Glutamate system gene polymorphisms and antipsychotic response in first-episode psychosis

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Learning objective

- Explain the importance of pharmacogenetic studies of glutamate genes in patients treated with antipsychotics

Concept of Trans-Diagnostic Research in Psychiatry

- Biological findings (genetic, pathophysiologic) in mental disorders are relatively non-specific
- Mental health diagnoses are syndromes based on patient reports and clinical observation, and often require longitudinal information to refine the diagnosis
  - Currently defined diagnoses may not be appropriate phenotypes for genetic or neuropathologic study
  - Classes of medications are effective for some symptoms across diagnoses
  - NIMH moving toward studies of patients with same symptom domains (eg psychosis) regardless of clinical diagnosis

Common risk alleles across psychiatric disorders

- Pooled genome-wide data with ~30,000 cases and controls
- Genetic loci are associated with disease risk across five major psychiatric disorders

Assessment Question #1

Which of the following findings suggests value in studying psychiatric illness across psychiatric diagnoses?

A. Antipsychotics only work in patients with schizophrenia
B. There is no overlap in symptoms of depression and schizophrenia
C. Only major depressive disorder is responsive to psychotherapy
D. Recent genetic studies indicate common risk alleles across major psychiatric diagnoses
Assessment Question #1

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First Episode as an Ideal Research Population

- Minimize confounding by chronicity
- Minimize confounding of previous treatment
  - Up/down regulation of neurotransmitter receptors
  - Does not select for a treatment-resistant phenotype
- Help to explain the substantial variability in disease morbidity after first-episode

Glutamate at a glance

- The major excitatory neurotransmitter in the CNS
  - Can “turn on” virtually all CNS neurons
- N-methyl-d-aspartate (NMDA) receptor antagonists such as PCP induce positive and negative symptoms of psychosis
- Glutamate polymorphisms may be associated schizophrenia risk, cognition, and negative symptom response

Glutamate Hypothesis

PCP (NMDA antagonist) ➔ Decreased NMDA receptor function ➔ Increased mesolimbic dopamine ➔ Negative symptoms of schizophrenia ➔ Increased mesolimbic dopamine ➔ Positive symptoms of schizophrenia

Pharmacogenetic Studies of Antipsychotic Response

Limited success of genetic pathophysiology and pharmacogenomic studies of dopamine-related genes

Pharmacogenetic Studies of Antipsychotic Response

PCP (NMDA antagonist) ➔ Decreased NMDA receptor function ➔ Increased mesolimbic dopamine ➔ Positive symptoms of schizophrenia ➔ Increased mesolimbic dopamine ➔ Negative symptoms of schizophrenia

Glutamate Hypothesis: Pharmacogenetics

We will examine “upstream” factors that may affect antipsychotic response
Assessment Question #2

Which of the following is a compelling reason to study glutamate-genes in pharmacogenomic studies of antipsychotic response?

A. Dietary glutamate is correlated with psychosis
B. The primary mechanism of antipsychotics is NMDA antagonism
C. NMDA models of psychosis produce positive and negative symptoms which are attenuated by antipsychotics
D. Glutamate is converted to dopamine

Hypothesis

- Genetic polymorphisms in glutamate genes will partially explain the variability seen in clinical response to antipsychotics

Study Design: Patients and Intervention

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>12-55 y/o</td>
<td>Serious medical illness</td>
<td>Total n=88</td>
</tr>
<tr>
<td>Non-organic psychosis</td>
<td>Failed drug screen</td>
<td>6 weeks of flexibly-dosed antipsychotics</td>
</tr>
<tr>
<td>Less than 16 weeks of antipsychotic treatment prior to enrollment</td>
<td>Pregnancy</td>
<td>Risperidone = drug of choice (n=70)</td>
</tr>
<tr>
<td>3-5 days free of treatment</td>
<td></td>
<td>Other antipsychotics allowed where clinically preferred (n=18)</td>
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Study Design: Evaluations and Genotyping

<table>
<thead>
<tr>
<th>Evaluations</th>
<th>Genotyping</th>
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<tbody>
<tr>
<td>Clinical evaluation</td>
<td>Affymetrix Genome-Wide Human SNP Array 6.0</td>
</tr>
<tr>
<td>Blood for genotyping</td>
<td>1.8 million genetic markers</td>
</tr>
<tr>
<td>fMRI tasks</td>
<td>906,600 single nucleotide polymorphisms (SNPs)</td>
</tr>
<tr>
<td>Eye movement tests</td>
<td>Allows for candidate-gene or genome-wide study methods</td>
</tr>
<tr>
<td>Computerized neuropsychological tests</td>
<td>Drug level</td>
</tr>
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Clinical Evaluations: BPRS

- Brief Psychiatric Rating Scale (BPRS)
  - 18-24 item (depending on version) clinician-rated scale based on patient interview
  - Evaluates numerous psychiatric symptoms
  - Validated in MDD, BPD, and Sz

  1. Somatic concern
  2. Anxiety
  3. Emotional withdrawal
  4. Conceptual disorganization
  5. Guilt feelings
  6. Tension
  7. Mannerisms and posturing
  8. Grandiosity
  9. Depressive mood
  10. Hostility
  11. Suspiciousness
  12. Hallucinatory behavior
  13. Motor retardation
  14. Uncooperativeness
  15. Unusual thought content
  16. Blunted affect
  17. Excitement
  18. Disorientation

Novel Glutamate Panel

- 3894 SNPs in 58 candidate genes
- Clinical covariates in model: race, baseline BPRS score, diagnosis, dose (chlorpromazine equivalents)

Ionotropic Receptors | Metabotropic Receptors | Downstream Signaling | Transport and Secretion | Metabolism
--- | --- | --- | --- | ---
GRIA1 | GRIA2 | GLUL | SLC1A2 | GLS
GRIA3 | GRIA4 | GRM1 | GNAQ | ADORA1
GRIA5 | GRIA6 | GRIK2 | ADCY7 | AVP
GRIA7 | GRIA8 | GRIK3 | HOMER1 | SLC1A1
GRIA9 | GRIA10 | GRIK4 | APP | ALDH5A1
GRIA11 | GRIA12 | GRIK5 | GRIN1 | APP
GRIA13 | GRIA14 | GRIK6 | GRM2 | HOMER2
GRIA15 | GRIA16 | GRIK7 | GRM3 | ITPR1
GRIA17 | GRIA18 | GRIK8 | GRM4 | CACNA1A
GRIA19 | GRIA20 | GRIK9 | GRM5 | CDK5R1
GRIA21 | GRIA22 | GRIK10 | GRM6 | MAPK1
GRIA23 | GRIA24 | GRIK11 | CLN3 | IL1B
GRIA25 | GRIA26 | GRIK12 | PLA2G6 | SLC1A6
GRIA27 | GRIA28 | GRIK13 | P2RX7 | GLUL
GRIA29 | GRIA30 | GRIK14 | SLC17A6 | SLC7A11
GRIA31 | GRIA32 | GRIK15 | SLC17A8 | SRR

Demographics

<table>
<thead>
<tr>
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<th>Sz (n=69)</th>
<th>BP (n=11)</th>
<th>MOD (n=8)</th>
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</thead>
<tbody>
<tr>
<td>Age (St Dev)</td>
<td>23.9 (6.5)</td>
<td>26.7 (8.6)</td>
<td>20.4 (7.2)</td>
</tr>
<tr>
<td>%Male</td>
<td>69</td>
<td>46</td>
<td>50</td>
</tr>
<tr>
<td>%White</td>
<td>49</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>BPRS Total Baseline (St Dev) *</td>
<td>47.1 (9.3)</td>
<td>37.3 (7.9)</td>
<td>44.4 (7.8)</td>
</tr>
<tr>
<td>BPRS Total End (St Dev)</td>
<td>38.2 (8.5)</td>
<td>27.1 (4.6)</td>
<td>32.9 (8.9)</td>
</tr>
<tr>
<td>BPRS Total Change Score (St Dev)</td>
<td>9.0 (8.0)</td>
<td>10.2 (9.2)</td>
<td>11.5 (5.8)</td>
</tr>
</tbody>
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* p<0.01

Results

- Seven of the 20 SNPs most strongly associated BPRS Total change score were in GRM7 (all p<0.0025)
  - Primarily driven by changes in positive symptoms
  - Multiple comparisons

Potential Mechanisms

- Agonism of mGluR7 (encoded by GRM7) decreases NMDA activity
- The functional role of the GRM7 SNPs in this study are unknown, and they may be linked to functional SNPs

Clinical Improvement Across Genotypes

Response rates (>20% reduction in BPRS total):
- 58% vs. 36% vs. 0%

Conclusions and Future Directions

- Polymorphisms in glutamate genes, such as GRM7, may be associated with antipsychotic response in first-episode psychosis
- Our results are consistent with the hypothesis that altered NMDA function may represent a mechanism for treatment resistance or persistent symptoms during the course of early treatment.
- Identifying SNPs that affect gene expression or protein function in these genes will allow for more focused candidate gene studies
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