Psychiatric Genetics:
Lessons from the
Disrupted in Schizophrenia 1
Locus

Pippa Thomson
Research Fellow, University of Edinburgh
Introduction to Schizophrenia

- Emil Kraeplin, 1887: dementia praecox (paranoia, grandiose delusions, auditory hallucinations, abnormal emotional reg., bizarre thoughts)—partly genetic.

  "dementia praecox not at all infrequently is familial, often appearing in brothers and sisters."

- Eugen Bleuler, 1911: key is dissociative thinking; also delusions, hallucinations, affective disturbance, autism. He coined the term, "schizophrenia".

  "Of the thousands of associative threads that guide our thinking, this disease seems to interrupt, quite haphazardly, sometimes single threads, sometimes a whole group, and sometimes whole segments of them."
Schizophrenia is characterized by:

Deteriorating ability to function in every day life and ... a combination of the following:

• –Hallucinations.
• –Delusions.
• –Thought disorder.
• –Movement disorder.
• –Inappropriate emotional expression.

Affects multiple brain regions & functions
Positive symptoms:

characteristics that are present, but should not be.

• –Hallucinations (almost always auditory)
• –Delusions of grandeur or persecution
• –Disordered thought processes (thoughts skip from one topic to another)
• –Bizarre (strange) behaviors
Negative symptoms:

characteristics that should be present, but are not.

- Social withdrawal
- Little emotion
- Loss of pleasure
- Reduced motivation; poor focus on tasks
- Reduced speech and movement

Negative symptoms are usually stable over time and difficult to treat.
**Time course of schizophrenia**

Age of onset: typically late teens to early twenties

Evidence of subtle abnormalities in motor, social and cognitive skills

**Figure 1**

The early stages of psychosis

- Behavioral adaptation
- Psychological symptoms

- Premorbid
- Psychosis risk
- First onset
- Established

- Birth
- 15
- 20
- 25
- 40

Age (y)

- Onset of psychotic symptoms
- Onset of prodromal symptoms
- Onset of functional decline

McGlashan, MD & Woods, 2011, Psychiatric Times
Chronic disorder

• After 10 yrs
  – 25% completely recovered
  – 25% much improved, relatively independent
  – 25% improved, but require extensive support networks
  – 15% hospitalized, unimproved
  – 10% dead (mostly suicide)
Clues from epidemiology

As we search for ‘the holy grail' — the etiology and pathophysiology of — we can be guided by some simple and very consistent observations concerning the epidemiology of the disorder.

These include the following:

1. has a similar clinical presentation and a similar prevalence throughout the world — a lifetime prevalence of approximately 1%. Because is at present a lifetime disorder, the lifetime prevalence and the point prevalence are essentially the same.

2. has been present for centuries, as inferred from literary descriptions.

3. ‘Classic' cases begin in young adult life.

4. Males are more frequently and severely affected.

5. The illness tends to run in families.

6. Despite the fact that the majority of people with do not marry or have children, the disease persists in the population.

Andreasen, 2000, Brain Research Reviews
Schizophrenia in different cultures

Sartorius et al, 1996, Psychological medicine

Affects ~1% of population worldwide

10% lifetime incidence of suicide in schizophrenia

Estimated total cost £6.7 billion in 2004/05

Annual incidence rates per 10000 population, age 15-54 for “narrow” definition

Aarhus 0.7
Nottingham 1.4
Moskow 0.7
Nagasaki 1.0
Chandigarh 1.1 / 0.9
Predictors of Schizophrenia

- Place/time of birth
  - Winter
  - Urban
  - Influenza
  - Respiratory
  - Rubella
  - Poliovirus
  - CNS
  - Famine
  - Bereavement
  - Flood
  - Unwantedness
  - Maternal depr
  - Rh incompatibility
  - Hypoxia
  - CNS damage
  - Low birth weight
  - Pre-eclampsia

- Infection

- Prenatal

- Obstetric

DOI: 10.1371/journal.pmed.0020212.g001
Evidence for a *substantial* genetic contribution to risk
- Evidence for *overlap* between DSMIV categories
- *Uncertainty* about genetic architecture & distribution of risk
Psychiatric Disorders

Autism, Bipolar, Dementia, Depression, Schizophrenia

• Overlapping signs & symptoms
• Lack of objective & categorical diagnostic tools

• Genetic heterogeneity
• Allelic heterogeneity
• Heterogeneous classes of genomic variation, including missense, regulatory, macro and micro chromosomal variants (copy number variants)
• Some replicated gene findings
• Plausible & convergent biological pathways
Contribution of common variants

Ripke et al., Nature Genetics 43, 969–976 (2011)
Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs.

Lee SH, DeCandia TR, Ripke S, Yang J; Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ); International Schizophrenia Consortium (ISC); Molecular Genetics of Schizophrenia Collaboration (MGS), Sullivan PF, Goddard ME, Keller MC, Visscher PM, Wray NR.

The total variance explained by SNPs ($h^2$) found in CNS$^+$ genes and other genes and by those not in genes totals 0.23.

Of this, a proportion (0.31) is attributed to SNPs in CNS$^+$ genes, which is greater than expected by chance ($P = 7.6 \times 10^{-8}$), given that the CNS$^+$ genes cover 0.20 of the length of the genome (Mb) and represent 0.21 of the SNP count ($N$ SNPs). Error bars, 95% confidence intervals of the estimates.
Genetic architecture of schizophrenia

Gorlov IP et al., AJHG
Copy Number Variants in Schizophrenia

Rare Structural Variants Disrupt Multiple Genes in Neurodevelopmental Pathways in Schizophrenia

Tom Walsh,† Jon M.McClellan,†† Shane E. McCarthy,‡ Anjene M. Addington,§ Sarah B. Pierce,¶ Greg M. Cooper,* Alex S. Nord,* Mary Kusenda,* Dheeraj Malhotra,* Abhishek Bhandari,* Sunday M. Stoy,* Caitlin F. Riepe,* Patricia Roccona,* Wad Makarev,* B. Lakshmi,* Robert L. Findling,* Linnarri Sikk, Thomas Stromberg,* Barry Merriman,* Nitin Gogtay,* Philip Butler,* Kristen Eckstrand,* Laila Noeby,* Peter Gochman,* Robert Long,* Zugen Chen,* Sean Davis,*†† Carl Baker,* Evan E. Eichler,* Paul S. Meltzer,* Stanley F. Nelson,* Andrew B. Singleton,*† Ming K. Lee,* Judith R. Rapoport,* Mary-Claire King,*‡‡ Jonathan Sebat†

Schizophrenia is a devastating neurodevelopmental disorder whose genetic influences remain elusive. We hypothesize that individually rare structural variants contribute to the illness. Microdeletions and microduplications >100 kilobases were identified by microarray comparative genomic hybridization of genomic DNA from 150 individuals with schizophrenia and 268 ancestry-matched controls. All variants were validated by high-resolution platforms. Novel deletions and duplications of genes were present in 5% of controls versus 15% of cases and 20% of young-onset cases, both highly significant differences. The association was independently replicated in patients with childhood-onset schizophrenia as compared with their parents. Mutations in cases disrupted genes disproportionately from signaling networks controlling neurodevelopment, including neuregulin and glutamate pathways. These results suggest that multiple, individually rare mutations altering genes in neurodevelopmental pathways contribute to schizophrenia.

www.sciencemag.org SCIENCE VOL 320 25 APRIL 2008

LETTERS

Large recurrent microdeletions associated with schizophrenia


Table 2 | Significant association of deletions at 1q21.1, 15q11.2 and 15q13.3 with schizophrenia and related psychoses in the combined samples

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>Germany</td>
<td>2 of 911</td>
<td>1 of 2,197</td>
<td>3 of 911</td>
</tr>
<tr>
<td>Scotland</td>
<td>2 of 451</td>
<td>0 of 441</td>
<td>5 of 451</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>0 of 806</td>
<td>0 of 409</td>
<td>5 of 806</td>
</tr>
<tr>
<td>Norway</td>
<td>0 of 237</td>
<td>0 of 272</td>
<td>0 of 237</td>
</tr>
<tr>
<td>Denmark*</td>
<td>3 of 442</td>
<td>0 of 1,437</td>
<td>3 of 442</td>
</tr>
<tr>
<td>China*</td>
<td>0 of 438</td>
<td>0 of 463</td>
<td>0 of 438</td>
</tr>
<tr>
<td>Phase II OR</td>
<td>2.82</td>
<td>1.0</td>
<td>2.82</td>
</tr>
<tr>
<td>P-value</td>
<td>5.6 × 10−4</td>
<td>6.0 × 10−4</td>
<td>6.0 × 10−4</td>
</tr>
<tr>
<td>Phase I and II</td>
<td>2.18</td>
<td>1.01</td>
<td>2.18</td>
</tr>
<tr>
<td>P-value</td>
<td>3.5 × 10−4</td>
<td>6.0 × 10−4</td>
<td>6.0 × 10−4</td>
</tr>
</tbody>
</table>

The three deletions nominally in phase I were tested for association in follow up samples from Germany, Scotland, The Netherlands, Denmark, Norway and China. All three deletions associate with schizophrenia and related psychoses in the combined phase (and all samples (the multiple testing significance threshold is: 0.05/66 = 7.6 × 10−4). ORs (and P-values in the table) are corrected for the 66 tests from the exact Cochran-Mantel–Haenszel test and are two-sided. Coordinates are based on Build 36 assembly of the human genome. 95% confidence intervals are given within brackets. NA, not analyzed.

LETTERS

Rare chromosomal deletions and duplications increase risk of schizophrenia

The International Schizophrenia Consortium*
Neurexin 1 (NRXN1) Deletions in Schizophrenia
George Kirov, Dan Rujescu, Andres Ingason, David A. Collier, Michael C. O’Donovan, and Michael J. Owen

ALL: $P = .000013$, OR = 4.78, 95% CI = 2.44–9.37.
Exonic: $P = .0000037$, OR = 7.44, 95% CI = 3.22–17.18.

Copy Number Variants in NRXN1 in All Studies, Filtered for >100 kb. The shorter form of the gene encodes for the NRXN1β form, while the longer one encodes for the NRXN1α form. Red bars are deletions in cases ($n=8798$); blue are those in controls ($n=42054$).

### Rethinking the Genetic Architecture of Schizophrenia

*Mitchell & Porteous, Psychological Medicine, 2010*

#### Nominating Candidate Genes Through Molecular Cytogenetics

<table>
<thead>
<tr>
<th>Single-gene mutations</th>
<th>Location</th>
<th>Associated phenotypes</th>
<th>Nature of mutation(s)</th>
<th>Gene length (kb)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA13</td>
<td>7p12.3</td>
<td>BD, MD, SZ</td>
<td>Translocation, point mutations</td>
<td>449</td>
<td>1</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>7q35</td>
<td>ADHD, ASD, E, OCD, SZ, TS</td>
<td>CNV, point mutations</td>
<td>2305</td>
<td>2–6</td>
</tr>
<tr>
<td>DISC1</td>
<td>1q42.2</td>
<td>ASD, BD, MD, SZ</td>
<td>Translocation, point mutations</td>
<td>414</td>
<td>7–9</td>
</tr>
<tr>
<td>ERBB4</td>
<td>2q34</td>
<td>SZ</td>
<td>CNV</td>
<td>1163</td>
<td>10</td>
</tr>
<tr>
<td>GRIK4</td>
<td>11q23.3</td>
<td>BD, MR, SZ</td>
<td>Translocation</td>
<td>326</td>
<td>11</td>
</tr>
<tr>
<td>NPAS3</td>
<td>14q13.1</td>
<td>ID, SZ</td>
<td>Translocation</td>
<td>865</td>
<td>12</td>
</tr>
<tr>
<td>NRXN1</td>
<td>2p16.3</td>
<td>ASD, SZ</td>
<td>CNV, point mutations</td>
<td>1112</td>
<td>3, 13</td>
</tr>
<tr>
<td>PCM1</td>
<td>8p22</td>
<td>SZ</td>
<td>Point mutations</td>
<td>111</td>
<td>14</td>
</tr>
<tr>
<td>PDE4B</td>
<td>1p31.3</td>
<td>SZ</td>
<td>Translocation</td>
<td>582</td>
<td>15</td>
</tr>
<tr>
<td>PINK1</td>
<td>1p36.12</td>
<td>ANX, MD, OCD, PD, SZ</td>
<td>Point mutations</td>
<td>18</td>
<td>16, 17</td>
</tr>
<tr>
<td>SYNGR1</td>
<td>22q13.1</td>
<td>BD, SZ</td>
<td>Point mutations</td>
<td>36</td>
<td>18, 19</td>
</tr>
</tbody>
</table>

#### Genetic & Phenotypic Heterogeneity

#### Importance of Rare Variants

#### Biological Networks & Converging Pathways
A balanced t(1:11) translocation linked to schizophrenia

• Translocation linked to schizophrenia, depression & bipolar disorder

• DISC1 associated with these disorders in many different populations

• Developmentally regulated, with particularly high levels in developing hippocampus

• Consistent with “developmental hypothesis” of schizophrenia

• Interacts with multiple proteins involved in neurodevelopment, cytoskeletal function and cell signalling (Y2H)

• Altered subcellular distribution in PM brains of psychotic individuals

StClair et al, Lancet, 1990; Blackwood et al, Psy Genet, 1999
DISC1 translocation co-segregates with mental illness. A translocation increases risk by 50-fold.

(1;11)(q42;q14) translocation

- schizophrenia
- recurrent major depression
- bipolar affective disorder
- unaffected
- minor diagnosis
DISC1 Interacts with Multiple Proteins Involved in Brain Development, Signalling & the Synapse

Over 50 confirmed interactors
- PDE4
- NDE1
- NDEL1
- GSK3β
- AKAP450

DISC1 is expressed in neurons & glia.
DISC1 locates to the nucleus, centrosome, mitochondria, cytoskeleton, growth cone, pre- & post-synaptic density
Multiple DISC1 Interactors Co-locate at the Centrosome
Bradshaw & Porteous, 2010, Neuropharmacology

Multiple DISC1 Interactors are Independent Risk Factors for SZ, BP or MDD
Bradshaw & Porteous, 2010, Neuropharmacology
DISC1 – PDE4B interaction

- PDE4B involved in degradation of cAMP
- Binding of DISC1 to PDE4B inhibits PDE4B activity resulting in decreased cAMP
- PDE4B is involved in learning and memory
- Inhibitors of PDE4B are being investigated as antidepressants, antipsychotics & cognitive enhancers
- Independently linked to SCZ

Millar et al Science, 310, 1187-1191 (2005)
PDE4B & PDE4D are Risk Factors for SZ

PDE4B

translocation breakpoint in familial SCZ/psychosis Scottish

association with SCZ Finnish (Tomppo et al 2009)

association with SCZ Scandinavian (Kahler et al 2010)

association with SCZ Scottish (Pickard et al 2007)


PDE4B1
PDE4B3
PDE4B2

PDE4D

association with SCZ Finnish (Tomppo et al 2009)
DISC1, PDE4 & the LIS1/NDE1/NDEL1 Complex


cAMP hydrolysis

neuronal progenitor proliferation & neuronal migration
cAMP Dependent Dynamics of DISC1 Interaction
Impact of NDE1 Phosphorylation on Neurite Extension
Bradshaw et al, 2011, in revision

\[ p = 0.0095 \]
Disc1 RNAi in utero inhibits neuronal migration in mouse brain

Kamiya et al, Nature Cell Biol, 2005

Reduced Migration, Polarity & Arborisation
Disc1 regulates integration of newly formed neurons in the adult brain

Duan et al 2007 Cell, 130, 1-13

Retroviral-mediated RNAi knock down of DISC1 in adult mouse brain

DISC1 orchestrates the tempo of functional integration of newborn neurons in the adult brain
Example of DISC1 mouse models

- ENU generated mouse mutants

- Two independent lines with missense mutations
  - Q31L (Glutamine-Leucine)
    > Q - hydrophillic; L – hydrophobic
  - L100P (Leucine-Proline)
    > Predicted to cause transition in polypeptide chain direction

- Normal levels of DISC1 protein in brain
- L100P line models schizophrenia; Q31L, depression

Clapcote et al, 2007, Neuron
## Effects of altered DISC1 on behaviour

### Phenotype

<table>
<thead>
<tr>
<th></th>
<th>31L/31L 100P/100P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (elevated plus-maze)</td>
<td>= =</td>
</tr>
<tr>
<td>Horizontal activity</td>
<td>= &gt;&gt;</td>
</tr>
<tr>
<td>Vertical activity</td>
<td>= &gt;</td>
</tr>
<tr>
<td>Prepulse inhibition (PPI)</td>
<td>&lt; &lt;&lt;</td>
</tr>
<tr>
<td>Acoustic startle response</td>
<td>= &lt;</td>
</tr>
<tr>
<td>Startle reactivity</td>
<td>= &lt;</td>
</tr>
<tr>
<td>Latent inhibition (LI)</td>
<td>&lt;&lt; &lt;&lt;</td>
</tr>
<tr>
<td>Working memory (T maze)</td>
<td>&lt; &lt;&lt;</td>
</tr>
<tr>
<td>Spatial learning and memory (Morris water maze)</td>
<td>= =</td>
</tr>
<tr>
<td>Forced swim immobility (FST)</td>
<td>&gt; =</td>
</tr>
<tr>
<td>Sociability and social novelty</td>
<td>= =</td>
</tr>
<tr>
<td>Sucrose consumption</td>
<td>&lt; =</td>
</tr>
<tr>
<td>Brain volume</td>
<td>&lt; &lt;&lt;</td>
</tr>
<tr>
<td>PDE4B activity</td>
<td>&lt;&lt; =</td>
</tr>
</tbody>
</table>

### Drug Treatment

<table>
<thead>
<tr>
<th></th>
<th>31L/31L 100P/100P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>Clozapine = +</td>
</tr>
<tr>
<td></td>
<td>Bupropion +++ =</td>
</tr>
</tbody>
</table>

Altered PDE4 activity
Disc1^{100p} modulates expression of Nrxn1 & 3
Brown et al, Molecular Psychiatry, 2011

Most significant differences between Disc1^{100p} and wild type seen at:

- E18: synapse formation, neuronal maturation
- P7: neurite outgrowth, myelination, synaptic pruning and apoptosis
Rare Variants of DISC1

*Song et al, BBRC 2008*

- Exome sequencing of ~300 SZ subjects
- Tested for prevalence in ~10,000 normal individuals
- Ascertainment?
- Replication?
R37 is located within a nuclear localisation signal, a mitochondrial targeting signal, and a PDE4B / GSK3β binding domain.

R37W alters DISC1 spine density & increases PDE4B binding.

Song et al, BBRC 2008
DISC1 variants 37W and 607F disrupt its nuclear targeting and regulatory role in ATF4-mediated transcription

Elise L.V. Malavasi, Fumiaki Ogawa, David J. Porteous and J. Kirsty Millar*
Full sequencing of the 500kb region in 1500 samples

- Schizophrenia n= 240
- Bipolar Disorder n= 221
- Major Depressive Disorder n= 192
- Lothian Birth Cohort 1936 n= 889
DISC1 Locus
Abundance of rare variants

- 60% Novel variants

Common variants $\geq 0.01$ MAF: 708
Rare variants $< 0.01$ MAF: 2010

- Exonic variants: 34
- Synonymous variants: 12
- Non-synonymous variants: 22
- Predicted Stop mutations: 1

$R^2$ linear = 0.987
So how much variation is there?

*Mark-Recapture*

\[ N = \frac{MC}{R}, \]

<table>
<thead>
<tr>
<th></th>
<th>1000G CSHL</th>
<th>1000G EUR</th>
<th>Overlap</th>
<th>Total</th>
<th>Lincoln-Petersen</th>
<th>Modified Peterson</th>
<th>% Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2718</td>
<td>1515</td>
<td>1027</td>
<td>3206</td>
<td>4009.5</td>
<td>4008.7</td>
<td>80.0</td>
</tr>
<tr>
<td>&gt;1%</td>
<td>708</td>
<td>885</td>
<td>692</td>
<td>901</td>
<td>905.5</td>
<td>905.5</td>
<td>99.6</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>2010</td>
<td>630</td>
<td>335</td>
<td>2305</td>
<td>3780.0</td>
<td>3775.6</td>
<td>61.0</td>
</tr>
</tbody>
</table>
Multiple Novel Amino Acid Substitutions
e.g. R37W in rMDD & A83V in BP

SOM Supplementary Figure 3. Annotation of exonic SNPs on the predicted protein domains of TRAX (A) and DISC1 (B). The position of exonic SNPs and diagnostic class in which they were identified are shown: synonymous (black) and non-synonymous (red). SNPs not seen in previously published sequencing projects are underlined.
DISC1 Locus
Statistical Analysis

Case vs. Control Analysis
Quantitative trait analysis of LBC1936

- DISC1 is associated with higher levels of neuroticism, increased anxiety & depression in females.

1. Individual variants
2. Gene-wide
Recurrent Major Depression (rMDD)

Odds Ratio = 3.48, 95% CI = 1.95-6.23, unadjusted $p$-value = $6.3 \times 10^{-5}$

gene-wide empirical $p=0.026$
Segregation in families

Family 155
1  suicide
2
3
4  AT
5  AT
6
7  AT

Family 303
1  AT
2  TT
3
4  AT
5  AT
6  TT
7  AT

Family 318
1  AT
2  TT
3
4
Unknown
No psychiatric diagnosis
rMDD
BP2 with rMDD
Minor depression
Gene-wide analysis

• People with more variants should have higher risk for disease or lower function for quantitative traits

• Use *number of* SNPs for each person as predictor in a regression model (BURDEN)
  – we know or guess that some bases are more likely to matter: analyse by *functional* group
  – *rarer* variants may have larger effects: use MAF cut offs (VTTEST)
## Summary of nominally significant burden results

### Case-Control

<table>
<thead>
<tr>
<th>Trait</th>
<th>SNP Subset</th>
<th>Test</th>
<th>Burden@</th>
<th>Threshold</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rMDD Regulation</td>
<td>Regulation</td>
<td>BURDEN</td>
<td>1.39</td>
<td>-</td>
<td>0.044</td>
</tr>
<tr>
<td>rMDD Conserved</td>
<td>Conserved</td>
<td>VTTEST</td>
<td>1.20</td>
<td>0.0018 (31)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

### Quantitative Traits

<table>
<thead>
<tr>
<th>Trait</th>
<th>SNP Subset</th>
<th>Test</th>
<th>Correlation</th>
<th>Threshold#</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression trait Transcription</td>
<td>BURDEN</td>
<td>0.062</td>
<td>-</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>IQ age 11 Promoter</td>
<td>VTTEST</td>
<td>-0.097</td>
<td>0.31 (3)</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>IQ age 11 Proteins</td>
<td>VTTEST</td>
<td>-0.101</td>
<td>0.0007 (12)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>IQ age 70 Conserved</td>
<td>VTTEST</td>
<td>-0.074</td>
<td>0.0013 (21)</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>IQ change Promoter</td>
<td>VTTEST</td>
<td>-0.064</td>
<td>0.0006 (2)</td>
<td>0.047</td>
<td></td>
</tr>
</tbody>
</table>
Common SNP variants in the promoter and 5’ region regulate DISC1 expression
DISC1 expression is highly heritable

\( h^2 = 0.50, \ P = 2 \times 10^{-22} \)

Strong evidence for 5’ cis acting SNPs moderating regulation

\( \sim 25\% \) variance, \( P = 6 \times 10^{-34} \)

Spatial working memory

\( \text{rs2793094, } P=3 \times 10^{-4} \)

Recurrent major depressive disorder

\( \text{rs12137417, } P=5 \times 10^{-4} \)

Lifetime panic

\( \text{rs12137417, } P=7 \times 10^{-4} \)
Dosage effect of expression haplotype on mean age of onset for depression

\[ P=0.0018 \]
\[ P=0.072 \]
\[ P=0.070 \]

Thomson et al., Molecular Psychiatry, 2012
Summary Conclusions

• Directed resequencing of TRAX/DISC1 in ~1,500 cases and controls identified ~78% of SNPs >1%, ~24% of SNPs <1%
• Non-synonymous amino acid substitutions, both common and rare, are associated with altered biological function, e.g. 607F & 37W
• Carriers of rare variants are not exclusively cases
  – Penetrance, Expressivity & Epistasis
• Strongest association is with recurrent Major Depression
• Putative regulatory variants are associated with
  – Altered DISC1 expression & function
  – IQ at Age 70 & Cognitive ageing
  – Recurrent Major Depressive Disorder
  – Age of Onset of Depression
The emerging spectrum of allelic variation in schizophrenia

B.J. Mowry
& J. Gratten

EXPERT REVIEW

Risk allele frequency

Effect Size

Molecular Psychiatry (2012), 1 - 15
Ongoing studies

• Generation Scotland GWAS
  – 10,000 Scottish individuals
  – Analysis of depression and related traits

• DISC1 interactome
  – 260 genes that interact with DISC1

• Exome sequencing:
  – Extreme depression and families

• Investigating the functional effects of variants:
  – Biological effects of risk variants – GPR50
Future Developments

• Polygenic Risk Scores
  – “Genome-wide burden analysis”
  – An explanation of incomplete penetrance?
  – Models of disease prediction (G x E)
  – Alzheimer’s & Parkinson’s diseases

• Evolutionary Perspective - "Nothing in Biology Makes Sense Except in the Light of Evolution"
Acknowledgements

• Kamna Ramakrishnan, Dinesh Soares, Kathy Evans, Kirsty Millar, Sarah Harris, John Starr, Douglas Blackwood, Andrew McIntosh, Ian Deary & David Porteous, University of Edinburgh Molecular Medicine Centre, Division of Psychiatry and Centre for Cognitive Ageing and Cognitive Epidemiology, Edinburgh, UK.

• Allan McRae, Peter Visscher, Queensland Institute of Medical Research, Brisbane, Australia

• William Hennah, Institute for Molecular Medicine, Helsinki, Finland

• Melissa De La Bastide, Jennifer Parla, Shane McCarthy, Danea Rebolini, Laura Cardone, Maureen Bell, Elena Ghiban, James D Watson & W Richard McCombie, Stanley Institute for Cognitive Genomics, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA.

• Funding
  – Stanley Medical Research Institute
  – UK Medical Research Council
  – UK Biotechnology and Biological Sciences Council
  – Lifelong Health and Wellbeing Initiative.
  – Age UK
  – Chief Scientists Office, Scotland.
  – Wellcome Trust
Surviving participants of Scottish Mental Survey 1947
- Nationwide IQ testing, aged 11
  (N = 70,805), Moray House Test

Identified people in Edinburgh area born in 1936
- 1091 tested
- Mean age about 70 when re-tested
- Relatively healthy
- Screening to remove those with dementia

DISC1 is associated with higher levels of neuroticism, increased anxiety & depression in females.
Scottish Family Health Study

An ethically sound, family- and population-based infrastructure to identify the genetic basis of common complex diseases.

A cross-disciplinary collaboration between all five Scottish University Medical

Executive: Professor David Porteous University of Edinburgh
Professor Anna Dominiczak University of Glasgow
Professor Andrew Morris University of Dundee
Professor Blair Smith University of Aberdeen
Dr Christian Delles University of Glasgow

www.generationscotland.org