Major Depressive Disorder: Stage 1 Genomewide Association in Population-Based Samples.

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Critique

- Unrealistic sample sizes
- Sparse genotyping
- Imhomogeneity of samples
- Epidemiological sampling frame unknown
- Minimal phenotypes
- Controls not “draws from the same population” as cases
- Controls just unaffected, not at low liability
- Cases not directly evaluated by pros
- Replication not intrinsic
Primary phenotype definition

- **Major depressive disorder (MDD)**
- **Dysphoria along with**
  - Physical signs & symptoms
  - Impairment
  - Persistent & pervasive
  - Not normal sadness or grief
- **Excludes depression due to other psychiatric and medical causes**
Importance of MDD

- **Common**
  - Lifetime prevalence ~15%
  - Increasing importance to psychiatry
- **Chronic – recurrent for most (~75%)**
- **Increased mortality (suicide & other)**
- **Considerable morbidity**
  - By 2020, projected to become 2\textsuperscript{nd} leading cause of disability in world
Evidence for genetic influence on phenotype

• Complex trait
• Indirect data from genetic epidemiological studies
  - Twin studies, heritability ~40% (or higher)
  - Adoption studies consistent
  - Familial - risk to 1\textsuperscript{st} degree relatives RR=2.8
• Evidence from the Netherlands consistent
Genomewide Linkage Studies (MDD & N)
# Genomewide Association Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>$N_{total}$</th>
<th>IP?</th>
<th>Ancestry</th>
<th>Status</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>GAIN</td>
<td>3,200</td>
<td>No</td>
<td>EUR</td>
<td>In progress</td>
<td>4,600+Stage 2</td>
</tr>
<tr>
<td>Pfizer</td>
<td>500</td>
<td>Yes</td>
<td>EUR</td>
<td>Complete</td>
<td>No controls</td>
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<tr>
<td>GSK</td>
<td>2,000</td>
<td>Yes</td>
<td>EUR</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Academic 1</td>
<td>3,000</td>
<td>No</td>
<td>EUR</td>
<td>In progress</td>
<td>Pooling</td>
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<tr>
<td>Academic 2</td>
<td>2,000</td>
<td>No</td>
<td>Mixed</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Academic 3</td>
<td>2,000</td>
<td>No</td>
<td>Mixed</td>
<td>Planned</td>
<td></td>
</tr>
</tbody>
</table>
Restrictions on data use

IRB approvals & consents:
• Allow the future use of DNA samples/phenotype data and information derived from them for genetic studies;
• Permit the use of the samples and information derived from them for research on phenotypes other than MDD;
• Do not impose any restrictions on sharing samples and information derived from them with other investigators; and
• Do not restrict the use of the samples and information derived from them in any other way, as long as the anonymity of the participants is guaranteed.
1,600 CASES with MDD: Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl, 2003-present)

- Collaborative study within the Netherlands (4 academic centers, 2 non-academic centers)
- Longitudinal cohort study following 2,850 persons, 18-65 years
- Five assessments: baseline and after 1, 2, 4 and 8 years
- Designed to be representative for MDD patients → Covers different range of psychopathology and settings
Inclusion & exclusion criteria for MDD cases

Inclusion criteria:

- Confirmed MDD diagnosis according to CIDI interview, version 2.1
- Age 18-65 years

Exclusion criteria:

- Insufficient knowledge of Dutch language
- Ancestry other than North-European
- Other psychiatric disorder, e.g. bipolar disorder, OCD, severe addiction, psychosis, mood disorder due to a general medical condition
Recruitment of MDD cases

**Community**
- Random sample
  - n=10152
  - 30% refusal
- Psychiatric interview
  - n=7076
  - 30% refusal
- MDD diagnosis
  - N=640
  - 30% refusal, 15% dropout
- NESDA baseline
  - n=350
  - 300 MDD cases

**Primary care**
- Random GP sample of 19596, from 60 GPs
  - 50% not-returned
- Screening list (K-10), n=9798
  - 42% screen pos n=4115
  - 9% refusal
- Phone screen CIDI-SF n=3744
  - 45% screen pos, n=1684
  - 8% exclusion
- NESDA baseline
  - n=1407
  - 800 MDD cases

**Mental Health Care**
- Newly admitted MHO patients
  - MDD diagnosis at Intake, n=1390
  - 7% exclusion
- Phone screen
  - n=1293
  - 32% refusal
  - 10% exclusion
- NESDA baseline
  - n=750
  - 650 MDD cases
### Key clinical features for MDD

<table>
<thead>
<tr>
<th>Positive family history(%)</th>
<th>71%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent episode</td>
<td>≥2 episodes: 47%</td>
</tr>
<tr>
<td>Age of onset</td>
<td>&gt;30:  39%</td>
</tr>
<tr>
<td>Any of these</td>
<td>95.1%</td>
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</tbody>
</table>
## CONTROLS: Netherlands Twin Register (NTR)

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<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Twins</td>
<td>3386</td>
<td>4225</td>
<td>3413</td>
<td>3231</td>
<td>4610</td>
<td>4523</td>
<td>4017</td>
</tr>
<tr>
<td>Siblings</td>
<td>n/a</td>
<td>n/a</td>
<td>1481</td>
<td>1517</td>
<td>1474</td>
<td>1454</td>
<td>1264</td>
</tr>
<tr>
<td>Fathers</td>
<td>1439</td>
<td>1774</td>
<td>1572</td>
<td>n/a</td>
<td>n/a</td>
<td>1266</td>
<td>1058</td>
</tr>
<tr>
<td>Mothers</td>
<td>1607</td>
<td>1920</td>
<td>1688</td>
<td>n/a</td>
<td>n/a</td>
<td>1529</td>
<td>1333</td>
</tr>
<tr>
<td>Spouses</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>708</td>
<td>1527</td>
<td>945</td>
</tr>
<tr>
<td>Total</td>
<td>6432</td>
<td>7919</td>
<td>8154</td>
<td>4753</td>
<td>6795</td>
<td>10299</td>
<td>8617</td>
</tr>
</tbody>
</table>

In total, questionnaire data available for 20,496 individuals.
Selection of 1,600 controls

- DNA, mRNA (challenged/unchallenged) and lymphocytes (immortalized cell lines) present
- Only unrelated individuals are selected
- Proband & parents born in the Netherlands or Western-Europe
- NEVER a high score (> mean + 0.6 SD) on personality traits associated with depression (neuroticism, anxious depression, trait anxiety, borderline personality) in the 15 year follow-up period
- NO reports of clinical depression (YASR/Beck inventories, CIDI interview) or use of antidepressant medication EVER, up to biobanking
Matching of cases and controls

- All cases and controls are drawn from the same population
- Very homogeneous subject ancestries
- Cases and controls come from ongoing prospective studies
- Comparable composition across age, sex, marital status, SES
Matching of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>MDD cases (NESDA)</th>
<th>Controls (NTR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean ± SD)</strong></td>
<td>41.6 yrs ± 12.8</td>
<td>43.9 yrs ± 13.3</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>68.9%</td>
<td>66.5%</td>
</tr>
<tr>
<td><strong>Married/partner</strong></td>
<td>66.5%</td>
<td>75.8%</td>
</tr>
<tr>
<td><strong>Educational level</strong></td>
<td>Lower: 33.3%</td>
<td>Lower: 25.3%</td>
</tr>
<tr>
<td></td>
<td>Middle: 31.4%</td>
<td>Middle: 31.7%</td>
</tr>
<tr>
<td></td>
<td>Higher: 33.5%</td>
<td>Higher: 38.6%</td>
</tr>
<tr>
<td><strong>North-European ancestry</strong></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Phenotype</td>
<td>NESDA Cases</td>
<td>NTR Controls</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>CIDI - MDD information (episodes &amp; age of onset)</td>
<td>Yes</td>
<td>n/a</td>
</tr>
<tr>
<td>Depression severity (Inventory of Depressive Symptoms)</td>
<td>Yes</td>
<td>n/a</td>
</tr>
<tr>
<td>Family history of MDD</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anxiety severity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Personality (neuroticism &amp; extraversion)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prospective follow-up</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Demography - age, sex, ancestry, marital status, &amp; educational attainment</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stressful life events</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Leisure time exercise behavior</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Licit &amp; illicit substance use</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thyroid function (TSH &amp; free T&lt;sub&gt;3&lt;/sub&gt;, 99% of subjects)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cortisol profile (six time points, 75% of subjects)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Heart Rate Variability (and other indices of autonomic nervous system functioning via VU-AMS system, 95% of subjects)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Future Plans

• Increase Stage 1 sample (N=3,200 now)
  - Can increase now to total of 4,600 or 8,000

• “Stage 1b” – alternate genotyping
  - Subset of best SNPs
  - Promising SNPs with technical issues
  - Fill in sparse regions
  - “Too hard” – MHC & mitochondrial tag SNPs

• Stage 2 – N=14,000 & special samples

• Stage 3