POST-GENOMIC ERA OF THE BRAIN

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CONFLICT OF INTEREST
Research Funding
• Janssen (Alzheimer's, Antibody, PET)
• Astra Zeneca (Fibromyalgia)
• Bristol Myers Squibb (Schizophrenia)
• Numology (Scientific Advisor; ADHD, Depression)
• Avid (Alzheimer's; autopsy; PET)
• Thought Technology (EEG biofeedback)
• American Heart Association / Dean Medicine (Vascular Dementia)
• Soterion (Research Fellow, PET)

ACKNOWLEDGMENT
Gregor Johann Mendel (1822 – 1884)
Hynčice, Czech Republic
“father of modern genetics”

Mendel’s Laws of Inheritance 29,000 pea plants:
1/4 recessive alleles, 2/4 hybrid, 1/4 dominant
Criticized, ignored: now seminal

WATSON & CRICK 1953

NOBEL PRIZE 1962

Rosalind Franklin

Franklin and Gosling 1953 Nature 25;171(4356):740-1
**GENOME 2003**

- 46 chromosomes
- 30,000 genes
- 3 billion chemical bases

**GENOME ADVANCES**

- Cost $2.7 billion
- Took 13 years 1990 to 2003
- Now $3000 in a few hours
- Storage data
  - Google
  - Amazon

**NUCLEOTIDES**

Information

- Bases
  - Adenine – Thymine
  - Cytosine – Guanine

Backbone

- Phosphates & Sugars
Chromosome = DNA Double Helix

Heritabilities of most psychiatric illnesses is high

- Autism 90%
- Bipolar Disorder 80%
- Schizophrenia 80%
- Major Depression 40%
- Anxiety Disorders 30%

SNP

Single Nucleotide Polymorphism
- Abnormal nucleotide
- Usually cytosine to thymine
- Disease
- Response to medication and drugs

GWAS
Genome-Wide Association Studies

The p450 drug metabolizing enzymes genes (e.g. DME genes)

- There is one specific gene for each enzyme.
- There is extensive variability in allele distribution of these genes.
- There is considerable variability in the distribution of these polymorphisms across different ethnic groups.
CYP2D6

- The most frequently genotyped psychiatric pharmacogenomic gene
- Highly variable with over 100 described variants
- Important psychotropic substrates include paroxetine, fluoxetine, venlafaxine, risperidol, and haloperidal
- http://ki.se/ki/jsp/polopoly.jsp

The Four Clinical Phenotypes

- Poor Metabolizers (PM)
- Intermediate Metabolizers (IM)
- Extensive Metabolizers (EM)
- Ultrarapid Metabolizers (URM)

FATAL DOXEPIN POISONING

43-year-old man
Alcohol abuse, suicidal

- Nonfunctional CYP2D6 genotype
- Total absence of CYP2D6 enzyme
- Poor metabolizer

**Fluoxetine-related death**

- 9-year-old ADHD, OCD, Tourette’s
- 10 months: Gastrointestinal distress, fever, incoordination, disorientation, status epilepticus, cardiac arrest
- Fluoxetine and norfluoxetine ↑
- Cause death: fluoxetine toxicity
- Social welfare investigate adoptive parents
- Polymorphism P450 CYP2D6
- Poor metabolism of fluoxetine


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**PRODRUGS**

Cocaine prodrug for morphine

- Day 7 Difficulty breastfeeding, lethargy
- Day 11 Regained birth weight
- Day 12 Grey skin, milk intake poor
- Day 13 Dead

Morphine ↑
Mother ultra-rapid metabolizer (CYP2D6)


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**TAMOXIFEN**

Prodrug for active metabolite
Endoxifen for Breast Cancer

2 CYP2D6 alleles better outcome
No CYP2D6 alleles worse outcome

*Schroth et al JAMA. 2009;302(13):1429-1436*

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**Inhibition of CYP2D6 Affects Endoxifen Concentrations**

- *Wt/Wt, no inhibitor*
- *Venlafaxine, Sertraline, Paroxetine* *4/*4, no inhibitor*

*Jin Y et al: J Natl Cancer Inst 97:30, 2005*
David A. Flockhart, Indiana University School of Medicine, Division of Clinical Pharmacology, Indianapolis, Indiana 46202
ANTI-HIV ↓ CYP3A4, CYP2D6
DRUG LEVELS ↑

- Fluoxetine, duloxetine
  serotonin syndrome
- Trazodone
  nausea, dizziness, hypotension, syncope
- Alprazolam, midazolam, and triazolam
  oversedation, death
- Carbamazepine toxicity
- Clozaril, pimozide, chlorpromazine, haloperidol,
  olanzapine, risperidone toxicity
- Bupropion toxicity
- TCAs toxicity
- Amphetamine toxicity

ANTIRETROVIRAL INDUCTION
RARE

Ritonavir, nelfinavir
↓ oxazepam, lorazepam, temazepam
  (glucuronidation)
Nevirapine
↓ amphetamines
Efavirenz, nevirapine, ritonavir
  opiate withdrawal
  (induction CYP 3A4)
Carbamazepine
  Virologic failure

Carbamazepine and Steven Johnson Syndrome:
An example of rapid adoption

- Asian patients were shown to have a higher
  risk of skin reactions if they had an HLA-B
  *1502 allele
- On December 12, 2007, the FDA issued a
  warning stating that in at risk patients of Asian
  ancestry genotyping was necessary prior to
  prescribing carbamazepine

Copy Number Variation (CNV)

- Relatively new area of study
- Looks for association between disease
  and variations in numbers of copies of any
  region of the human genome (e.g.
  containing a gene or not)
SINGLE GENE

Huntington disease

Expands nucleotide triplet for protein huntingtin

SAME CHROMOSOMAL DELETION

Two syndromes Knoll et al., 1989

Angelman
Maternal chromosome

Prader-Willi
Paternal chromosome

Nicholls, 1994