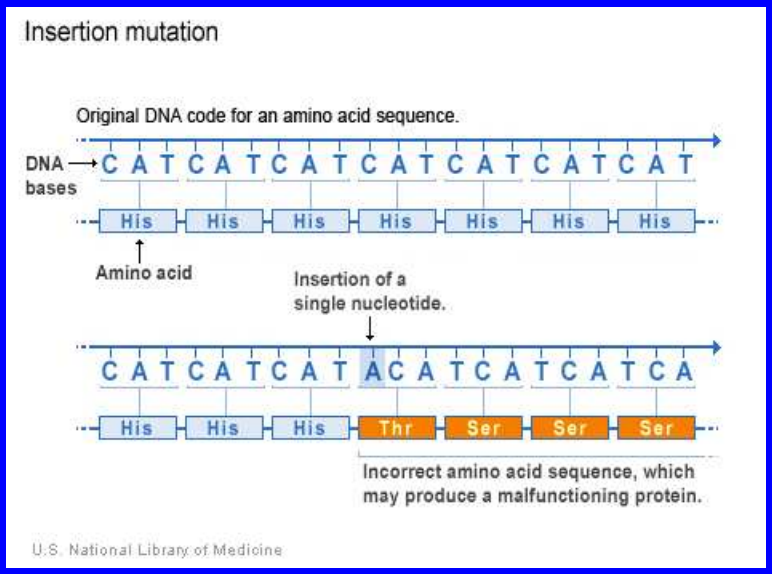
http://ghr.nlm.nih.gov/handbook/illustrations/mutationtypes?show=missense

Nonsense mutation



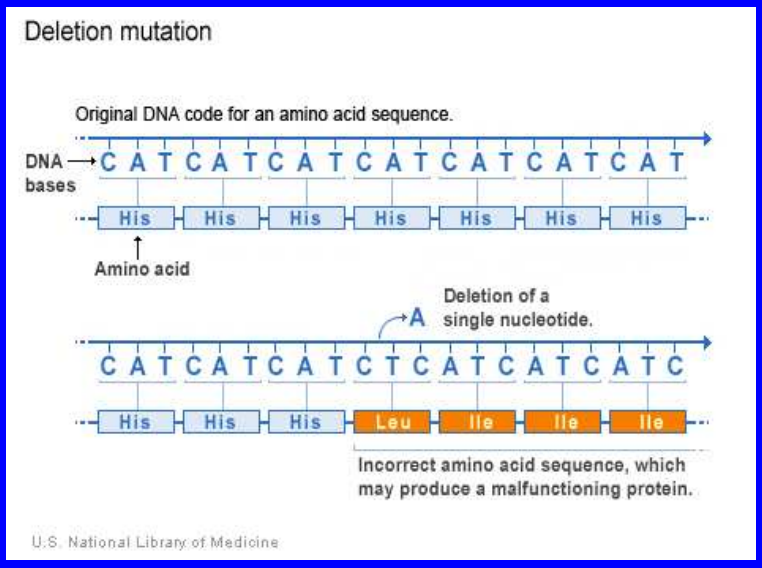
http://ghr.nlm.nih.gov/handbook/illustrations/mutationtypes?show=nonsense

Insertion mutation



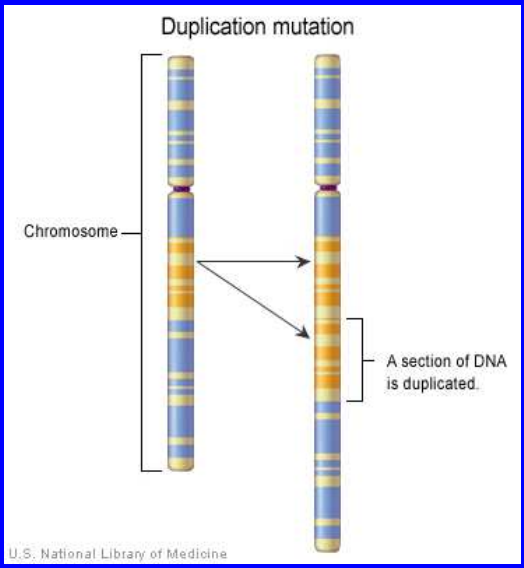
http://ghr.nlm.nih.gov/handbook/illustrations/mutationtypes?show=insertion

Deletion mutation



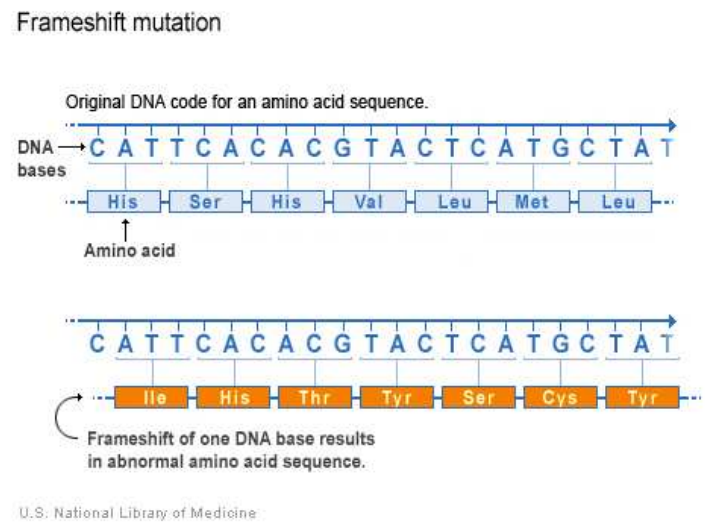
http://ghr.nlm.nih.gov/handbook/illustrations/mutationtypes?show=deletion

Duplication mutation



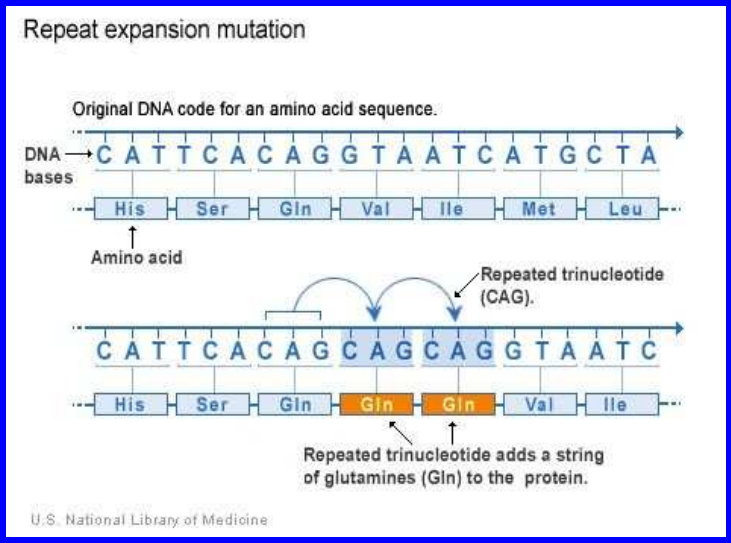
http://ghr.nlm.nih.gov/handbook/illustrations/mutationtypes?show=duplication

Frameshift mutation



http://ghr.nlm.nih.gov/handbook/illustrations/mutationtypes?show=frameshift

Repeat expansion mutation



http://ghr.nlm.nih.gov/handbook/illustrations/mutationtypes?show=repeatexpansion

Genetic variability due to preserved mutations results in a range of "genotypes" for a particular gene.

The inherited genotype creates a predictable "phenotype" that results in diverse functionality of a particular gene pair.

We inherit 2 copies of each gene, one from mom and one from dad.

The genotype of each gene can result in:

- **"Wild type" gene activity**
- **Increased gene activity**
- **Decreased gene activity**
- **Poor/No gene activity**

Depending on the final protein products of each gene pair, the resulting phenotype can have a wide range of consequences. The phenotype results from the combined genotypes of the two gene copies.

Some examples of variant phenotypes:

Structural proteins.

Receptors that various molecules bind to.

Enzymes that synthesize neurotransmitters.

Enzymes that metabolize endogenous molecules.

Enzymes that metabolize exogenous molecules (drugs).

Enzymes required for various metabolic processes.

Proteins important for healthy immune functioning.

Promoter sequences that determine how many gene products to make.

Proteins that serve as transport pumps.

Currently, over 135 medications contain pharmocogenetic information in their FDA approved product insert

Some examples:

codeine – Black Box Warning

carbamazepine – Black Box Warning

aripiprazole - "poor CYP2D6 metabolizers have 60% increased active drug exposure."

US Food and Drug Administration.
Table of Pharmacogenomic Biomarkers in Drug Labels.
http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
Revised August 18, 2014.

Differing Metabolic Pathways

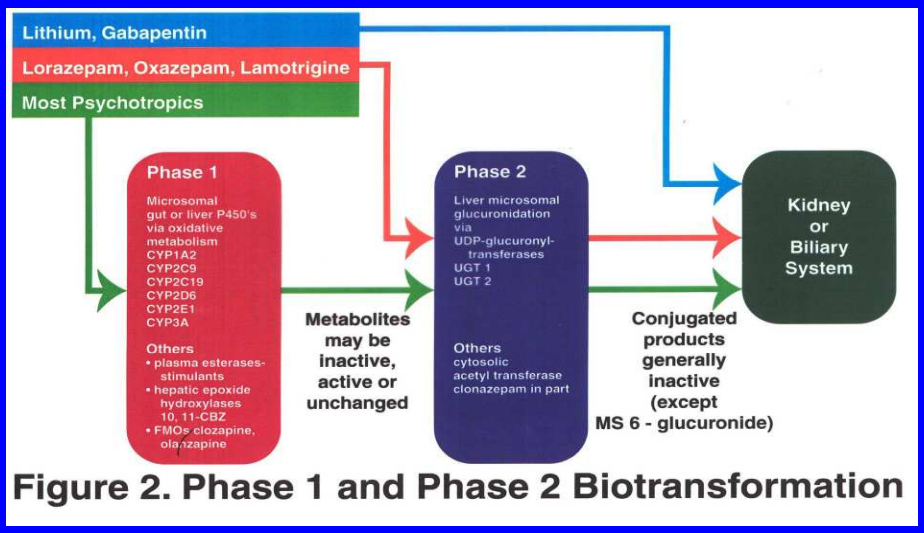


Figure 2. Phase 1 and Phase 2 Biotransformation

Drug Metabolism

Phase I Metabolism

Cytochrome P450 Enzyme System

Nomenclature:

Cyto = microsomal vesicles

Chrome = colored

P = protein

450 = absorb light at 450 nanometer wavelength

2 = family = 40-55% homologous amino acid sequence

D = subfamily > 55% homologous amino acid sequence

6 = single gene

CYP450 Enzyme System

Roughly 60 human CYP450 enzymes identified.

Account for approximately 80 percent of enzymes involved in drug metabolism.

Of these 60 CYP450 enzymes, approximately 90% of human drug oxidation is accomplished by just 6:

1A2	2D6
2C9	2E1
2C19	3A4

All 6 have genetic polymorphisms

CYP450 Enzyme System

Genetic Polymorphisms Include:

Extensive Metabolizer = normal functioning genes

Poor Metabolizer = gene defect or inactivation

Intermediate Metabolizer = one normal and one defective/inactive gene

Ultra-rapid Metabolizer = increased gene activity or multiple gene copies

CYP450 Enzyme System

Drug interactions include:

- None
- Substrate
- Inhibitor
- Inducer
- Substrate/Inhibitor
- Substrate/Inducer

Currently available pharmacogenetic tests relevant to the practice of psychiatry

Metabolic Enzymes:

Phase I Cytochrome P450 enzymes

CYP450 2D6
numerous substrates (see table)

CYP450 2C19
(es)citalopram, diazepam, sertraline

CYP450 2B6
methadone, bupropion

CYP450 1A2
clozapine, olanzapine, fluvoxamine

CYP450 2D6

Most studied cytochrome P450 gene.

Over 75 alleles differentiated to date – the most phenotypes of any metabolic enzyme.

Primary metabolic pathway for many psychotropics.

Many drugs are strong or moderate inhibitors.

Ethnic variability:

Approximately 10% of Caucasians are **poor metabolizers**.

Approximately 2% of Asians are **poor metabolizers**.

Approximately 1% of the population are **ultra-rapid metabolizers**.

Highest incidence of **ultra-rapid metabolizers** are in individuals from Middle Eastern and North African descent.

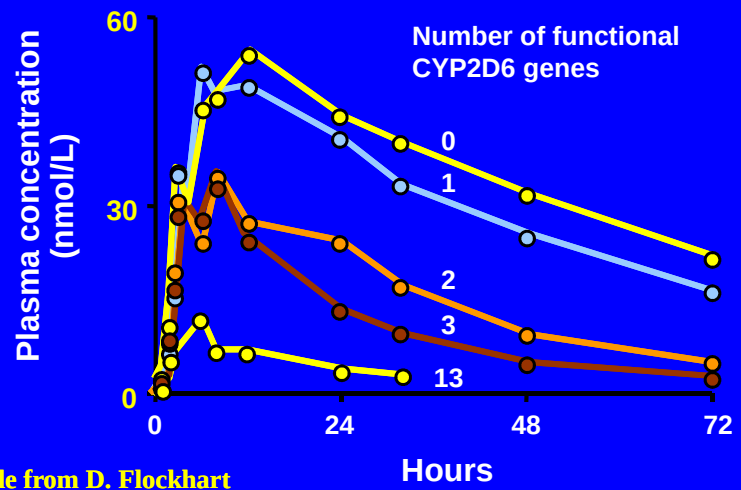
CYP450 2D6 Polymorphisms:

www.imm.ki.se/CYPalleles/

Designation	Characteristic mutation(s)	Enzyme activity	Allelic frequency (%)
*CYP2D6*1*	Wild type	Normal	
*CYP2D6*2*	$G_{1749}C$, $C_{2938}T$, $G_{4268}C$ substitutions	Normal	30
*CYP2D6*3*	A_{2637} deletion	Deficient	2
*CYP2D6*4*	$G_{1934}A$ substitution	Deficient	22
*CYP2D6*5*	Gene deletion	Deficient	2
*CYP2D6*6*	T_{1795} deletion	Deficient	2
*CYP2D6*7*	$A_{3023}C$ substitution	Deficient	0·1
*CYP2D6*8*	$G_{1846}T$ substitution	Deficient	0·1
*CYP2D6*9*	(A_{2701}–A_{2703}) or (G_{2702}–A_{2704}) deletion	Decreased	1·5
*CYP2D6*10*	$C_{188}T$, $G_{1749}C$, $G_{4268}C$ substitutions	Decreased	1·5
*CYP2D6*11*	$G_{971}C$ substitution	Deficient	0·1
*CYP2D6*12*	$G_{212}A$ substitution	Deficient	0·1
*CYP2D6*13*	Hybrid: *2D7* exon 1, *2D6* exons 2–9	Deficient	0·1
*CYP2D6*14*	$G_{1846}A$ substitution	Deficient	0·1
*CYP2D6*15*	T_{226} insertion	Deficient	0·1
*CYP2D6*16*	Hybrid: *2D7* exons 1–7, *2D6* exons 8–9	Deficient	0·1
*CYP2D6*1* × 2	Gene duplication	Increased	1
*CYP2D6*2* × 2	Gene duplication	Increased	1·5
*CYP2D6*4* × 2	Gene duplication	Deficient	0·5

Gene duplication

Effect of functional CYP2D6 gene number after ingesting Nortriptyline 25mg at time "0"



Slide from D. Flockhart

Codeine's Black Box Warning

Codeine Sulfate
(codeine sulfate)

***morphine is 20 times more potent than codeine

BOXED WARNING
Respiratory depression and death reported in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

codeine → Extensive metabolizer CYP 2D6 → morphine analgesia

codeine → Ultra-rapid metabolizer CYP 2D6 → morphine risk of death

Cytochrome P450 2D6 Substrates

Antidepressants:
amitriptyline
clomipramine
desipramine
duloxetine
fluoxetine
imipramine
paroxetine
venlafaxine
doxepine

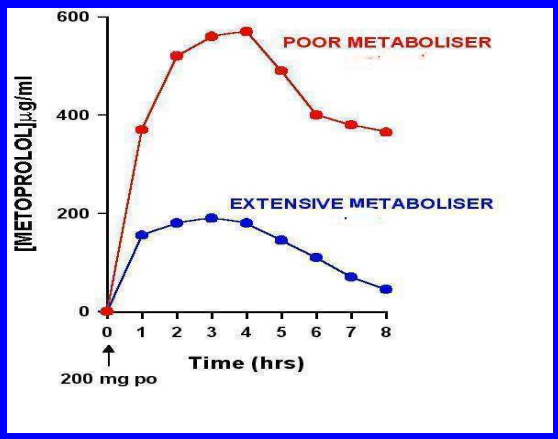
Antipsychotics:
haloperidol
risperidone
thioridazine
aripiprazole
brexpiprazole
iloperidone

Analgesics:
codeine
hydrocodone
oxycodone
tramadol

Other:
tamoxifen
atomoxetine
dextromethorphan
Beta blockers

Adapted from - http://medicine.iupui.edu/clinpharm/ddis/clinical-table/

Clinical Implications of CYP2D6 variants:

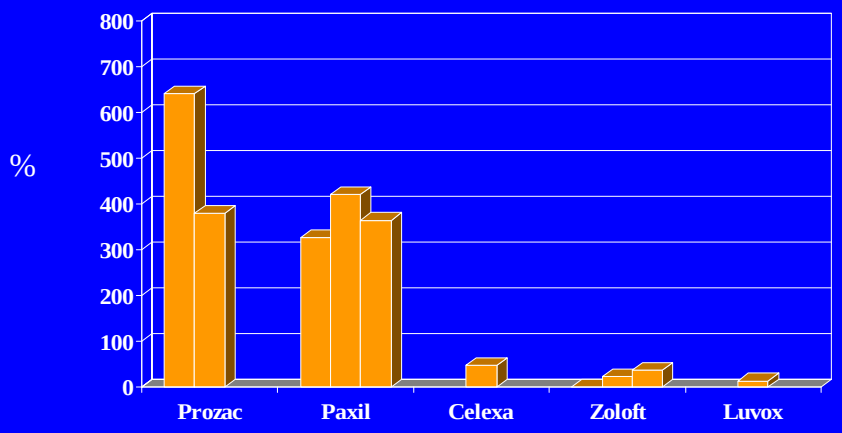


CYP450 Drug-Drug Interactions

- Fluoxetine/paroxetine both potent inhibitors of CYP2D6.
- Desipramine/nortriptyline primarily metabolized by CYP2D6.
- 1988 – reports surfaced about cardiotoxicity in patients who were treated with both fluoxetine and desipramine.
- Began intensive research into the liver's CYP450 enzyme system.

SSRIs Effect on Desipramine Levels at CYP450-2D6

% Change in plasma desipramine levels after adding an SSRI



Preskorn S; "Pharmacology of SSRIs"; Clin. Pharmacokinet.; 1997; 32 Suppl. 1: 1-21

Drug Metabolism

Phase II Metabolism

Conjugation

- Molecules are added to the drug making it more water soluble
  - Glucuronidation
  - Sulfation
  - Methylation

Phase II Metabolism = Conjugation

- Glucuronidation
  - Located in the endoplasmic reticulum
  - Primary site is the liver
  - Secondary site is the gut
  - Most common and most important type of Phase II enzymes are members of the family uridine 5'-diphosphate glucuronosyltransferases (UGT's)

Phase II Metabolism = Conjugation

- Glucuronidation
- uridine 5'-diphosphate glucuronosyltransferases (UGT's)
  - Over 1000 exogenous substrates
  - Have inhibitors and inducers
  - Nomenclature (developed in 1997) exists based on amino acid similarity
  - Examples:
    - UGT1A6, 1A9 and 2B7 - valproate
    - UGT1A4 – asenapine, lamotrigine
    - UGT2B15 – lorazepam and oxezepam

Phase II Metabolism = Conjugation

- Methylation
  - Catechol-O-Methyl transferase (COMT)
    - Discovered 1957
    - Metabolizes catecholamines
  - Histamine N-Methyltransferase (HNMT)
    - Inhibitors prolong histamine actitvity and result in increased inflammatory action
  - Thiopurine Methyltransferase (TPMT)

Currently available pharmacogenetic tests relevant to the practice of psychiatry

Metabolic Enzymes:

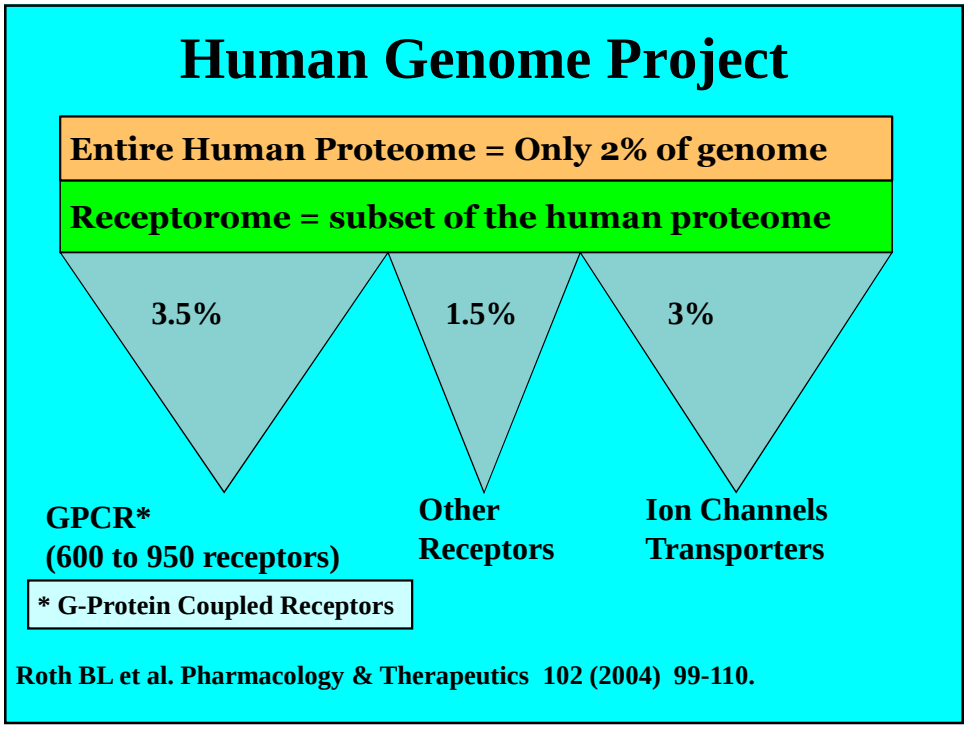
Phase II Metabolic enzymes

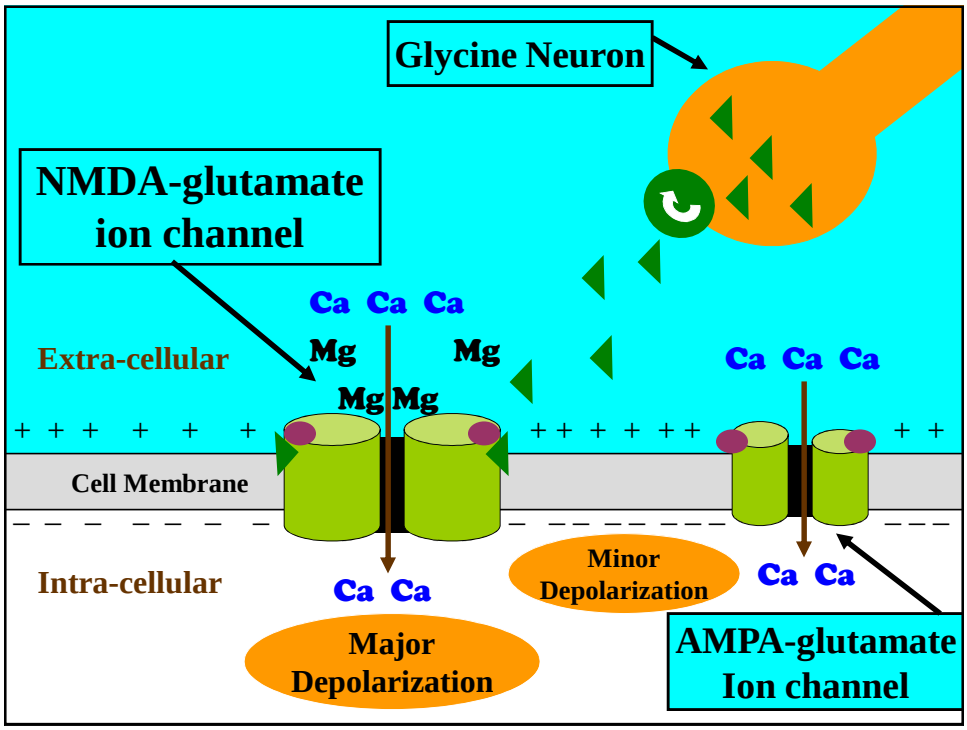
UGT2B15

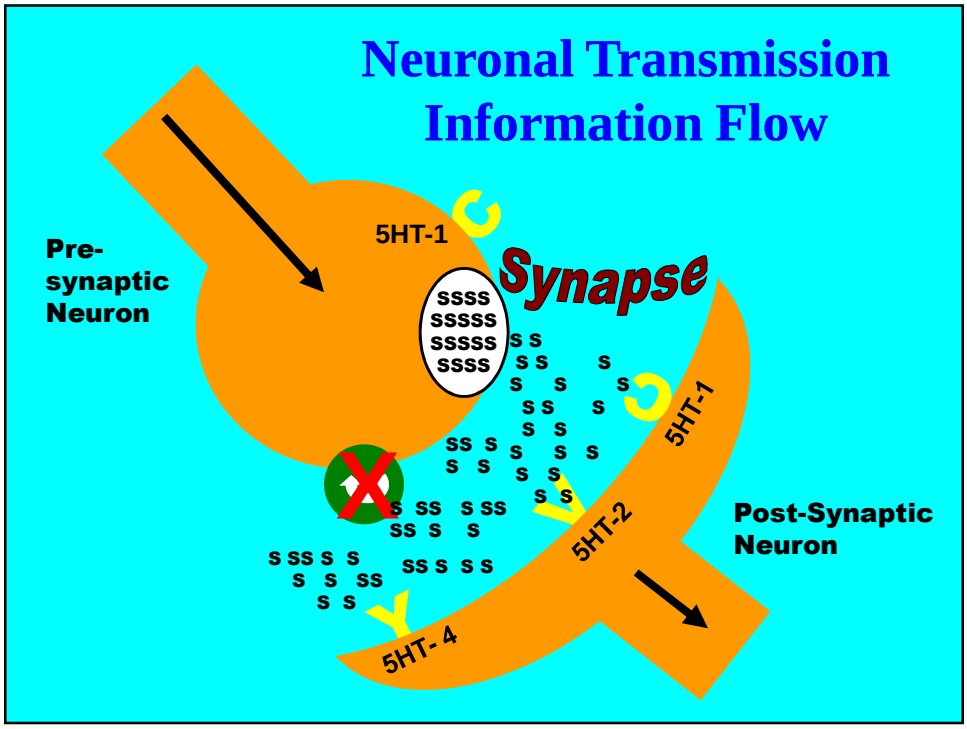
extensive, intermediate and poor
lorazepam and oxazepam metabolism

COMT

Val158Met polymorphism
inactivates dopamine, norepinephrine and epinephrine


Human Genome Project
Entire Human Proteome = Only 2% of genome
Receptorome = subset of the human proteome
3.5%
1.5%
3%
GPCR*
(600 to 950 receptors)
Other
Receptors
Ion Channels
Transporters
* G-Protein Coupled Receptors
Roth BL et al. Pharmacology & Therapeutics 102 (2004) 99-110.


Glycine Neuron
NMDA-glutamate
ion channel
Ca Ca Ca
Mg
Mg
Mg Mg
Extra-cellular
Ca Ca Ca
Cell Membrane
Intra-cellular
Ca Ca
Minor
Depolarization
Ca Ca
Major
Depolarization
AMPA-glutamate
Ion channel



Currently available pharmacogenetic tests relevant to the practice of psychiatry

Receptors:

Serotonin 5HT-2A receptor
gene's name = HTR2A
phenotype may predict side effects of some SSRIs

Gene Promoter Sequences:

Dopamine D-2 receptor = DRD2 gene's promoter
variant phenotype predicts poor response to clozapine, olanzapine and risperidone

Serotonin 5HT-2C receptor = HTR2C gene's promoter
variant phenotype predicts less metabolic side effects to clozapine and olanzapine

Currently available pharmacogenetic tests relevant to the practice of psychiatry

Transport pumps:

Serotonin Transport Pump (SERT or 5-HTT) =
Gene Analyzed: SLC6A4

promoter region of this gene varies in size

"short" promoter contains 14 repeats

"long" promoter contains 16 repeats

this polymorphic region has been named the 5-HTT-linked polymorphic region (5-HTTLPR)

Phenotypes: s,s; l,l; s,l; l,s

many additional allelic variants have been found

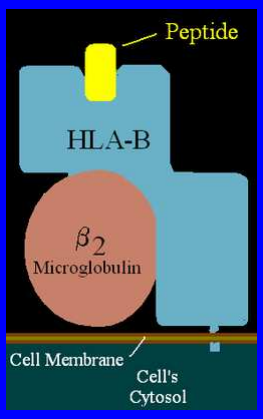
***100s of peer-reviewed research articles contradictory**

***Phelps J: "Knowing One's Genome: Are We Ready?"; *Psychiatric Times*; July 2015.**

Currently available pharmacogenetic tests relevant to the practice of psychiatry

The Human Leukocyte Antigen-B (HLA-B) *1502 gene is a member of the major histocompatability complex, class I, B genes.

These are a large family of genes that create a protein complex on the surface of cells to help the immune system identify "self" from "enemy" by inserting small peptides from inside the cell to the cell's surface where it can be evaluated by the immune system.



Cell surface antigen:

HLA-B*1502 – having one of these genes greatly increases the risk of developing a life threatening skin rash.

The above illustration was "copied" and "pasted" from Wikipedia.

Carbamazepine's Black Box Warning

Carbamazepine

BOXED WARNING
Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) reported; increased risk with presence of HLA-B*1502 allele. Screen patients with ancestry in genetically at risk populations for the presence of HLA-B*1502 prior to initiation of therapy. Avoid in patients testing (+) for the allele unless benefits clearly outweigh risks. Aplastic anemia and agranulocytosis reported; obtain complete pretreatment hematological testing as a baseline and monitor closely if a patient exhibits low/decreased WBC or platelet counts during treatment. Consider discontinuation if evidence of significant bone marrow depression develops.

Stevens-Johnson syndrome/ toxic epidermal necrolysis

(SJS/TEN) is a severe skin reaction most often triggered by particular medications. Although Stevens-Johnson syndrome and toxic epidermal necrolysis were once thought to be separate conditions, they are now considered part of a continuum. Stevens-Johnson syndrome represents the less severe end of the disease spectrum, and toxic epidermal necrolysis represents the more severe end.

Stevens-Johnson syndrome/ toxic epidermal necrolysis

The drugs most frequently associated with SJS/TEN include several medications that are used to treat seizures (particularly carbamazepine, lamotrigine, and phenytoin); allopurinol, which is used to treat kidney stones and a form of arthritis called gout; a class of antibiotic drugs called sulfonamides; nevirapine, which is used to treat HIV infection; and a type of non-steroidal anti-inflammatory drugs (NSAIDs) called oxicams.

Stevens-Johnson syndrome/ toxic epidermal necrolysis

Association between HLA-B∗1502 Allele and Antiepileptic Drug-Induced Cutaneous Reactions in Han Chinese

24 Hong Kong Han Chinese individuals who developed adverse cutaneous reactions while being treated with carbamazepine, phenytoin and lamotrigine were matched with 48 anti-epileptic drug tolerant controls.

"HLA-B∗1502 was associated with severe cutaneous reactions (SCR) induced by AEDs, which included carbamazepine, phenytoin, and lamotrigine (p = 0.001, odds ratio = 17.6), but was not associated with maculopapular exanthema (MPE) (p=0.32)."

Man CBL, Kwan P, et al. Association between HLA-B∗1502 Allele and Antiepileptic Drug-Induced Cutaneous Reactions in Han Chinese. *Epilepsia; 48(5):1015–1018, 2007*

Currently available pharmacogenetic tests relevant to the practice of psychiatry

Biochemical pathway enzyme:

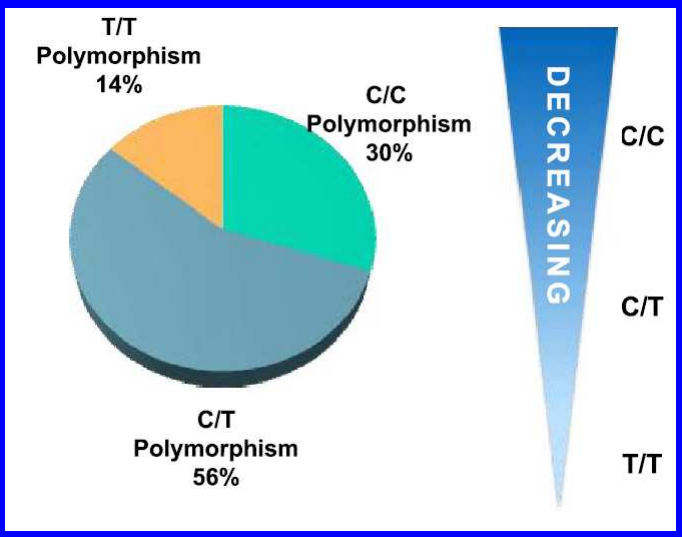
MTHFR = Methylene TetraHydroFolate Reductase

Serotonin, dopamine and norepinephrine all need to be synthesized in the brain. One important carbon donor in their synthesis is a metabolite of folic acid = L-methylfolate.

However, folic acid does not cross the blood-brain-barrier. Folic acid is metabolized by a multi-step process, with the critical point involving the final reduction by MTHFR to form L-methylfolate, which significantly can cross the blood-brain-barrier.

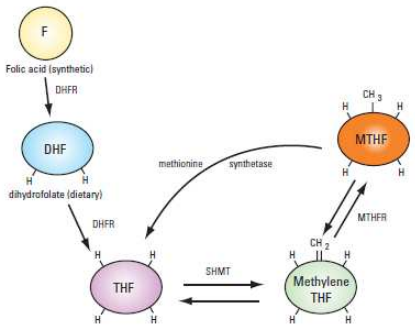
Of many existing mutations on the MTHFR gene, two separate single nucleotide polymorphisms can decrease the functional activity of the MTHFR enzyme, with a resulting decrease in the formation of L-methylfolate.

Methylene TetraHydroFolate Reductase (MTHFR) Polymorphism = C677T



Synthesis of L-methylfolate from folic acid

FIGURE 1.
Formation of L-methylfolate from folic acid[48]



F=folic acid; DHFR=dihydrofolate reductase; CH_3=methyl group; H=hydrogen; DHF=dihydrofolate; MTHFR=methylene tetrahydrofolate reductase; SHMT=serine hydroxy methyl transferase; CH_2=methylene; THF=tetrahydrofolate.

Stahl SM. *Essential Psychopharmacology*. 3rd ed. New York, NY: Cambridge University Press. In press. Reproduced with permission. Copyright Neuroscience Education Institute.

Stahl SM. *CNS Spectr*. Vol 12, No 10. 2007.

The Evolving Story of Folate in Depression and the Therapeutic Potential of L-Methylfolate

"L-methylfolate is a useful treatment for depression that has proved to be resistant to a course of SSRI treatment."

75 patients with SSRI resistant Major Depressive Disorder. L-methylfolate 15mg/day versus placebo for 60 days.

Treatment	Response Rate	Side effects	NNT
SSRI + 15mg L-methylfolate	32.3%	No difference	6
SSRI + Placebo	14.6%	No difference	N/A

Papakostas GI, Shelton RC, et al. L-Methylfolate as Adjunctive Therapy for SSRI-Resistant Major Depression: Results of Two Randomized, Double-Blind, Parallel-Sequential Trials. *Am J Psychiatry*. 2012; 169:1267–1274.

Nelson JC. The Evolving Story of Folate in Depression and the Therapeutic Potential of L-Methylfolate (Editorial). *Am J Psychiatry*. 2012; 169:1223-1225.

Pharmacogenomics is in its infancy, but it is here to stay

Three pillars of knowledge for rational medication prescribing

Effective pharmacotherapy

Pharmaco-Kinetics	Pharmaco-Genomics	Pharmaco-Dynamics
What the body does to the drug	How genes impact a drug's effectiveness	What the drug does to the body

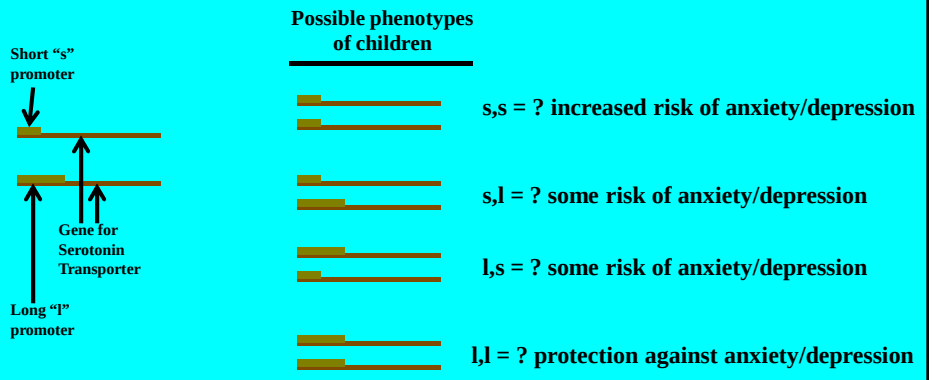
A glimpse into the future . . .

Epigenetics

Carey, Nessa; *The Epigenetics Revolution*; New York; Columbia University Press; 2012

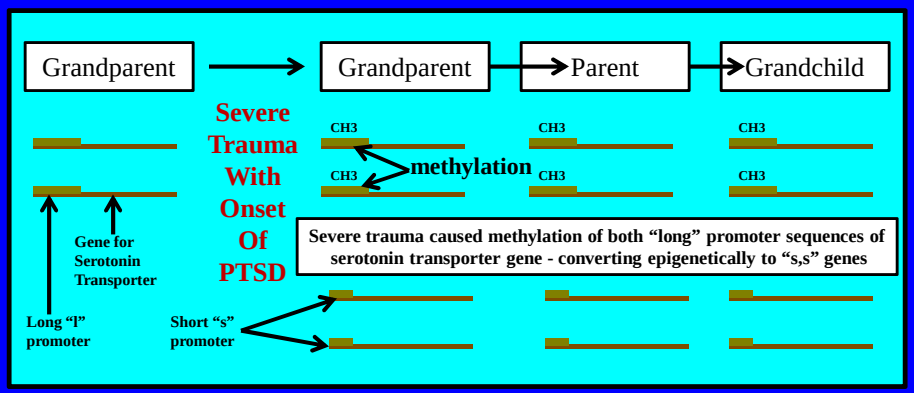
Epigenetics may facilitate novel treatment modalities

Phenotype of the serotonin transport pump gene's (SLC6A4) promoter sequence



Epigenetics may facilitate novel treatment modalities

- Epigenetic modifications
  - Methylation (add –CH3) of gene promoter sequences
  - may explain heritability of previous generation's trauma induced PTSD increasing current generation's risk

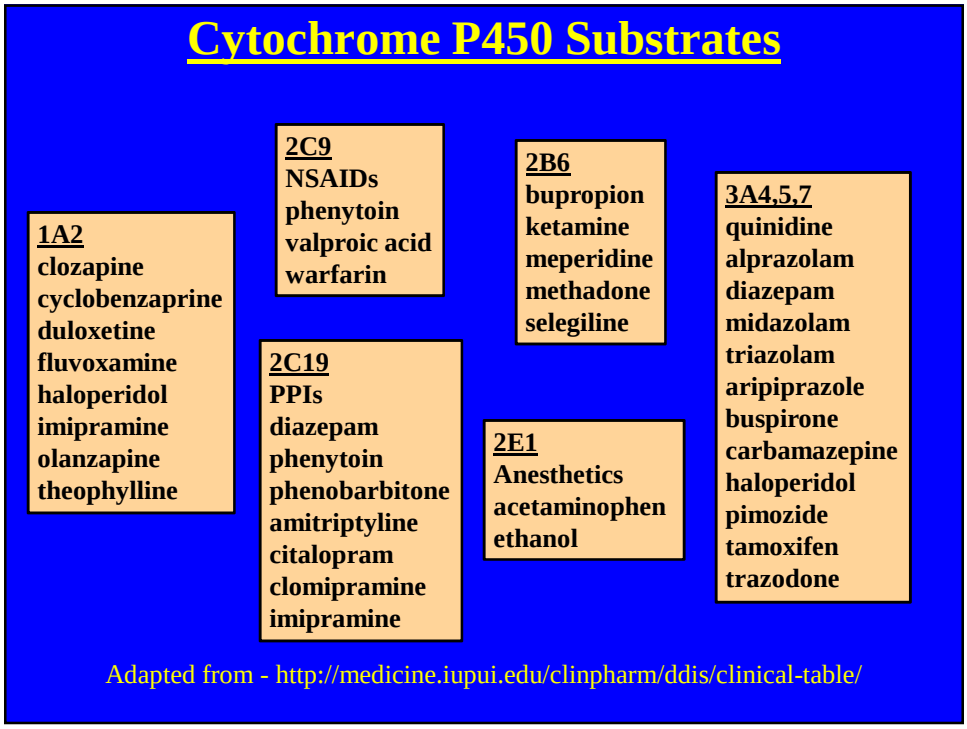


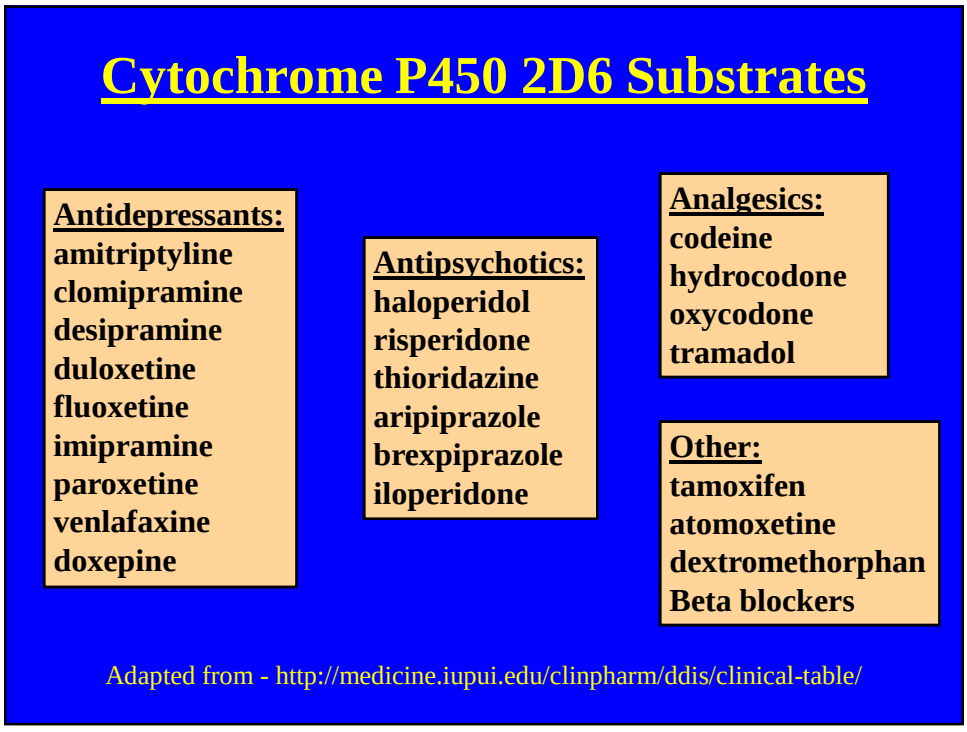
Questions?

Cytochrome P450 Drug/Drug Interaction Resource

Indiana University Dept of Medicine
Clinical Pharmacology
Research Institute (R2), Room 402
950 West Walnut Street
Indianapolis, IN 46202
Ph: (317) 274-2810
Fax:(317) 274-2704

http://medicine.iupui.edu/clinpharm/ddis/clinical-table/


Cytochrome P450 Substrates
1A2
clozapine
cyclobenzaprine
duloxetine
fluvoxamine
haloperidol
imipramine
olanzapine
theophylline
2C9
NSAIDs
phenytoin
valproic acid
warfarin
2C19
PPIs
diazepam
phenytoin
phenobarbitone
amitriptyline
citalopram
clomipramine
imipramine
2B6
bupropion
ketamine
meperidine
methadone
selegiline
2E1
Anesthetics
acetaminophen
ethanol
3A4,5,7
quinidine
alprazolam
diazepam
midazolam
triazolam
aripiprazole
buspirone
carbamazepine
haloperidol
pimozide
tamoxifen
trazodone
Adapted from - http://medicine.iupui.edu/clinpharm/ddis/clinical-table/


Cytochrome P450 2D6 Substrates
Antidepressants:
amitriptyline
clomipramine
desipramine
duloxetine
fluoxetine
imipramine
paroxetine
venlafaxine
doxepine
Antipsychotics:
haloperidol
risperidone
thioridazine
aripiprazole
brexpiprazole
iloperidone
Analgesics:
codeine
hydrocodone
oxycodone
tramadol
Other:
tamoxifen
atomoxetine
dextromethorphan
Beta blockers
Adapted from - http://medicine.iupui.edu/clinpharm/ddis/clinical-table/

Cytochrome P450 Inhibitors

1A2
amiodarone
cimetidine
fluoroquinolones
fluvoxamine

2C9
amiodarone
fluconazole
isoniazid
metronidazole

2C19
cimetidine
esomeprazole
felbamate
fluoxetine
fluvoxamine
isoniazid
ketoconazole
lansoprazole
omeprazole
contraceptives
pantoprazole

2D6
bupropion
fluoxetine
paroxetine
quinidine
duloxetine
amiodarone
cimetidine

2E1
disulfuram

3A4,5,7
indinavir
nelfinavir
ritonavir
clarithromycin
itraconazole
ketoconazole
nefazodone
erythromycin
grapefruit juice
verapamil
suboxone
diltiazem
cimetidine

Adapted from - http://medicine.iupui.edu/clinpharm/ddis/clinical-table/

Cytochrome P450 Inducers

1A2
carbamazepine
chargrilled meat
rifampin
Tobacco

2C19
efavirenz
rifampin
ritonavir
St. John's Wort

2C9
carbamazepine
nevirapine
phenobarbital
rifampin
St. John's Wort

2E1
ethanol
isoniazid

3A4,5,7
carbamazepine
efavirenz
nevirapine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's Wort
troglitazone

Adapted from - http://medicine.iupui.edu/clinpharm/ddis/clinical-table/

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