Biomarkers in Depression

Major Questions: UP vs BP? (major treatment considerations)
Identification of at-risk individuals; ? Prodomal
Rx Response

1. CNS markers
   1. CSF chemical measures -- proteomics, metabolomics
   2. Regional morphometric measures -- left subgenual anterior cingulate volume
   3. \textit{in vivo} functional neuroimaging measures -- PET -- Area 25 Activity

   4. Provocative \textit{in vivo} neuroimaging measures (task and chemical induced changes)
      --- fMRI Amygdala activation
      --- Reward Circuitry metabolism in response to AMPT
      (? Rebound hypomania to AMPT useful to distinguish UP/BP)?

2. Peripheral markers
   1. Plasma or serum chemical measures -- proteomics, metabolomics promising
   2. Peripheral, accessible tissue -- transcriptomics, & intracellular signaling

3. Physiological markers
   MEG, high density EEG to study \textit{in vivo} regional plasticity

**** Pharmacogenomics to predict therapeutic response & side effects
Pharmacogenomics of Antidep response

- Antidepressants are effective in ~50% of patients; current Rx is “trial & error” (with weeks-long trials)

- Individual variation in outcome may have a partial genetic basis
  - outcome and side-effect patterns vary less between illness episodes than between individuals
  - outcome of treatment may run in families

- Approach -- Study a large group of people who were all treated with the same medication and followed longitudinally
  - STAR*D Cohort: 1953 people, all with major depression ("real world patients"), all treated initially with an SSRI, citalopram (12 weeks @ level 1). 1 yr f/u

- Test for association between outcomes (response, side effects) and genotypes
Pharmacogenomic Study Strategy

- Genes selected and scored by expert panel
- 68 Genes sampled by first 768 SNPs selected for inclusion in Phase 1 screen
- Sampled with SNPs selected from HapMap Phase 1 at $r^2 \leq 0.80$
- Performed at Illumina, Inc. using BeadArray and GoldenGate assay
- 99.78% of samples were successfully genotyped
- 97.92% of SNPs produced usable data
- 100% agreement among 11,280 blind duplicates
- Additional SNPs near positive association signals genotyped at NIMH Lab using Taqman; 100% agreement between Illumina data and Taqman data based on blind duplicates
Analysis Plan

- Split sample design: 2/3 test and 1/3 replication
  - Split samples matched on gender and self-reported race
- All SNPs screened by allelic and genotypic tests
- Based on power analysis, alpha was set at 0.01 for the test sample and 0.05 for the replication sample
- Pass criteria: same allele, same test, same phenotype

Outcome phenotype:

- Remitters: score of $\leq 5$ at the last visit on the QIDS-C
- Responders: at least a 50% reduction from baseline on the QIDS-C
Variation in the Gene Encoding the Serotonin 2A Receptor Is Associated with Outcome of Antidepressant Treatment


rs7997012
rs2178865
p<3.7 x 10^{-5}
Secondary Screen of HTR2A Response Phenotype (whites)

- The allele associated with better outcome was ~7 times more common in whites than blacks.
- Blacks also had a less favorable outcome, overall, than whites in this sample.
The allele associated with better outcome is also associated with greater SERT binding capacity.

T-map showing $[^{11}C]DASB$ Binding

<table>
<thead>
<tr>
<th>HTR2a Genotype</th>
<th>SERT Binding Capacity (TH)</th>
<th>R$^2$</th>
<th>p</th>
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<tbody>
<tr>
<td>A/A</td>
<td>n=18</td>
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<tr>
<td>A/G</td>
<td>n=12</td>
<td></td>
<td></td>
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<tr>
<td>G/G</td>
<td>n=7</td>
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R$^2$=0.25
p < 0.0002
Other Genes associated with Treatment Response

SNPs ordered by physical position

HTR2A
BCL2
GRIK4

FDR 30%
Bcl-2 represents a gene conferring responsivity to antidepressants.

Participants homozygous for the response-associated allele were 40% more likely to go into full remission after 6 weeks of citalopram.
Bcl-2 SNPS regulate Bcl-2 mRNA, protein levels & sensitivity to apoptosis

Bcl-2 +/- mice show reduced DG neuroblasts (doublecortin)

Bcl-2 mRNA

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<tr>
<th></th>
<th>AA</th>
<th>AG</th>
<th>GG</th>
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<tbody>
<tr>
<td>P=0.004</td>
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<tr>
<td>P=0.042</td>
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<td></td>
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<tr>
<td>P=0.505</td>
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AA   AG   GG

WT HET

0 2000 4000 6000 8000

n=5 n=7

Bcl-2 mRNA levels

Bcl-2 protein levels

DCX +ve cells/DG

Bcl-2 mRNA

Bcl-2 protein

Bcl-2 +/- mice show reduced DG neuroblasts (doublecortin)
Bcl-2 +/- mice develop learned helplessness at a markedly greater rate, and fail to respond to citalopram.
Genes Associated with Antidepressant Responsiveness

Neuroplastic Δs in critical circuits modulating mood, motor, cognition
GluR6 KO mice display hyperlocomotion, aggression and increased exploratory behaviors (all lithium responsive)

**Hyperactivity**

- **CFT - 5 days**

  - Time spent in the center of the open field (1st day)

**Aggression**

- Frequency of attacks on the intruder

**“Risk taking”/Exploratory**

- Distance travelled

**Social behaviors**

- Total duration

<table>
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<tr>
<th>Con</th>
<th>GluR6 ko</th>
<th>GluR5 ko</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=12 (WT), 13 (GluR6 KO), 13 (GluR5 KO)</td>
<td>N=12 (WT), 13 (GluR6 KO), 13 (GluR5 KO)</td>
<td>N=12 (WT), 13 (GluR6 KO), 13 (GluR5 KO)</td>
</tr>
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Conclusions

- Outcome of citalopram treatment is related to common variants in at least 3 genes (likely more)

- WGS Pharmacogenomic studies have the potential to play an important role in personalizing Rx for this heterogeneous (but devastating group of illnesses)
Collaborators – STAR*D Study

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