Presentation Outline

I. Genetic Mapping for Human Complex Diseases

II. Mutation Identification for Bipolar Disorder

III. Pharmacogenetics

IV. Clinical Application
I. Single Nucleotide Polymorphisms (SNPs)

- ~11 million sites in the human genome
- 3 billion bases/genome: 1 SNP/1000 bases
- Each person has ~7 million common SNPs (inherit) and ~30 new SNPs occurred as mutations

**Definition:**
- Genetic markers
- SNP
- Allele
- Genotype
- Linkage Disequilibrium (LD)
- Haplotype
Genetic Mapping of Drug Response Using GWA, Candidate Gene Study, or Clinical Trail

- **Family design**
- **Chromosome interval**
- **Candidate genes**
- **Disease mutation**
  - Met
  - Val
  - Ser
  - Leu
  - Pro
  - Gln

- **Genomic scans**
- **LD mapping**
- **Gene sequencing**

- **Population Design, responder, non-responders**

- **SNP**

- **Narrow down susceptible region(s) by LD mapping**

- **and/Or**

- **LD**

- **stop**
Statistical association between an allele and a phenotypic trait arises in three possible situations:

1. The allele itself is functional and directly affects the expression of the phenotype (e.g. BD)
2. The allele is in LD with an allele at another locus that directly affects the expression of the phenotype
3. The relationship is due to chance and therefore is an artifact, e.g., from confounding or selection bias
## Confirmed Genetic Contributors to Common Human Diseases

<table>
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<tr>
<th>Year</th>
<th>MEIS1</th>
<th>CDKN2A</th>
<th>LBXCOR1</th>
<th>8q24 #2 BTBD9</th>
<th>8q24 #3 C3</th>
<th>8q24 #4 8q24</th>
<th>8q24 #5 ORMDL3</th>
<th>8q24 #6 4q25</th>
<th>ATG16L1</th>
<th>TCF2</th>
<th>5p13 GCKR</th>
<th>10q21 FTO</th>
<th>LOXL1</th>
<th>IRGM C12orf01L7R</th>
<th>NKKX2-3 ERBB3 TRAF1</th>
<th>IL12B KIAA0300 STAT4</th>
<th>3p21 CD226 ABCG8</th>
<th>1q24 16p13 GALNT2</th>
<th>PTPN2 PTPN2 PSRC1</th>
<th>1q24</th>
<th>TCF2 SH2B3 NCF1</th>
<th>CDKN2B/A FGFR2 TBL2</th>
<th>CD25 LOC387715 IGF2BP2 TNRC9 TRIB1</th>
<th>IRF5 8q24 CDKAL1 MAP3K1 KCTD10</th>
<th>PCSK9 IL23R HHEX LSP1 ANGLPT3</th>
<th>PPARγ NOD2 CTLA4 KCNJ11 PTPN22 CFH TCF7L2 SLC30A8 8q24 GRIN3A</th>
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</table>

### Conditions

- Cholesterol
- Obesity
- Coronary Disease
- QT interval
- Atrial Fibrillation
- Type 2 Diabetes
- Prostate cancer
- Breast cancer
- Colon cancer
- Age Related Macular Degeneration
- Crohn’s Disease
- Type 1 Diabetes
- Systemic Lupus Erythematosus
- Asthma
- Restless leg syndrome
- Gallstone disease
- Multiple sclerosis
- Rheumatoid arthritis
- Glaucoma
Published GWA through 9/2011, 1617 published GWA at $p<5\times10^{-8}$ for 249 traits
II. Mutation Identification for Bipolar Disorder
Genetic Epidemiology
Studies of BD

- Family studies:
  Heritability at 60-85%

- Twin studies: Concordant rate is 33-80% in MZ; 0-8% in DZ

- Adoption study

BD Clinics

- BD occurs most frequently, 1%
- High incidence of comorbid
- Major impact on the patient’s quality of life
Selection Criteria for Candidate Gene(s)

- Evidence of pathophysiological relevance in the disorder (e.g., BD, type 2 diabetes, Alzheimer disease)
- Location of the gene(s) in confirmed and replicated chromosomal susceptibility regions
- Evidence from disease-like animal model

<table>
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<tr>
<th>Human locus</th>
<th>Present study</th>
<th>Autoimmune models in rodents</th>
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<td>NPL &gt; 0.05</td>
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<tr>
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<td>17q22-25</td>
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<td>19q13</td>
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<tr>
<td>22q13</td>
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(Xu C et al., 2002-2012)
20 genome-wide linkage scans, 27 genome-wide association, 641 genes and 35 meta-analyses: 8q, 12q23-24, 15q, 18p11.2, 18q22, 21q21-23, and 22q11-13

Phenopedia/Genopedia (http://www.hugenavigator.net) on Aug 20, 2010
Structure of TRPM2

SNP Selection Criteria
1) TagSNPs defined by HapMap and ABI-SNPbrowser
2) located in exons, exon-intron boundaries, or potential regulatory regions, e.g., 3’ or 5’ untranslated regions
3) high minor allele frequencies (MAF)
Study Protocol

- SNP association
  \((X^2\text{ test, COCAPHASE})\)
- Define common haplotypes (Haploview)
- haplotypes association
  \((\text{COCAPHASE and Haploview})\)

Control: 268
BD: 178
Haplotype Blocks Consistent with Reported Haplotype Blocks

Oct 2002 …
χ² Results Presented as -\(\log_{10}\) Transformation of \(P\) values: Strong Association of I-18 SNP with BD

Xu C, et al., Bipolar Disorder 2006 131B:36
Transmission-Disequilibrium Test (TDT)

- To examine whether alleles transmitted from parents to their affected offspring deviate from the expected 50:50 Mendelian ratios

“Case” = transmitted alleles = 1 and 3
Not transmitted alleles = 2 and 4
Genome-Wide-Association Studies for SC and BP

Figure A1

Figure 2B
Sequencing Technology

Stratton, Nature 2009
Cost of Sequencing a Human Genome

- $2.7 Billion Human Genome Project
- $1.5 Million
- $100,000
- $50,000
- $1000

Timeline:
- 1990
- 2003
- 2008
- 2010
- 2020
NGS Data Viewed in Two Software Systems

A. NEXTGENE

Current Raw Read Sequence
Accuracy ~ 99%

B. MAQ
Genetic Characteristics for Complex Diseases

- No major single gene is sufficient or necessary for complex diseases (T2D, psychiatric disorders, or cancer)
- Interaction of multiple genes with small effect and low penetrance (e.g., 6q and 6p in BD, Schulze et al, 2004)
- A combination of several genetic (Epistasis) and/or environmental factors (Epigenetic influence)
Joint effect of IL12 Signalling Genes, IL12A, IL12RB2, and STAT4 on Risk of autoimmune disease

\[ y = 2.64x - 2.324 \]

\[ R^2 = 0.9055 \]
Presentation Outline

I. Genetic Mapping for Complex Diseases
II. Mutation identification for Bipolar Disorder
III. Pharmacogenetics
IV. Clinical Application
III. DNA Tragedy

A. Sajantila et al. / Forensic Science International 203 (2010) 44–52

PM or IM or EM or UM

Fortune - Oct 30, 2000
CYP2D6

Nortryptyline: Anti-depressant


Poor metabolizers

Ultra-rapid metabolizers

Dr. Chun Xu
Basis of Pharmacogenetics

50%-70% of treated patients show response to psychotropic therapies.

Trend molecular medicine 2002, 7:201

Dr. Chun Xu
Genetic Factors: Inter-Individual Differences in Drug Response

**Pharmacogenetics**: to study of genetic influences on an individual’s response to drugs.

**Pharmacogenomics**: The application of genomics to the study of human variability in drug response.
Pharmacogenetics

- Adverse drug reactions (ADRs): one of the top ten leading causes of death and illness
- ADRS: costs of 137-177 billion $US annually
- Genetic factors account for 20-95% (Ross et al., 2007)

Drugs with known genetically-linked potential for fatal adverse reactions (partial list):

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Prescribed For...</th>
<th>Adverse Reaction</th>
<th>Gene at Cause</th>
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<tbody>
<tr>
<td>Imipramine (Tofranil)</td>
<td>Depression, ATD</td>
<td>Heartbeat irregularity</td>
<td>CYP2D6</td>
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<td>Isoniazid (Laniazid)</td>
<td>Tuberculosis</td>
<td>Liver toxicity</td>
<td>NAT2</td>
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<tr>
<td>Warfarin (Coumadin)</td>
<td>Prevention of blood clots</td>
<td>Internal bleeding</td>
<td>CYP2C9</td>
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<tr>
<td>5-fluorouracil (Adrucil)</td>
<td>Cancer</td>
<td>Severe immune suppression</td>
<td>DPD</td>
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<tr>
<td>Clarithromycin (Biaxin)</td>
<td>Antibiotic</td>
<td>Heartbeat irregularity</td>
<td>KCNE2</td>
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<tr>
<td>Azathioprine (Imuran)</td>
<td>Rheumatoid arthritis</td>
<td>Severe immune suppression</td>
<td>TPMT</td>
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Genetic Information will be Evaluated in a diverse and large population

Drug Metabolizing Enzymes

Patients with Disease

MD genotypes her patients

Give Drug | High Dose | Low Dose | Alternate Drug

Xu et al., Advanced Drug Delivery Review 2002 54:1245
Xu et al., BBRC, 2002 290: 318
The Pharmacogenetics Approach to Therapeutics

Cited from Giacomini et al., 2007

http://www.pharmgkb.org
Goals of Pharmacogenetics

- Maximize drug efficacy
- Enhance drug safety
- Reduce drug toxicity
- Provide hopes to develop more efficient treatment strategies

“The right medicine to the right person at the right dosage at the right time”

--Tommy Thompson, former U.S. Health and Human Services
Presentation Outline

I. Genetic Mapping for Complex Diseases
II. Mutation Identification for Bipolar Disorder
III. Pharmacogenetics
IV. Clinical Application
IV. Potential Impact of Molecular Genetics and Pharmacogenetics on Disease Clinic

- Understanding etiology and pathophysiology of specific diseases (23andMe: https://www.23andme.com)
  http://www.navigenics.com
- Define susceptibility to disease → Prediction and prevention of the disease (e.g., genetic diagnostic testing) via established genetics risk profiling
- Provide molecular targets for developing new therapies

From Bench → Bedside → Health Economy and Policy
### Bipolar Disorder

**Related Diseases:**

557 genes have been reported with Bipolar Disorder

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<th>Gene</th>
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24 carriers, 50 traits, 100 diseases and 19 drug responses

e.g., type 2 diabetes: 11 SNPs

bipolar disorder: 1 SNP

https://www.23andme.com/
29 diseases and traits
12 drug responses:

- type 2 diabetes
- Alzheimer's disease
- Breast cancer
- Celiac disease
- Colon cancer
Genetic Testing from 23andMe and Navigenics

- Risk markers determined from GWAS
- Absolute risk = ‘relative risk’ and ‘average population disease risk’
- E.g., Alzheimer’s disease: 38% of AD have ApoE4 risk allele, only 14% in controls. The odds ratio (OR) for the ApoE4 risk allele is 3.7 = \(\frac{0.38}{0.62}\) / \(\frac{0.14}{0.86}\)
Adding Genetic Test to Your Clinical Practice

- Another tool in clinical decision making
- Individual genetic risk factors = environmental risk factors and family history
- Identify individuals with more than ten-fold relative risk of disease
- Pharmacogenetics/Pharmacogenomics → inform medication selection
- Nutrigenetics/Nutrigenomics → inform nutrient selection
- Genetic Counselors give personalized attention to you and your patient
Benefit of Genetic Testing

Knowing your genetic risks can help motivate you to take steps towards a healthier life.
Gene-Life Style in Human Longevity

- A variation in the gene FOXO3A has a positive effect on the life expectancy of humans (PNAS, 2009)

- Healthy lifestyle is also essential. Maintaining a healthy body weight, balance nutrition, good mood, proper exercise.

"Port wine, a diet rich in olive oil, and her sense of humor"

Mr. Davies was a keen gardener and grew 100lbs of tomatoes last year. He still keeps busy at aged 100 he has learned to speak French recently.
In 5-10 years, We will:

- Know the genetic contributors to neuropsychiatric disorders and other complex diseases
- Use genetic tests to diagnose diseases precisely
- Develop prognostic tests for promoting health through individualized therapy and lifestyle
- Create the world-leading centre of excellence in neuropsychiatric genetics, pharmacogenetics/pharmacogenomics, nutrigenetics/nutriogenomics, epigenetics/epigenomics at TTUHSC Paul L. Foster School of Medicine
- Develop genomic technologies for the benefit of our populations
Take Home Message

What is a SNP?

Location of SNPs on human DNA

How can a SNP map be used to predict drug response?

Phenotypes and prediction

Patients with efficacy in clinical trials

Patients without efficacy in clinical trials

Predictive of efficacy

Predictive of no efficacy

Human DNA

Section of SNP genotype profile

T

C
THANKS
FOR
YOUR
TIME