GENE-GENE INTERACTIONS IN EXPLAINING HERITABILITY ESTIMATES FOR PSYCHOTIC ILLNESS: MODELLING EPISTASIS

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DISCLOSURE

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PSYCHOTIC ILLNESS
Diagnostic boundaries unclear
Risk factors are promiscuous and extend beyond psychosis to a milieu of developmental disorders
Dimensional approach (RDoC?)

van Os & Kapur 2009
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Base-pair position</th>
<th>Nearest gene</th>
<th>Alleles</th>
<th>Frequency</th>
<th>Imputation quality score</th>
<th>p value</th>
<th>OR (95% CI)</th>
<th>Heterogeneity p value</th>
<th>Best-fit model (BIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2535629</td>
<td>3</td>
<td>52808259</td>
<td>ITIH3 (+ many)</td>
<td>G/A</td>
<td>0.651</td>
<td>0.942</td>
<td>2.54 × 10^{-1}²</td>
<td>1.10 (1.07–1.12)</td>
<td>0.27</td>
</tr>
<tr>
<td>rs11191454</td>
<td>10</td>
<td>104649994</td>
<td>AS3MT (+ many)</td>
<td>A/G</td>
<td>0.910</td>
<td>1.01</td>
<td>1.39 × 10^{-8}</td>
<td>1.13 (1.08–1.18)</td>
<td>0.32</td>
</tr>
<tr>
<td>rs1024582</td>
<td>12</td>
<td>2272507</td>
<td>CACNA1C</td>
<td>A/G</td>
<td>0.337</td>
<td>0.98</td>
<td>1.87 × 10^{-8}</td>
<td>1.07 (1.05–1.10)</td>
<td>0.0057</td>
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<tr>
<td>rs2799573</td>
<td>10</td>
<td>18641934</td>
<td>CACNB2</td>
<td>T/C</td>
<td>0.715</td>
<td>0.825</td>
<td>4.29 × 10^{-8}</td>
<td>1.08 (1.05–1.12)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Cross-Disorder Group of the Psychiatric Genomics Consortium Lancet 2013
<table>
<thead>
<tr>
<th>Locus</th>
<th>Copy number change</th>
<th>Odds ratio</th>
<th>Associated disorder(s)</th>
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</thead>
<tbody>
<tr>
<td>1q21.1</td>
<td>Deletion Duplication</td>
<td>6.6–15.54</td>
<td>Sz, MR, seizures, autism</td>
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<tr>
<td>2p16.3 (NRXN1)</td>
<td>Deletion Duplication</td>
<td>7.5–8.97</td>
<td>Sz, MR, seizures, autism</td>
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<tr>
<td>3p26.1</td>
<td>Deletion Duplication</td>
<td>NA</td>
<td>Sz, MR, autism</td>
</tr>
<tr>
<td>3q29</td>
<td>Deletion</td>
<td>17</td>
<td>Sz, MR, autism</td>
</tr>
<tr>
<td>5p13.2</td>
<td>Deletion Duplication</td>
<td>NA</td>
<td>Sz</td>
</tr>
<tr>
<td>7q11.2</td>
<td>Duplication</td>
<td>NA</td>
<td>Sz</td>
</tr>
<tr>
<td>7q22.1</td>
<td>Duplication</td>
<td>NA</td>
<td>Sz</td>
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<tr>
<td>7q36.3</td>
<td>Deletion Duplication</td>
<td>4–8.26</td>
<td>Sz</td>
</tr>
<tr>
<td>15q11.2</td>
<td>Deletion Duplication</td>
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<td>Sz, MR, autism</td>
</tr>
<tr>
<td>15q13.1</td>
<td>Duplication</td>
<td>NA</td>
<td>Sz</td>
</tr>
<tr>
<td>15q13.3</td>
<td>Deletion Duplication</td>
<td>9.9–12.1</td>
<td>Sz, MR, seizures</td>
</tr>
<tr>
<td>16p11.2</td>
<td>Duplication</td>
<td>8.3–26.3</td>
<td>Sz, MR, seizures, autism, ADHD, BD</td>
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<td>16p13.1</td>
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<td>Sz, MR, autism, ADHD</td>
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<tr>
<td>17p12</td>
<td>Deletion</td>
<td>7.82</td>
<td>Sz, HNPP</td>
</tr>
<tr>
<td>17q12</td>
<td>Deletion Duplication</td>
<td>∞</td>
<td>Sz</td>
</tr>
<tr>
<td>22q11.2</td>
<td>Deletion</td>
<td>21.6–∞</td>
<td>Sz, MR, autism, ADHD, OCD, anxiety, depression</td>
</tr>
</tbody>
</table>
GWAS META-ANALYSIS IN SCHIZOPHRENIA
[128 SNPs and 108 loci across 36,989 cases and 113,075 controls]

Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014
THE ‘MISSING HERITABILITY’ OF PSYCHOTIC ILLNESS

However, even these 108 genetic loci, identified by such enormous numbers of cases/controls, can explain only <25% of the heritability estimate for schizophrenia [70-80%]

‘Missing heritability’ applies to many disorders: where the total phenotypic variance that is explained by all known risk genes is less than the heritability evident from relationships among relatives

“Epistasis [G × G interactions] is a ubiquitous component of the genetic architecture of human health and disease” that may explain this ‘missing heritability’
Molecular mechanisms of epistasis within and between genes
Ben Lehner

*Trends Genet* 2011;27:323-331

Epistasis and quantitative traits: using model organisms to study gene–gene interactions
Trudy F. C. Mackay

*Nat Rev Genet* 2014;15:22-33

Detecting epistasis in human complex traits
Wen-Hua Wei, Gibran Hemani and Chris S. Haley

*Nat Rev Genet* 2014;15:722-733
HOW TO TRANSLATE THE ‘MENTAL HEALTH’ OF A MOUSE?

ETHOLOGICAL
Species-specific characteristics and settings: e.g. ethogram, nest building

TRANS-SPECIES
Positive symptoms: exploratory activity; prepulse inhibition
Negative symptoms: social behaviour
Cognitive dysfunction: working/recognition memory
HOW TO TRANSLATE THE ‘MENTAL HEALTH’ OF A MOUSE?

1. Activity monitor

2. Working memory

3. Recognition memory

4. Social behaviour

5. Prepulse inhibition

6. Elevated + maze

7. Light/dark box
How does simultaneous disruption of two risk genes alter the expression of schizophrenia-related phenotypes relative to individual disruption of either one of those genes?
PSYCHOTIC ILLNESS

Dimensional approach

van Os & Kapur 2009
PROBING GENE × GENE INTERACTIONS
Exploratory activity in a novel environment

O’Tuathaigh et al 2016
PROBING GENE × GENE INTERACTIONS
Prepulse inhibition

O’Tuathaigh et al 2016
PSYCHOTIC ILLNESS

Dimensional approach

More acute onset, better outcome

More insidious onset, poorer outcome

Psychosis:
delusions, hallucinations

Mania

Depression

Negative
symptoms

Cognitive
impairment

Affective dysregulation

Developmental impairment

van Os & Kapur 2009
PROBING GENE × GENE INTERACTIONS
Memory for a novel object

O’Tuathaigh et al 2016
PSYCHOTIC ILLNESS

Dimensional approach

van Os & Kapur 2009
NRG1 × DISC1
Double mutant

Sociability

NRG1 heterozygous - N
DISC1 heterozygous - D
DISC1 homozygous - D

Genotype

O’Tuathaigh et al 2016
PROBING GENE × GENE INTERACTIONS AND DIMENSIONALITY

NRG1 × DISC1 mutant model

- Exploratory activity and PPI influenced only by disruption of NRG1
  - No gene × gene interaction
- Recognition memory not influenced by disruption of either/both genes
  - No gene × gene interaction
- Sociability impaired only on co-disruption of both NRG1 and DISC1
  - Dimension-specific, ‘pure’ gene × gene interaction
- Psychosis phenotype influenced by interaction of risk genes with other risk genes in a dimension-specific manner?
- Epistasis neglected and requiring systematic investigation in risk for psychosis within a milieu of developmental disorders and dimensions of psychopathology
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