A Genetic Perspective on Mood Disorders
The genetic architecture of depression

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A brief history of depression genetics

Twin studies
Heritability 37%
Additive genetic model
Polderman (Nat Gen, 2015)

Candidate gene studies
>100 reports; inconsistency / failure to replicate
Border (Am J Psych, 2019), McIntosh (Neuron, 2019)

Genome-wide Association Studies

- Need for coordinated worldwide effort
- Consistency of measurement & genotyping
- Very large samples
- Psychiatric Genomics Consortium

- First depression GWAS, 2013, 9K cases, 9K controls
- No variants identified – estimated 40K cases needed

https://www.med.unc.edu/pgc
Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways.

Genetic correlation with clinical MDD

- Broadest MD ("Nerves")
  - $r_g = 0.79 \pm 0.07$, $P_{FDR} = 3.79 \times 10^{-25}$

- Probable MDD (limited criteria)
  - $r_g = 0.64 \pm 0.12$, $P_{FDR} = 7.95 \times 10^{-8}$

- ICD-coded MDD (HES)
  - $r_g = 0.63 \pm 0.10$, $P_{FDR} = 1.86 \times 10^{-8}$

Discovery
- 138K Psychiatric Genomics Consortium
- 361K UK Biobank*
- 307K 23andMe company
- 807K discovery sample size

Replication
- 1.2M 23andMe*
- Leave one out

See also Wray (Nature Genetics, 2018)
Results

102 independent variants associated with depression ($P < 5 \times 10^{-8}$)
269 Associated Genes

- Replication in 23andMe
  - Direction & $P < 0.05$ 97
  - $P = 4.8 \times 10^{-4}$ 87

Characterizing the genetic components of BD

Understanding the biology of BD

- Synaptic structure and activity
- Response to stimuli

Heritability enriched in conserved regions / CNS, cortex, cell type
Polygenic profiling

AGCCCAGTTGCTCCC
ATCACATTGGCC
GTCCATTATACA
GTACATTATGA

Out of sample polygenic prediction

Across 26 clinical cohorts
Prediction R²
OR 10th decile
Increased community, in/outpatient

Genetic correlations

Depressive symptoms
Neuroticism
Psychiatric disorders
Smoking, obesity and related diseases
Onset & end of menstruation
Education length & attainment
Your expected lifespan
Causal inferences

SNP effect for Ever vs Never Smoked

SNP effect for Depression

• Neuronal element
  – Neuron / Dendrite
  – Somatosensory neuron
  – Neuronal spine
  – Neuron projection
  – Synapse / Post-synapse
  – Excitatory synapse

• Neuronal process
  – Modulation of
    • Synaptic transmission
    • Synaptic structure
    • Synaptic activity
    • Synaptic plasticity

• Gene Set Enrichment
  – Neuronal process
    – Modulation of
      • Synaptic transmission
      • Synaptic structure
      • Synaptic activity
      • Synaptic plasticity

• SNP effect for Depression

Neuriticism

BMI

SNP effect for Ever vs Never Smoked

Depression

Smoking
Partitioned heritability analysis

Brain region

Brain cell type

CLINICAL TRANSLATION OF DISCOVERIES FROM DEPRESSION GWAS STUDIES

Visscher (AJHG, 2017)
Gene-drug interactions
37 of the depression genes are reported to interact with 220 drugs. These 220 drugs belong to 54 different drug classes.

How do Depression & Bipolar Disorder Differ?
Addressing heterogeneity through common variants

Major Depression
Bipolar Disorder

How do Depression & Bipolar Disorder Differ
Major Depression
Bipolar II Disorder
Bipolar I Disorder
Schizophrenia
How do Depression & Bipolar Disorder Differ

Major Depression
Bipolar II Disorder
Bipolar I Disorder
Schizophrenia

30 GWAS Loci for Bipolar Disorder

Prediction of BD types I and II from PRS

Stronger prediction of BDI from SCZ PRS
Stronger prediction of BDII from MDD PRS
Can genetics be used to stratify depression?

- >100 unique symptom correlations
- Many symptoms are bi-directional
- No constellation much more common
- Some symptoms more common after grief

- Can genetics be used to identify particular clusters?
- Is depression separable from the wellbeing spectrum?

Stratifying depression

Neurotic Depression
Vascular Depression
Major Depressive Disorder

Luc (MD NOT Neuro): 12
Depression NOT Neuro:
bipolar disorder, BMI, triglycerides, conscientiousness, morning chronotype

Adams (bioRXiv: 547828, in review)
What is the impact of depression?

- Correlations with disorder confounded
- Reverse causality
- Reporting bias

- Use genetic risk factors as instruments
- Measure score and strength of association
- Unconstrained approach PheWAS

MD Risk Score PheWAS

n=10,674 discovery
n=11,214 replication

*Selection for N>2,000 per trait

Shen (bioRXiv 617669)
Epigenetic changes

- Intersection of genetics & environment
- Modification to DNA not base sequence
- Famine
- Birth complications
- Stressful exposures
- Smoking & alcohol

DNA methylation and MDD
Step 1: Study sample 1: N = 3047, 1,223 cases

Step 2: LASSO regression
196 CpGs associated with MDD

Step 3: Independent sample
N\text{incidence} = 1607 (cases 190)
N\text{prevalence} = 1780 (cases 363)

DNA methylation (DNAm) predictors of MDD

Variance explained by DNAm score in all cases: prevalent cases, incident cases

Variance explained by MIDPRES 6.06 and DNAm score in prevalent cases

DNA methylation (DNAm) predictors of MDD
Summary

- GWAS Studies
  - 102 variant & 269 gene-depression associations
  - Genetic architecture, causal inference, risk prediction
  - Reveal biology, identify drug targets, stratify diverse aetiologies
  - Progress will continue as studies continue

Summary

- Polygenic & poly-epigenetic prediction
  - Tools to study the impact of risk
  - Combined with Mendelian Randomisation
  - Study risk factors & mechanisms, including environment
  - Capture smoking, alcohol, age & ageing

Challenges to further progress

- Diverse ancestries
  - GWAS European ancestry dominates
  - Exacerbation of health disparities
  - 75% disability in Low-middle income nations